CANCER FORUM

FORUM

Targeted and individualised therapies

PROGRESS IN TARGETED THERAPIES FOR CANCER: OVERVIEW

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Abstract

The explosion in knowledge about the molecular and cellular biology of cancer has led to the identification of many molecules or physiological processes that can be therapeutically exploited to treat cancer using so called 'targeted therapies'. While the concept of targeted therapy is not a new one, it is only in the last decade that these agents have become established in standard clinical practice. An overview of progress in the development of targeted agents to date and challenges faced in the future application of targeted therapy to cancer treatment is provided in this article and is the subject of this issue of *Cancer Forum.*

Targeted therapies for cancer can be broadly defined as treatments directed against abnormally activated molecules or physiological processes required for maintenance or progression of tumours. In recent years, many targeted therapies have become established in daily clinical practice and a huge number of agents are in various stages of pre-clinical and clinical development. The concept of targeted therapy however, is not a new one. Just over a hundred years ago Paul Erlich developed the concept of 'magic bullets' to specifically target disease while sparing normal tissues (Erlich also coined the term chemical therapy or 'chemotherapy'). Although treatment with radioiodine in the 1930s or tamoxifen in the 1970s perhaps represent the origins of targeted therapy for cancer, the modern era of targeted therapy was ushered in by the trials of rituximab, trastuzumab and imatinib at the beginning of this century. Since then there has been steady clinical progress with targeted therapies, used alone or in combination with conventional therapies, finding new indications in many tumour types, including cancers previously considered untreatable.

The development of targeted agents and their use in cancer treatment have been made possible by major advances in the understanding of cancer biology, in particular the identification of targets important for cancer maintenance and progression, and technological innovations that have allowed these targets to be therapeutically manipulated. However, significant challenges in the clinical application of targeted therapies remain, including finding predictive markers to identify which patients are likely to benefit from which treatments, the development of acquired resistance, management of long-term toxicities and the financial costs of these agents.

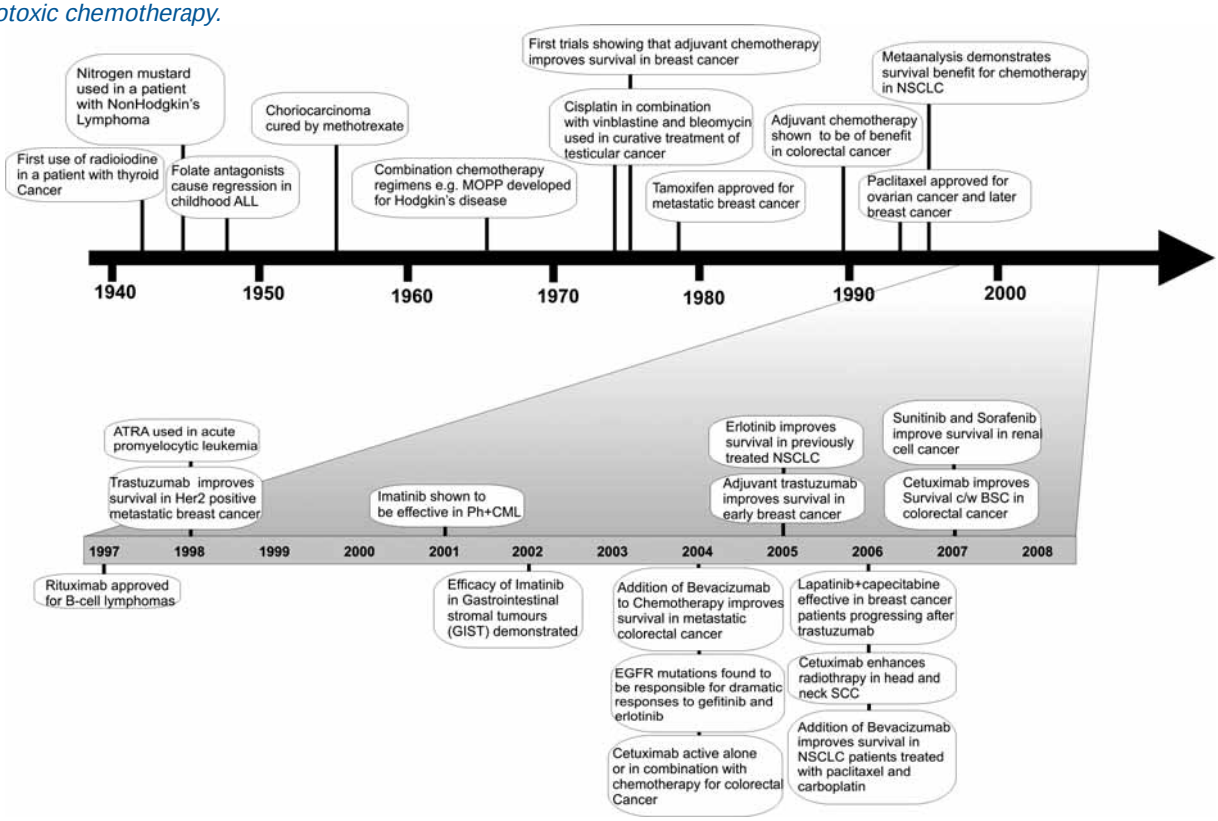
Historical backdrop

The recent progress in targeted therapies must be viewed against the backdrop of the achievements of cytotoxic chemotherapy over the last half century or so (see timeline, figure 1). The observation of profound lymphoid and myeloid suppression in World War I soldiers exposed to nitrogen mustard led to the use of mustine in patients with lymphoma in the 1940s.[1] Since then, a range of cytotoxic drugs have been developed, including alkylating agents, vinca alkaloids, podophyllotoxins, antimetabolites, topoisomerase inhibitors, platinum analogs and taxanes. The largely empiric use of these drugs resulted in cures in germ cell tumours and certain leukaemias and lymphomas. Concurrent chemotherapy with radiotherapy provided potentially curative treatment for head and neck cancer, lung cancer, cervical cancer, anal squamous cell carcinoma and other cancers, albeit at the expense of significant toxicity. Adjuvant chemotherapy after surgery in breast, colon, or lung cancer improves survival. Additionally, in many tumour types, chemotherapy can improve survival and quality of life in patients with metastatic disease. However, limitations of traditional cytotoxic chemotherapy include low response rates and frequent toxicities to normal tissue. Efforts to combine different cytotoxic agents or increase dose (by techniques including the use of growth factor support, autologous bone marrow or peripheral stem cell transplantation) have in general not resulted in further improvements in outcomes, indicating a ceiling of efficacy for current cytotoxic drugs.

Tamoxifen

Tamoxifen is arguably the first and most successful targeted therapy to date. For over a century it was

Figure 1: *Timeline of the progress in the clinical application of targeted therapies for cancer in the historical context of cytotoxic chemotherapy.*



recognised that oophorectomy, hypophysectomy and adrenalectomy were effective treatments in some women with breast cancer. The identification of the estrogen receptor in the 1950s and the development of an assay for the estrogen receptor led to a method to identify patients who would benefit from endocrine ablative surgery. Tamoxifen (initially called ICI-46,474) was developed as a post-coital contraceptive (it failed as it caused ovulation). Pre-clinical studies demonstrated that tamoxifen was able to block estrogen from binding to estrogen receptors in tumours and prevented the growth of mammary tumours in rats. These findings led to clinical studies beginning in the 1970s that established the use of tamoxifen in metastatic breast cancer and in the adjuvant setting for women with hormone receptor positive tumours.[2] Tamoxifen has also been reported to prevent the development of new breast cancers by 50% in high risk women.[3]

Modern era of targeted therapy

In the last three decades there have been major advances in unraveling the molecular processes that underpin cancer. Increasingly detailed appreciation of the biology of cancer has led to the identification of specific molecules or processes (eg. angiogenesis) that are crucial to the maintenance and progression of tumours.[4] Coinciding with this has been the development of new technologies such as high throughput screening, structure-based design and monoclonal antibody technology, that have allowed discovery of agents that modulate these targets (so called targeted therapies). Small molecules designed to inhibit signal transduction pathways by inhibiting protein kinases and monoclonal antibodies targeting cell surface receptors represent the most commonly used approaches to date. These agents have demonstrated efficacy across a broad range of tumour types.

This issue of *Cancer Forum* provides an update about the current status of targeted therapy in breast cancer, lung cancer, colorectal cancer, ovarian cancer, renal cancer, sarcoma and haematologic malignancies. At the time of writing, 15 such therapies are approved by the Therapeutic Goods Administration (TGA) (see table 1).

Early success for the use of targeted therapies as single agents was seen with trastuzumab in breast cancer,[5] imatinib in chronic myeloid leukaemia (CML)[6] and rituximab in B-cell lymphomas.[7] Tumour types considered resistant to standard cytotoxic treatments, such as gastrointestinal stromal tumours (GIST) and renal cell carcinoma, have responded to agents such as imatinib and sunitinib.[8-10] Survival benefits observed with the epidermal growth factor receptor (EGFR) inhibitors erlotinib in non-small cell lung cancer (NSCLC)[11] and cetuximab in colorectal cancer,[12] indicated that these agents might be beneficial in a broader set of tumour types.

Notably, the strategy of combining targeted therapies with cytotoxic chemotherapy and radiotherapy has proved to be fruitful. This is particularly the case for monoclonal antibodies, where combinations of rituximab,[13,14] trastuzumab,[15-17] bevacizumab[18,19] and cetuximab with chemotherapy (as well as radiation in the case of cetuximab[20]) have become important and in many cases standard of care regimens in lymphoma, breast cancer, colorectal cancer, lung cancer and head and neck cancer. Less promising results have been seen with small molecules, where to date many combination studies have not demonstrated improved outcomes

(with the exception of lapatinib in combination with capecitabine in breast cancer and possibly erlotinib in combination with gemcitabine in pancreatic cancer).[21-22]

The application of targeted therapies to cancer has required a shift from empiricism and a 'one treatment fits all' algorithm, to one based on understanding the mechanism of disease and targeting pathogenesis. This is exemplified by the clinical development of imatinib, the first tyrosine kinase inhibitor to be used in humans.

Imatinib was developed to target the molecular abnormality responsible for CML, but has found applications in other malignancies. Screening of chemical libraries and medicinal chemistry efforts in the 1980s led to the identification of a compound (now known as imatinib, formerly known as STI571 and CGP57148B) that potently inhibited BCR-ABL (the fusion protein product of the t 9:22 translocation known as the Philadelphia(Ph) chromosome which is the molecular driver of CML).[23] Encouraging pre-clinical studies with this drug[24] led to a Phase I clinical trial that was conducted in patients with Philadelphia chromosome positive (Ph+) CML.[6] Significant efficacy with minor toxicities was observed in these patients.[6] Soon after this, imatinib was studied in and found to have activity in CML in blast crisis and Ph+ Acute lymphocytic leukaemia. This led to US Food and Drug Authority (FDA) approval of imatinib for Ph+CML in 2001. Imatinib also inhibits two other kinases C-KIT (CD117) and platelet derived growth factor receptor (PDGFR). This lead to the study of imatinib in gastrointestinal stromal tumours, where it received accelerated FDA approval on the basis of response rates in tumors with mutations in either C-KIT or PDGFR.[8] Since then, further mechanism-based studies led to exploration of the use of imatinib in tumours with activating mutations or gene rearrangements, resulting in increased expression of receptor or ligand.[25] As a result of these studies imatinib is now approved for: chronic myelomononocytic leukemia (TEL-PDGFRb fusion gene); aggressive systemic mastocytosis (C-KIT mutations); hypereosinophilic syndrome and/or chronic eosinophilic leukemia (FIP1L1-PDGFRa fusion kinase); and dermatofibrosarcoma protuberans (COL1A1/PDGFB fusion).

A concern was that the dramatic responses seen with imatinib in CML and GIST represented the exception rather than the rule and that few solid tumours would be dependant on or 'addicted' to a single oncogenic mutation and therefore contain a targetable molecular 'Achilles heel'.[6,8,26] This scepticism is supported by large-scale genomic studies of cancer genomes which show that individual tumours may contain multiple potentially pathogenic mutations.[27,28] These data emphasise the importance of developing bio-informatic tools that can provide an assessment of complex signalling networks to identify which pathways drive a particular cancer and the necessity of developing combinations of drugs that inhibit multiple different pathways.

Another approach is to identify small subsets of patients within a tumour type that are driven by the mutation of interest. Again, imatinib provides an instructive example. Phase II studies of imatinib in unselected patients with melanoma were conducted with disappointing results.[29,30] However, recently KIT-activating mutations were reported in a small subset of patients with acral and mucosal locations.[31,32] Phase II studies of imatinib in patients with melanomas found to have KIT mutations have commenced with preliminary positive results.[33]

Table 1: *TGA approved targeted therapies*

Small molecules		**Targets (or drug class)**
	Imatinib (Glivec)*	BCR-ABL, PDGFR, C-KIT
	Gefitinib (Iressa)*	EGFR
	Erlotinib (Tarceva)*	EGFR
	Sorafenib (Nexavar)	VEGFR, PDGFR, C-KIT, raf, Scf
	Nilotinib (Tasigna)	BCR-ABL, PDGFR, C-KIT
	Dastinib (Sprycel)*	BCR-ABL
	Lapatinib (Tykerb)*	EGFR, erbB2
	Sunitinib (Sutent)	VEGFR, PDGFR, C-KIT, Ret, Flt-3,
	Bortezimib (Velcade)*	(Proteosome inhibitor)
	Octreotide (Sandostatin)*	Somatostatin receptor
Monoclonal antibodies		
	Rituximab (Mabthera)*	CD20
	Trastuzumab (Herceptin)*	erbB2 (HER2)
	Cetuximab (Erbitux)*	EGFR
	Bevacizumab (Avastin)	VEGF
	Alemtuzumab (Campath)	CD52

TGA approved targeted therapies for cancer as of July 2008. Note this list excludes hormonal therapies for breast and prostate cancer. Asterisk (*) indicates Pharmaceutical Benefits Scheme approval for specific indications.

Challenges for targeted therapy

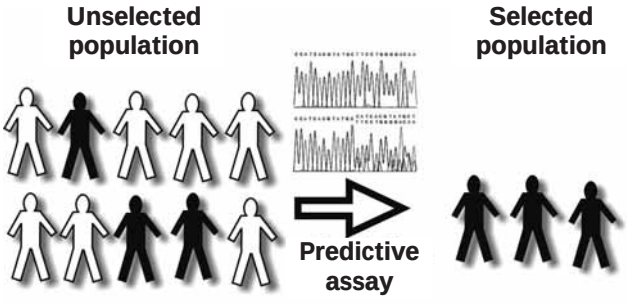
The concept of individualised medicine involves selection of the right drug for the right person at the right dose and schedule (figure 2). Current molecular modelling and medicinal chemistry efforts have enabled the development of inhibitors of many kinases implicated in cancer; monoclonal antibody technology allows for design of specific humanised antibodies to target essentially any protein. Previously 'un-druggable targets', such as those involving protein protein interactions are now 'druggable', allowing the development of new classes of targeted agents such as proapoptotic BH3 mimetics.[34] The challenge moving forward is to identify which patients will benefit from this growing armamentarium of targeted therapies.

It is however, fair to say that the progress in the molecular characterisation of tumours has not been matched by the development of clinically useful predictive biomarkers. For example, although much has been learned about the mechanisms of angiogenesis in tumours and bevacizumab has been shown to be of clinical benefit in combination with chemotherapy in colorectal cancer, in non small cell lung cancer and perhaps breast cancer, there are no predictive markers that predict which patients are most likely to benefit from this therapy. The importance of predictive and prognostic biomarkers is explored in the article by Sally Lord and colleagues.

To date, tests for specific genetic markers (ie. mutations, amplifications or gene rearrangements) conducted in tumour tissue have proven the most robust predictive markers. However, it is likely that ongoing genomic and proteomic studies will uncover other suitable biomarkers as illustrated by tests such as Oncotype Dx in breast cancer.[35] It is also likely that high throughput platforms which allow cheap and rapid screening for hundreds of mutations,[36] or next generation sequencing that allows sequencing of entire cancer genomes (as discussed by David Bowtell in this issue of *Cancer Forum*) and non-invasive molecular profiling methods in circulating tumour cells,[37] plasma DNA,[37] or utilising proteomic studies of plasma,[38] will be valuable sources of predictive and prognostic markers that will direct treatments in the near future. In addition, as Rod Hicks and Rob Ware point out in their article, molecular imaging with technologies such as positron emission tomography will also provide important means to select patients for treatment and to monitor response to therapy.

Another challenge is the development of acquired resistance to initially effective therapies. Patients receiving imatinib for CML or GIST may develop resistance to imatinib after many months or even years of successful treatment. Similarly, patients with NSCLC responding to EGFR TKIs gefitinib and erlotinib invariably become resistant to these agents. Recently, the mechanisms responsible for acquired resistance have begun to be appreciated and new strategies to overcome this problem are under development. In CML and in GIST, a frequent observation in patients with acquired resistance to imatinib is a point mutation in the ABL, KIT or PDGFR kinase domain that interferes with the binding of imatinib.[39] This approach may be overcome by structurally distinct second generation inhibitors such as nilotinib, dasatinib or sunitinib. In NSCLC resistance occurs through secondary mutations in the EGFR that prevent binding of gefitinib or erlotinib to the active site of the EGFR tyrosine kinase,[40] or through subversion of alternative signaling pathways such as occurs with amplification of c-met.[41] Strategies under investigation to overcome acquired resistance to EGFR inhibitors include the use of irreversible inhibitors of the EGFR, such as PF00299804 or BIBW 2992, or combinations of EGFR inhibitors and met inhibitors. For other classes of targeted agents such as antiangiogenic therapies, the mechanisms of resistance (both intrinsic and acquired) remain poorly understood.

Figure 2: *The role of predictive markers in individualised medicine. If a given drug is only active in 30% of unselected patients of a given tumour type, a predictive marker can be used to identify those patients prior to treatment. This allows the therapy to be delivered to a selected population more likely to benefit and spares patients unlikely to benefit from receiving an ineffectual treatment.*



There has also been appreciation of the distinct profile of toxicities of targeted therapies. Examples of common toxicities include: rash toxicity and diarrhoea from EGFR inhibitors; hypertension from VEGF inhibitors; congestive cardiac failure from trastuzumab; hypothyroidism and hair depigmentation from sunitinib; and hand foot syndrome from multitargeted tyrosine kinase inhibitors. In addition, there are rare but serious complications of targeted therapies such as fatal haemorrhage or reversible posterior leuko-encephalopathy with VEGF inhibitors. Long-term management of toxicities of targeted agents are particularly relevant, as unlike cytotoxic chemotherapy, which is typically used for a limited number of cycles, targeted agents are frequently used in ongoing maintenance treatments for months or years.

Finally, the financial costs of targeted therapies are significant. Novel targeted agents are frequently many times more costly than their cytotoxic predecessors. Trastuzumab, imatinib, bevacizumab and rituximab together accounted for over $8 billion in sales in 2005.[42] Treatment with cetuximab or bevacizumab can currently cost patients in excess of $4000 a month. These considerable costs raise issues of how much individuals or the broader community are prepared to pay for sometimes incremental benefits provided by these drugs, as well as ethical issues regarding equity of access to treatment.

Conclusions

While there has been remarkable progress in a relatively short time in the application of targeted therapies to cancer treatment, there remains a long way to go before cancer can be considered a chronic disease. Few targeted agents (with the exception of adjuvant tamoxifen or trastuzumab) have been shown to cure patients. The survival benefits from the addition of targeted agents to chemotherapy, while significant, are generally incremental and measured in months. Further progress requires understanding of the molecular drivers of cancer and development of clinically useful tools to identify which patients will benefit from which treatments. Combinations of agents acting on different targets alone or in combination with conventional agents will need to be developed and tailored to the particular genetic makeup of individual tumours. Strategies will be needed to prevent or overcome acquired resistance to treatments and to manage long-term toxicities of targeted agents. These challenges will need to be addressed to realise the promise of targeted therapies in delivering individualised medicine for all patients with cancer.

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IMPACT OF GENE TECHNOLOGIES ON PERSONALISED CANCER THERAPY

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Abstract

Given that cancer is driven by inherited and acquired defects in our genetic code, the ability to profile genes and their activities has the potential to impact substantially on the prevention and treatment of cancer. The last decade has seen very rapid advances in the ability to measure both an individual's genetic predisposition to cancer and the mutational load within a cancer sample. Identification of germline mutations in genes such as BRCA1, BRCA2 and MSH1, that are associated with greatly increased risk of breast, ovarian, colorectal and other cancers, has led to the development of integrated management strategies for measurement and management of genetic risk in a clinical setting. Very recently, technical advances have made it possible to identify genes that confer a much lower, but still significant, risk of cancer. Low-risk genes will present major challenges in devising risk-management strategies, because complex gene-gene and gene-environment interactions are likely to have a significant impact on overall cancer risk. The ability to measure somatic DNA changes in the cancer genome has led to clinically available tests that can predict response to treatment and aggressiveness of disease. The availability of such tests will increase as their utility is validated and technical advances make them faster, cheaper and more comprehensive. The current revolution in DNA sequencing technology promises the availability of affordable whole genome sequence information within a few years.

Our genetic predisposition to cancer

Cancer can be thought of as a corruption of the DNA software code that controls normal cellular processes. Errors in the code may be present in the germline or acquired throughout life, as somatic mutations. Some germline changes can have a profound impact, increasing the risk of cancer greatly and these are referred to as being 'highly penetrant' and 'high-risk'. For example, germline mutations in BRCA1 that inactivate the protein can result in a 60-70% lifetime risk of breast cancer in women.[1] For high-risk cancer genes there is a close correspondence between presence of the mutation in an individual and appearance of the disease (cancer), making it possible to identify such mutations through the use of linkage studies involving families with strong cancer predisposition pedigrees. A number of high-risk cancer genes were identified in the 1990s and over the last decade a great deal has been learned about approaches to genetic testing for high-risk families. Integrated risk-management strategies for individuals carrying high-risk genes are now an established aspect of modern cancer care (overviewed *Cancer Forum*, November 2007 Vol 31 No.3).

High-risk genes account for a small proportion of all cancers and it appears that inherited cancer risk for most people is determined by the concerted impact of a number of genes in their genome, each of which may individually confer low risk, but which interact in an additive or even synergistic manner. As such, genetic cancer risk for most people is probably more akin to being dealt a good or bad hand of genes, rather than being the product of a single gene. A low risk gene implies that it is weakly penetrant, that is, only a minor proportion of individuals with the genetic change will manifest the disease. As a result, traditional linkage studies are ineffective at identifying such genes and other approaches must be used to find them. Whereas a high-risk mutation typically has a profound impact on a gene, a low risk change may have only a subtle impact on protein abundance or activity and therefore may not be readily obvious. Indeed, many low risk changes can be viewed as genetic polymorphisms that constitute part of normal human variation.

The HapMap is an international consortium that aims to identify the millions of single nucleotide polymorphisms (SNP) in the human population that confer difference between one person and another.[2] The identification of these SNP's and the development of technologies to type hundreds of thousands of SNP's in large numbers of individuals in an affordable manner made it possible to perform SNP-based genome-wide association studies to search for low risk genes.[3] In the last two years these studies have led to the identification of low-risk genes for cancers of the breast, prostate and colon.[4-10] As predicted, most of these genes increase risk slightly (less than two-fold), but appear to have a synergistic interaction. The impact of the SNP on gene function has not been obvious for some low risk genes, and in such cases it is not known whether the defect is associated with the specific SNP or whether the SNP simply marks a more significant nearby change. For example, a very robust association has been found between SNPs at chromosome position 8q24 and colorectal and prostate cancer risk, although the mechanism of action of the genetic change was not identified in these studies.[8-11] Genome-wide association studies require thousands of cases and controls to generate robust statistical associations. As a result, many studies are at the limit of what is possible and there is a substantial risk of finding chance associations between the presence of a given SNP and cancer risk. The most compelling findings are those that are replicated in completely independent studies as has been achieved for several new, low-risk breast and colon cancer genes. The finding that the presence of

some low risk genes can increase the risk of disease in individuals bearing high-risk mutations, such as in BRCA1 or BRCA2, adds weight to their importance.[12]

Although the field is at a very early stage, low risk cancer genes can clearly be found using advanced genetic technologies and very large patient cohorts, established through the formation of international research consortia. While they may confer relatively low risk individually, their effect appears to be compounded through gene-gene interactions.[4] Collectively, low risk genes are likely to account for a large proportion of cancers, if as expected the risk alleles are frequent in the population. Despite this progress, it is presently unclear how and when testing for these genes should be integrated into clinical practice. We don't yet fully understand how most low risk genes interact with the rest of the genome to confer overall risk – a key parameter in deciding risk-management options. Additionally, it is possible that the impact of many low risk genes will be strongly influenced by the environment (gene-environment interaction). While such interactions remain to be defined, it is likely that modification of diet and lifestyle factors may become the predominant approaches to the preventative management of individuals carrying low risk genes, rather than more drastic surgical interventions. Cost and the potentially negative psychological impact of testing will need to be weighed against the advantages of detection of low but significant genetic risk.

One of the most significant implications of detecting low risk genes may be in targeted early detection testing. It is estimated that only about half the population account for ~90% those at risk of breast cancer.[13] In addition to significant cost savings through more targeted screening, the ability to identify those most at risk may make early detection testing feasible for low incidence cancers for which population-based screening is impractical. For example, population-based early detection testing for ovarian cancer is hampered by an unacceptably low positive predictive power of current testing regimes, however this might be improved through more focused screening of those most at risk.[14]

Genetic profiling of the cancer genome

The genomes of cancer cells carry a range of somatically-acquired changes which include alterations in gene copy number (amplifications/deletions), gene expression, methylation, novel gene fusions (translocations) and point mutations. Some of these changes are so called passenger mutations – inconsequential events acquired as a result of an unstable genome – which are distinct from important driver mutations that provide selective advantages to the cancer cell.[15] While it is believed that the constellation of driver mutations within a given cancer cell generally act in concert, some mutations can be of sufficient importance that reversing their effect can have a profound impact on the growth of the tumour and therefore represent excellent therapeutic targets. Amplification of HER2 in breast cancer, the BCR-ABL translocation in chronic myeloid leukaemia, epidermal growth factor receptor (EGFR) in lung cancer, and C-KIT mutations in gastrointestinal stromal tumours are good examples of mutations that result in a state of oncogene addiction by the cancer cell that when inhibited with agents such as trastuzumab, gefitinib and imatinib, lead to a significant therapeutic response.

These oncogenes and their corresponding diseases also exemplify the value of developing diagnostic molecular tests in conjunction with a targeted therapeutic, since detecting the presence of the driver oncogene provides a strong predictor of therapeutic response to the molecularly targeted agent. Recent studies showing that the presence of K-RAS or PTEN mutations can attenuate responses to molecular agents targeting HER2 or EGFR mutations, extends the concept of using molecular diagnostics to probe the network of other genetic events that may influence therapeutic response.[16-18] This concept is further exemplified by the development of gene expression profiling tests such as Oncotype Dx and Mammaprint, which monitor the expression of multiple genes to provide prognostic information that can guide clinical decision-making.[19-22] These tests, available commercially and in increasing clinical use, have been developed from a large number of DNA microarray-based studies performed over the last decade. While still in clinical development, it appears likely that such tests will also impact on the management of disease, such as diffuse large cell B lymphoma and carcinoma of unknown primary.[23,24] Key mutational events can also provide biomarkers of the presence of disease. The development of highly sensitive polymerase chain reaction based tests are widely used to monitor therapeutic response and recurrence in chronic myeloid leukaemia and other types of leukaemia.[25]

Given the importance of targets such as HER2 and BCR-ABL, systematic screens for mutations in thousands of genes in cancer genomes have commenced in order to provide new therapeutic approaches. Pioneering studies involving screens of all protein kinases in the genome led to the identification of B-RAF mutations in melanoma and other cancers, a potentially important new therapeutic target.[26] More recently, researchers have screened all known protein coding genes in a handful of breast and colorectal cancer samples, leading to the identification of several hundred new 'CAN' genes, putative driver mutations for these diseases.[27,28] Organised international consortia such as the Cancer Genome Atlas and the International Cancer Genomics Consortium are embarking on screens that aim to catalogue all significant mutation events in common cancers by screening hundreds of cancer samples for each disease. While this work is providing an unprecedented view of the cancer genome, a sobering finding so far has been the general absence of new, common, high-frequency mutations that could be ideal therapeutic targets.[27] These findings point to the importance of developing highly multiplexed tests that can search for a range of possible mutations in an individual's cancer to assist clinical decision-making. OncoMap provides such an example, where mutations in multiple therapeutically relevant genes are screened by mass spectrometry.[29]

Future of genetics in personalised medicine

There are now numerous examples of the value of genetic profiling in measuring genetic risk, monitoring disease response and recurrence, in prognostication and prediction of therapeutic response. The recent development of Poly ADP-ribose polymerase inhibitors targeting tumours with germline mutations in BRCA1 or BRCA2 is a potent example of how knowledge of germline status can be exploited therapeutically.[30] Although some cancers, particularly leukaemia and some sarcomas, appear to be predictably driven by dominant common oncogenic events, the pattern that appears to be emerging for most solid cancers is one of molecular heterogeneity both within and between individual cancer patients.[28] Very recent studies have identified new genes associated with small, but significant increases in cancer risk. These studies also suggest a complex pattern of events where overall genetic cancer risk will be dependent on the interplay of multiple genes within an individual's genome. All these findings point to the need for rapid, affordable and particularly, ultra-high throughput methods of probing the germline and the cancer genome.

The last few years have seen unprecedented innovation in DNA sequencing technologies.[31] So-called 'next generation' sequencers have already reduced the cost and increased the throughput of DNA sequencing several orders of magnitude, effectively replacing sequencing factories with desk-top boxes. Although not quite there yet, novel sequencing technologies are very likely to make available affordable whole genome sequencing, within the next few years. Such capability will have a profound impact on our ability to measure germline genetic risk and probe molecular change in cancer genomes. Integrating this welter of complex information into evidence-based medicine that works for the patient will be the great medical challenge of our time.

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THE ROLE OF PROGNOSTIC AND PREDICTIVE MARKERS IN CANCER

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Abstract

New genomic and proteomic technologies have led to important therapeutic advances in oncology. This article describes how the discovery of molecular prognostic markers to classify an individual patient's risk of disease events and predictive markers to classify response to specific treatment options are used to guide the selection of treatment and identify targets for the development of new molecular-targeted therapies. Prognostic markers can be used to determine the need for further treatment. Patients at very low risk of disease events can safely avoid treatment if risks of adverse events outweigh the estimated benefits. Alternatively, high-risk patients may benefit from a more aggressive treatment regimen. Predictive markers are used to select the most appropriate treatment by identifying patients most likely to respond and avoiding treatment for patients unlikely to respond or those at unacceptably high risk of adverse events. The clinical value of molecular markers depends on a series of factors: the reproducibility of the laboratory methods used for marker measurement; the accuracy of the marker to classify patient prognosis or response to treatment compared to conventional clinico-pathological criteria; its validity when used in independent populations; and the impact of using this information to guide treatment selection on patient outcomes. Randomised control trials are essential to assess the effectiveness and optimal use of prognostic and predictive markers and biomarker-guided therapies.

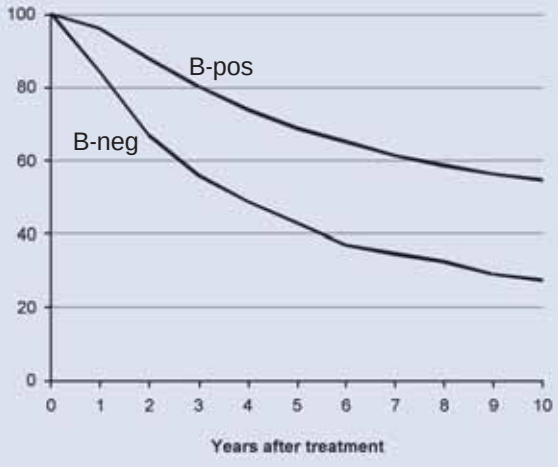
The clinical management of the patient with cancer is largely based on the use of a standardised set of clinical and pathological criteria for diagnosis and classification of the extent of disease. Cancer staging systems have been developed to organise this information in a clinically meaningful way to estimate patient prognosis and guide the selection of effective treatments. However, patients with the same diagnosis and pathological characteristics can show wide variability in clinical outcomes and response to treatment. The use of new genomic and proteomic technologies for the investigation of the molecular mechanisms of disease and response to therapies has led to the discovery of molecular markers for more accurate classification of a patient's risk of disease events (prognostic markers) and response to specific treatment options (predictive markers). Here, we describe the role of prognostic and predictive markers for the selection of existing treatments and the identification of novel molecular targets for the development of new treatments in oncology.

Discovery and validation of molecular markers

The term 'biomarker' can be used to refer to any characteristic that can be objectively measured as an indicator of normal or pathological biological processes or the response to a therapy.[1] In oncology, biomarkers can include: basic clinical characteristics such as patient gender, age, weight and smoking status; inherited (germline) gene mutations or variants that predispose to cancer or response to treatment; and the pathological and molecular characteristics of the tumour. Potential candidate tumour markers include somatic mutations of the DNA sequence and epigenetic changes such as DNA methylation, that modify gene function in critical pathways involved in cancer pathogenesis or treatment action; or downstream DNA products such as levels of messenger ribonucleic acid or protein expression.

The discovery of a molecular marker begins by demonstrating that the presence, absence or level of the marker is associated with outcomes such as survival time or tumour response, with further evidence required to determine its clinical role (figure 1). Initial biomarker

Figure 1: *Identification of biomarkers*



Interpretation: Patients testing positive for Biomarker B (B-pos) have a better outcome on treatment A than patients with testing negative (B-neg). Log-rank test P<0.01

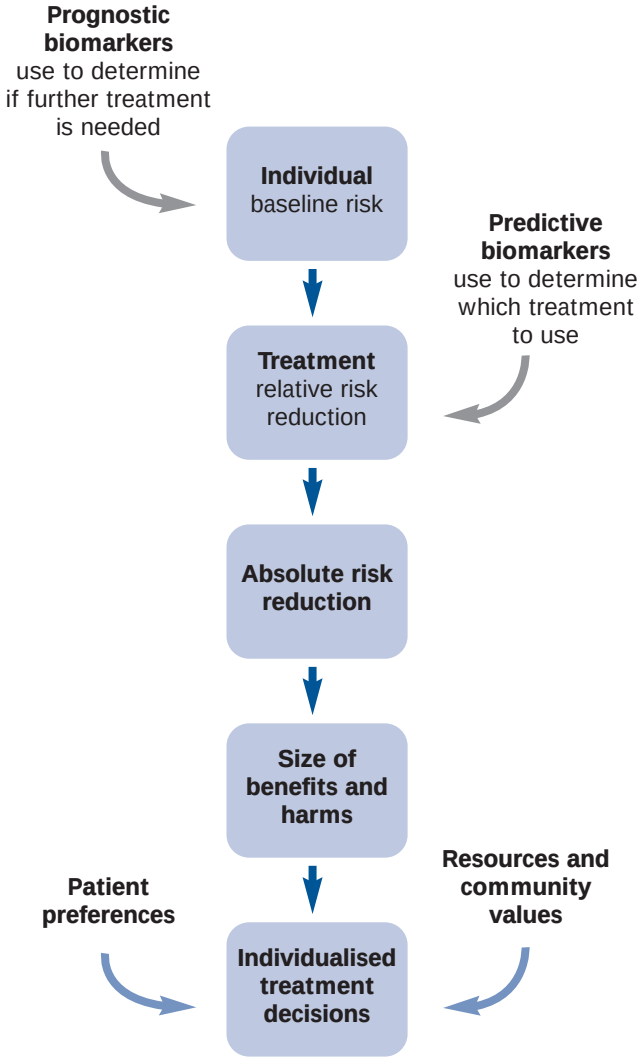
Additional evidence is needed to determine the clinical role of biomarker B.

Outstanding questions include:

- *Does biomarker B identify patients with a better prognosis; or does it predict which patients will respond to treatment A?*
- *Should biomarker B be used to select which patients should receive treatment A?*
- *Should treatment A be recommended to all B-positive patients?*
- *How does biomarker B compare to conventional clinico-pathological criteria to guide treatment decisions?*

studies are often undertaken retrospectively using specimens collected from a convenience sample of patients who may have received different treatments. The initial exploratory analysis may investigate large numbers of candidate markers. False positives are therefore common and there is a serious potential for over-fitting data when developing explanatory models, in particular, if few patients are available or few events have occurred. Thus, marker development involves an assessment of the reproducibility of the laboratory assay used for its measurement and validation of its discriminatory capabilities in independent populations.[2,3] After validation, the clinical role of the marker will depend on whether it provides prognostic or predictive information or both.[4] As displayed in figure 2 and discussed in the following sections, prognostic information can be used to determine the need for additional treatment, whereas predictive information can be used to select which treatment to use. The clinical value of using this information to guide the selection of treatment is tested in clinical trials. This evidence and other factors such as patient preferences, the resources of the health system and community values can then be used to individualise treatment decisions in the clinic (figure 2).

Figure 2: *The role of prognostic and predictive markers to guide individualised treatment decisions*



Prognostic markers

Prognostic markers can be used to classify patient risk of, or time to, cancer death and/or other disease events independent of the effects of treatment. For example, involvement of regional lymph nodes in patients with solid tumours is routinely used as a prognostic marker for survival.

In addition to the immediate value of prognostic information to help address patient questions about the expected natural history of their disease, prognostic markers can be used to identify patients at very low risk of disease events who can safely avoid treatment, or high-risk patients who may benefit from more aggressive treatment. For example, in women with early breast cancer, the absence of axillary lymph node metastasis together with other favourable prognostic markers, such as small size and low tumour grade, help to identify women at low risk of disease recurrence. These women may safely avoid adjuvant chemotherapy if the small benefits are unlikely to outweigh the harms of treatment-related adverse events. Alternatively, the presence of axillary node involvement can be used to identify high risk women who may benefit from the addition of more aggressive adjuvant chemotherapy regimens.

In theory, the absolute benefits of a treatment (eg. the number of disease events avoided per 1000 patients treated) are proportional to patient prognosis (absolute risk reduction = baseline risk x relative risk reduction from treatment, figure 2). Although in some situations where treatment is used to extend survival, the reverse may be true and low-risk patients will receive the maximum absolute life years gained. The other exception is if the effects of the planned treatment differ according to patient prognosis. Conclusions about the role of a prognostic marker therefore rely on additional evidence from randomised control trials (RCTs) to assess whether it also predicts treatment response.

Returning to the example of nodal status, RCTs comparing adjuvant chemotherapy with no chemotherapy in women with early breast cancer report that node-positive women have a higher annual death rate than node-negative women within each arm of the trial, but response to chemotherapy is similar for each group (figure 3a).[5] These results indicate that nodal status can provide important prognostic information to help decisions about whether further treatment is needed, but does not identify subgroups of women in whom chemotherapy will be more (or less) effective. Ideally, predictive markers could be used to select which chemotherapy regimen the patient is most likely to respond to.

Biomarkers that have a strong association (ie. show a high relative risk), for disease events may not necessarily be good at discriminating between patients at high or low-risk of these events, or may be no better than conventional tests.[6] Once a promising new molecular biomarker is identified, studies conducted in representative patient populations are needed to compare its prognostic accuracy with conventional

clinico-pathological markers. Further, the clinical value of this information depends on whether it leads to the use of more effective or safer treatments. Ideally, the efficacy of biomarker-guided treatment strategies can be addressed by prospective RCTs.

This is the rationale for the MINDACT trial, an RCT designed to assess the clinical value of a prognostic 70-gene signature for classifying risk of metastases in women with node negative early breast cancer.[7] A multi-centre retrospective analysis of data from a well-defined patient population indicates that this gene signature provides more accurate information for risk classification than conventional clinico-pathological staging systems alone.[8] The MINDACT trial will compare patient outcomes when this prognostic marker is used to guide the selection of adjuvant chemotherapy versus conventional criteria. It will also provide data to explore whether the marker also predicts response to standard chemotherapy regimens. Conclusions from these secondary analyses will depend on whether there is sufficient power to test for treatment interactions by marker status.

Prognostic markers can also have a role in the design of clinical trials. For example, they can be used to selectively recruit high-risk patients in order to maximise the efficiency of the trial to provide evidence about treatment efficacy.

Predictive markers

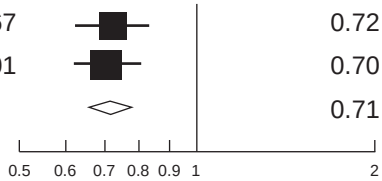
Predictive markers classify patients according to their predicted response or resistance to a treatment. Conventionally, treatments are selected using evidence from RCTs demonstrating their effectiveness in clinically representative populations. Unfortunately, even the most promising therapies that report a highly statistically significant and clinically relevant reduction in the risk of disease events are unlikely to benefit all patients. Some patients will still experience the disease event despite treatment, while others will not regardless of treatment received, and all patients will be at risk of treatment side-effects. The use of predictive markers clearly has enormous clinical implications to optimise the selection of treatments to those patients most likely to respond and avoid the use of treatment in patients unlikely to respond, or those at high risk of treatment-related adverse events. Non-responders may benefit from the earlier use of alternative therapies or can be identified as a population in need for the development of new treatments.

When an association between biomarker status and patient outcomes is first discovered in a group of patients who have all received treatment as shown in figure 1, it is not possible to conclude whether the marker is prognostic, predictive or both. RCTs designed to compare the effects of treatment between subgroups of patients classified by their biomarker status with a test for interaction (or heterogeneity) are needed to address this question. In some cases, a prognostic marker also predicts treatment response because it is also a therapeutic target. For example, oestrogen receptor expression provides prognostic information in women with early breast cancer and RCTs have provided evidence that it predicts response to hormonal therapy.[5] The discovery of a prognostic marker can also lead to the subsequent development of a molecular-targeted therapy. For example, the discovery that multiple gene copies/high level of expression of the HER-2/NEU gene protein is associated with poor prognosis in women with breast cancer, led to the development of trastuzamab, an antibody to HER-2/NEU.[9,10] Initial 'targeted' trials conducted in HER2-positive women with metastatic breast cancer have provided proof-of-concept evidence about the efficacy of trastuzamab and the use of the marker to select women for treatment.[11] Furthermore, 'non-targeted' trials comparing treatment response in HER2-positive and HER2-negative women would provide stronger evidence of its predictive ability.

For further illustration of these concepts, consider the development of treatments targeting epidermal growth factor receptor (EGFR) expression following the discovery that abnormal EGFR-mediated cell signalling has a critical role in tumorogenesis. A recent targeted trial of the EGFR inhibitor panitumumab in patients with EGFR-positive metastatic, chemotherapy refractory colorectal cancer, resulted in only a modest improvement in progression-free survival time compared to best supportive care alone.[12] A subsequent retrospective analysis of archival tissue samples from trial participants observed treatment response varied according to tumour K-RAS mutation status.[13] No

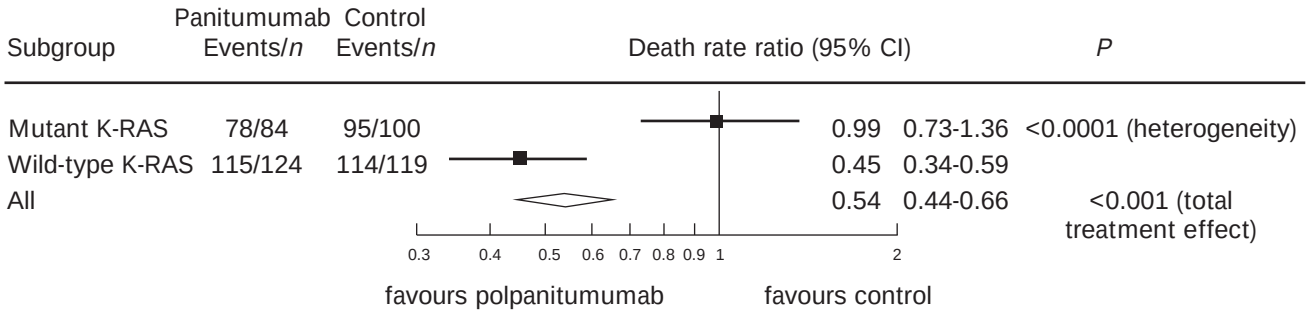
Figure 3a: *Prognostic marker – annual breast cancer mortality for polychemotherapy versus no chemotherapy in women with early breast cancer aged <50 years, by nodal status.*[1]

Subgroup	Poly-chemotherapy Events/*n*	Control Events/*n*	Death rate ratio (95% CI)		*P*
Node-negative	347/2225	449/2167	0.72	0.62-0.83	0.86 (heterogeneity)
Node-positive	561/1254	645/1201	0.70	0.62-0.80	
All			0.71	0.65-0.78	<0.00001 (total treatment effect)



1. Data extracted from EBCTG 2005[5]

Figure 3b: *Predictive marker – progression-free survival for panitumumab + best supportive care versus best supportive care in patients with metastatic colorectal cancer, by K-RAS mutation status.*[1]



1. Data for total treatment effect for trial participants (N=463)extracted from Van Cutsem et al 2007.[14]
   Data for subgroup analysis by K-RAS mutation status (N=427) extracted from Armado et al 2008.[15]

treatment effect was observed among patients with the K-RAS mutation indicating this marker may have a more important role than EGFR-status for treatment selection (figure 3b).

Finally, it is important to emphasise that the molecular pathways involved in carcinogenesis are complex. There are a growing number of examples where promising markers are yet to find a role in clinical practice. For example, p53 gene mutations are common in many cancers and have an important role in pathways involved in tumorogenesis that are also treatment targets, strongly suggesting its value as a prognostic and predictive marker. Even so, its role in improving treatment selection has not yet been established.[16] Thus, even the most compelling biological hypotheses regarding the prognostic or predictive ability of a marker, or the effectiveness of a molecular-targeted treatment need to be formally assessed in clinical trials to determine its optimal clinical use.

Conclusions

The discovery of clinically-relevant prognostic and predictive markers and the development of molecular-targeted therapies have led to important therapeutic advances in oncology. Two fundamental challenges for the development of new markers are firstly, the need for sound validation of the marker as a reproducible, accurate and independent classifier of prognosis and/or treatment response, and secondly, the need for advances in the efficiency of clinical trial designs for assessing the effectiveness of biomarker-guided therapies. Ultimately, the goal of individualised therapy will only be possible if these two challenges are adequately addressed.

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MOLECULAR IMAGING AND TARGETED THERAPIES

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Abstract

Molecular medicine represents a new approach to therapeutics and has significant implications for the practice of oncology in the future. Leveraging the rapidly increasing pace of technological and scientific innovation in molecular biology, there has been an explosion in the understanding of the key drivers of malignant transformation. New target discovery and development of therapeutic agents against these targets creates new challenges for the oncology community. Traditional staging and therapeutic response paradigms have limited capacity for detecting these targets and whether they are modulated by therapeutic intervention. Molecular imaging, which is reviewed below, offers unique promise as the means to select and monitor molecular targeted therapy. Use of radioactive chemicals and radiopharmaceuticals, directed at specific cellular targets, is an example of molecular targeted therapy and will logically be enhanced by improved understanding of tumour biology.

Elsewhere in this edition of *Cancer Forum* the progressive move from conventional chemotherapy toward molecular targeted therapies is described. In parallel with this trend towards molecular medicine, development of new approaches to tumour characterisation and therapeutic response assessment is required. This is vital because the recognised limitations of conventional structural imaging are likely to be even more compromised with respect to novel therapies, the success of which is likely to be based on target expression and its modulation.

To facilitate rational use of molecular targeted therapies, new laboratory diagnostic tests have developed to profile molecular markers known to be associated with particular clinical patterns of tumour behaviour. The concept of 'biomarkers' that have either prognostic significance, or are predictive of response to a particular therapy, has become entrenched in the development and validation of new cancer treatments. Hormone receptors, peptide receptors and tumour-associated antigens are routinely assayed in tissue samples to improve disease characterisation and to guide therapy selection for individual patients. With increasing frequency, analysis of the genetic characteristics of particular tumours using DNA microarrays and advanced proteomic analysis are being used to predict the natural history of the tumour and the likelihood of therapeutic response. In this context, it is salient to ask: What role may molecular imaging play?

Nuclear medicine as a quintessential molecular imaging tool

A number of imaging modalities have the capacity to move beyond structural characterisation of malignancy. These include magnetic resonance spectroscopy and targeted contrast agents for MRI or ultrasound. However, this discussion will be confined to nuclear medicine, particularly Positron Emission Tomography (PET), because radiotracer techniques are ideally suited to play a leading role in the coming era of targeted cancer therapy, and are generally at a more advanced stage of clinical development.

Nuclear medicine techniques depend upon molecular mechanisms operative in vivo. Minute (trace) quantities of radioactive materials, chosen because of their ability to participate in biological processes of interest, can provide highly sensitive indications of body function in health and disease. Largely independent of structural disturbances, nuclear medicine scanners increasingly offer high spatial resolution, but more particularly, high contrast. There is also a growing trend to incorporate CT scanners into hybrid imaging devices. Disordered metabolism or physiology can be detected with high sensitivity and the anatomical distribution of abnormality can be determined with greater precision than ever before. Nuclear medicine technology has an additional attraction in cancer medicine because tracers may become therapeutic agents if administered in high doses, or with substitution of the radioactive moiety to a radionuclide with appropriate particulate emissions.

Radioactive iodine as a prototypical molecular targeted therapy

Radioactive iodine-131 (^{131}I) has been used in clinical medicine since the early 1940s, yet this 'old' molecular imaging agent provides a good illustration of the important contribution to cancer care that can be made by radioactive compounds. Disturbed iodine metabolism of thyroid cancer cells has been successfully exploited to stage and delivers curative treatment to patients with this malignancy. As a substrate for the sodium/iodide symporter, tracer quantities of radioactive iodine can demonstrate even minute metastatic lesions, particularly in the absence of normal thyroid tissue. Iodine-avid metastatic lesions may be completely ablated using high doses of ^{131}I. Indeed, this tightly targeted radioactive agent was one of the first curative therapies for disseminated metastases from solid malignancy.

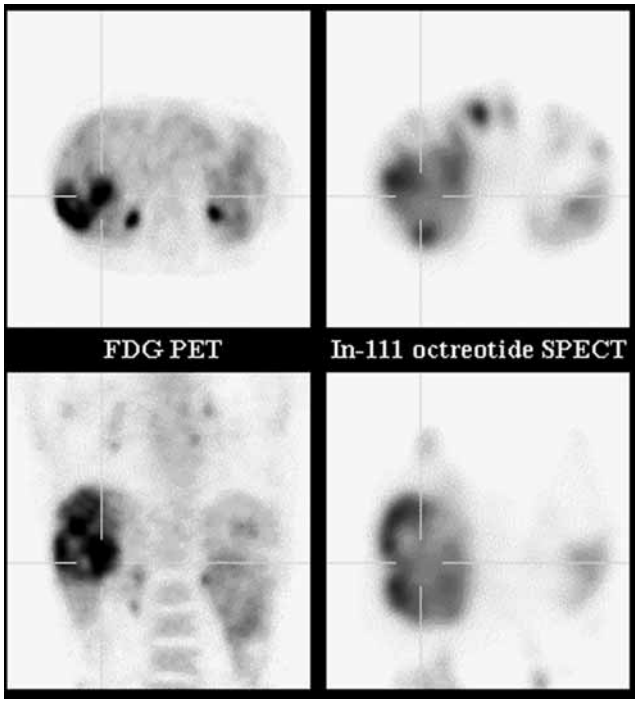
However, not all thyroid cancers are iodine-avid, reflecting heterogeneity of tumour biology between patients, and further molecular characterisation, for example using PET, has been shown to have prognostic and therapeutic implications.[1]

Tumour heterogeneity and targeted therapy

Heterogeneity of malignant cell clones in different sites within a single tumour and between different tumour sites in the body is a manifestation of the genomic instability that characterises cancer cells.[2] Heterogeneity may manifest itself as a differential therapeutic response to conventional chemotherapy agents and poses a greater threat to successful therapeutic outcomes when using highly selective molecular targeted therapies. Detection of different populations of cancer cells is impossible for structural imaging and limited by restricted tissue sampling for pathological techniques. However, as differing clones of malignant cells have different metabolic characteristics, there is a potential for *in vivo* profiling of these differences with molecular imaging (figure 1).

It is important to realise that there is a wide range of existing radioactive tracers that can be used with traditional single photon techniques and also for PET.

Figure 1: *Clonal heterogeneity appears to be a particular feature of neuroendocrine malignancy. In this patient with metastatic neuroendocrine carcinoma, co-registered images in transaxial (above) and coronal (below) planes demonstrate sites (cross-hairs) of high FDG uptake on PET (left panels) lacking in somatostatin receptor expression based on In-111 octreotide SPECT (right panels) scanning. This was despite high-uptake of In-111 octreotide at multiple other sites within the liver. These findings indicate that peptide-receptor radionuclide therapy would be unlikely to control all sites of disease if used as a single agent. Despite combined use of chemotherapy and peptide receptor radionuclide therapy, this patient demonstrated rapid disease progression of the FDG-avid disease.*



The rapidly expanding knowledge of molecular mechanisms of cancer provides an expanding array of relevant molecular targets that may be investigated radiolabelled agents. The following sections will provide some examples of existing radiolabelled molecular imaging probes that are being used in clinical or trial circumstances.

Altered substrate metabolism for assessment of response to targeted therapy

Several key genes involved in malignant transformation lead to uncontrolled cellular proliferation. This necessitates activation of cellular machinery controlling basic substrate fluxes and differentiates cancer cells from many normal tissues. PET tracers have been developed that reflect altered cancer cell glucose metabolism (F18- fluorodeoxyglucose or FDG), altered amino acid and protein metabolism (F18-fluoroehtyl-tyrosine or FET), altered sterol metabolism associated with increased cell membrane turnover (F18-fluorocholine of FCH) and increased nucleic acid formation (F18-fluoro-thymidine or FLT).

Although all of these PET tracers have been used as molecular imaging probes in basic and clinical cancer research settings, FDG has a pre-eminent role at present by virtue of a better predictive value for detecting most cancer types than conventional structural imaging standards.[3] Although it has been demonstrated repeatedly that the degree of disturbance of glucose metabolism in individual tumours carries independent prognostic information, FDG PET is mainly used for identifying the extent of cancer.[4-6] FET and FLT have found clinical utility in the brain for detecting active tumours, primarily because of the low uptake of these tracers in the normal brain compared to tumours (contrasting with FDG where normal brain uptake is very high and tumours may be difficult to distinguish).[7,8] However, the generally low uptake of these tracers into the malignant cells has rendered them less useful as predictors of cancer extent outside the brain. FCH has proved useful as a predictor of cancer extent in patients with breast and prostate cancer, particularly in tumour types of a more indolent nature where FDG uptake may be minimal or absent, and also for detecting active malignancy in the brain.[9]

In therapeutic monitoring applications, change in the degree of metabolic abnormality appears to be more important than the morphological extent. Reduction in FDG uptake has been shown to correlate with reduction in viable cell numbers, to precede lesion shrinkage in the setting of conventional cytotoxic therapies and to provide useful prognostic information.[10,11] It is likely that the advantages of molecular imaging over structural methods will become even more pertinent in the context of molecular targeted therapies that may arrest the growth of cancer cells rather than killing them. In patients where a chosen therapy proves ineffective, the delay inherent in relying upon measuring tumour response using standard anatomical paradigms may greatly disadvantage patients. The current response assessment paradigm relies on a percentage increase in tumour dimensions. For larger lesions to meet this criterion, the total volume of disease may need to increase very markedly. This increase in

tumour burden, accompanied by cumulative toxicity and cost, limits the opportunity of instituting alternative therapies. This will become an increasingly important consideration as the range of available cancer therapeutics inevitably increases.

In the era of targeted molecular therapy, tumour response assessment with FDG PET has already proven invaluable in monitoring the therapeutic effect of imatinib on gastrointestinal stromal tumours (GIST). A key molecular driver of these tumours is mutation of the C-KIT oncogene leading to constitutive activation of signaling pathways involved in cell growth, survival and proliferation. Imatinib normalises glucose transport into these tumours, and therefore FDG uptake, within days of commencing treatment. Despite significant improvement in patient survival, tumour regression is often undetectable or delayed using structural response criteria. In contrast, normalisation of FDG uptake demonstrated with PET scanning provides a reliable guide to the effectiveness of imatinib long before measurable tumour response criteria are satisfied and metabolic response is predictive of outcome.[12,13] Furthermore, some GIST patients have primary resistance to imatinib and the majority develop resistance to imatinib during treatment.[14] This drug resistance associated with absence of the relevant molecular target can be demonstrated using FDG PET imaging as a surrogate marker long before therapeutic failure is apparent from structural imaging. This is clinically important because second-line drugs such as sunitinib can also block the aberrant tyrosine kinase and improve clinical outcome in a percentage of imatinib resistant patients.[15]

FLT also has potential as a therapeutic monitoring tool for new molecular targeted therapies.[16] However, FLT PET is predominantly being undertaken in trial settings thus far.

Targeted therapy directed at neovascularisation and hypoxia

Lethal malignancy only develops when growing tumours are able to establish effective blood supplies. Molecular targeted therapies devised to interrupt tumour angiogenesis are now in regular clinical use. One such agent, bevacizumab, is a monoclonal antibody that blocks the interaction of vascular endothelial growth factor (VEGF) with vascular receptors. Trials have demonstrated effectiveness only in combination with standard chemotherapy agents and only in a percentage of patients.[17] Radiotracers that target VEGF receptors have been developed and explored in animal imaging.[18] While molecular imaging using such agents has the potential to enable identification of patients who will benefit from agents such as bevacizumab, or individual patient dosing, clinical demonstration is lacking.

Despite angiogenesis, it is often insufficient to supply adequate perfusion and the consequent tumour hypoxia has profound consequences for cancer therapy, because hypoxic cells are both radio and chemo-resistant. Special radiotherapy techniques such as dose painting and chemotherapeutic agents, that are active in a hypoxic environment, offer the potential for improving treatment outcomes for patients with hypoxic cell components within their tumours. The potential for improving treatment of hypoxic tumours with molecular imaging has been explored using several available PET radiotracers that are retained by hypoxic cells. F18 fluoro-misonidazole (FMISO) and F18-fluoro-azomycinarabinoside (FAZA) are two such PET agents that have been extensively investigated at the Peter MacCallum Cancer Centre in Melbourne. FAZA demonstrates higher quality images than FMISO due to more rapid washout from normal tissues, but both enable imaging of hypoxia *in vivo* that is not possible using invasive probe based measurements.

Using FMISO PET, it has been demonstrated in a Phase 2 trial that addition of hypoxia activated chemotherapy agent tirapazamine, to standard chemoradiotherapy in patients with advanced head and neck carcinoma, decreased loco-regional failure rates, predominantly in patients who demonstrated tumour hypoxia on PET imaging.[19]

Targeted therapy directed at cell receptors

Malignant cells frequently express large numbers of cell surface antigens that are present in a minority of normal cells, or that are expressed at much lower concentrations. The role of these over-expressed surface proteins is often unknown. However, it is clear that these cell surface components may fulfil an important role in cancer cell growth and development. For example, the abnormal tyrosine kinase of GIST tumours was originally recognised as a tumour-associated antigen CD 117. This antigen served to refine the pathological identification of these tumours before the functional role of the associated protein in tumorigenesis was recognised.

Over-expression of peptide hormone receptors has been recognised as a defining characteristic of neuroendocrine tumours for several decades. Symptoms relating to excessive hormone secretion may be clinically debilitating for patients with disseminated neuroendocrine tumours. Despite this, these tumours often display very indolent growth patterns with long survival, even without therapy. Chemotherapy and radiotherapy have generally low efficacy. However, molecularly targeted agents, such as octreotide, bind to over-expressed somatostatin receptors and can bring marked amelioration of symptoms caused by hormone secretion and diminish tumour growth rates.

Metabolic imaging with radiolabelled somatostatin analogues (indium 111-pentetreotide (Octreoscan) for single photon imaging and gallium 68-DOTA-octreotate for PET) can detect somatostatin receptor expressing tumours with very high sensitivity and thereby improve the staging and therapeutic planning. Radiolabelled peptides are an exciting option for therapy.[20] Agents such as high dose indium 111-pentetreotide and lutetium 177-DOTA-octreotate (LuTate) have been shown to provide patients who express a high density of somatostatin receptors on molecular imaging studies with significant relief of symptoms and low toxicity. LuTate therapy has the additional advantage of producing measurable tumour responses in a significant percentage of patients.[21]

Of note, metabolic heterogeneity is common in neuroendocrine tumours, and lesions in the same patient that appear identical on CT often demonstrate quite different molecular imaging characteristics. This information is crucial for treatment planning because tumour deposits that demonstrate low uptake of somatostatin radiotracers do not respond to radionuclide therapy. Interestingly, these tumour deposits are probably less differentiated as they usually display enhanced glucose metabolic activity on FDG scanning. In contrast, somatostatin receptors expressing tumours generally do not accumulate FDG to a significant degree. At the Peter MacCallum Cancer Centre patients with widespread neuroendocrine tumours are commonly assessed by molecular imaging to characterise both glucose metabolic status and somatostatin receptor expression prior to treatment selection. If a significant component of the tumour burden has high FDG avidity without somatostatin receptor expression, platinum and etoposide based chemotherapy is usually used as first line therapy, as this more aggressive component of the tumour burden generally determines the patient's outcome.

Monoclonal antibodies developed against cell surface antigens have been investigated for many years as therapeutic agents. For example, rituximab, a monoclonal antibody that targets the CD 20 surface antigen expressed on the surface of normal and malignant B cells, is both effective and has a low toxicity profile for the treatment of non Hodgkin-lymphoma. Several radiolabelled forms of anti-CD 20 monoclonal antibodies, including yttrium-90 -tiuxetan-ibritumomab (Zevalin) and iodine-131-tositumomab (Bexxar), have been approved for therapeutic use. Iodine-131-rituximab is also produced at Fremantle Hospital in Perth and Peter MacCallum Cancer Centre for use in therapeutic doses in patients with relapsed B cell NHL that is refractory to other therapies. Significant effectiveness and very low toxicity have been reported, and in clinical use the therapeutic dose is calculated on the basis of preceding tracer dose molecular imaging.[22]

Cancer research and drug discovery

The potential for molecular imaging in small animals to increase knowledge of drug effects in models of human cancer has been recognised around the world and has been embraced as a means of decreasing the time taken to identify agents that merit clinical trial and to decrease the cost of drug development.[23] The role of molecular imaging with radiolabelled tracers for research into molecular targeted therapies is important to recognise, but further discussion is outside of the scope of this article.

Conclusion

The revolution in molecular biology has led to an evolution of existing molecular imaging techniques to align themselves to become a vital component of a new paradigm in cancer management. The ability to assay non-invasively and in vivo the presence of a molecular target and its modulation during therapeutic intervention provides a unique and invaluable tool for molecular medicine. The future clinical application of PET will likely have greater impact in characterising the biology of disease than its current impressive role of counting lesions.

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EVOLUTION OF BIOLOGICAL THERAPIES IN NON-SMALL CELL LUNG CANCER

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Abstract

This article explores recent clinical developments of biological or targeted therapies in non-small cell lung cancer. Molecular research has given us a greater understanding of tumour biology and has led to identification of targets for therapy. A key pathway involves the epidermal growth factor receptor. Inhibitors of the tyrosine kinase domain (erlotinib, gefitinib) have had a clear impact in the treatment of advanced non-small cell lung cancer and a monoclonal antibody against epidermal growth factor receptor (cetuximab) also appears to have benefit. Inhibiting angiogenesis (or tumour blood supply growth) appears a promising approach with small but real gains being made with bevacizumab (a monoclonal antibody targeting the vascular endothelial growth factor receptor). Other new molecules targeting angiogenesis, apoptosis and intracellular growth pathways are being tested.

Until the late 1990s, it had not been clear that any effective systemic therapy existed in non-small cell lung cancer (NSCLC), although there was a suggestion of benefit with cisplatin in an earlier meta-analysis. Multiple studies have since demonstrated a survival and quality of life advantage with chemotherapy.

Nevertheless, the notion of targeted therapies has promised improved efficacy and reduced toxicity through greater selectivity of cancer cell processes. In this review, the development of these novel agents is discussed, with emphasis on the epidermal growth factor receptor (EGFR) pathway and angiogenesis.

Epidermal growth factor receptor inhibitors

The EGFR family has been known for over a decade as a potential therapeutic target. The receptors are implicated in cancer progression through effects on cell-cycle stimulation, apoptosis, angiogenesis and metastasis. Epidermal growth factor receptor over-expression has been shown to be an adverse prognostic factor in NSCLC.

The initial promise was seen with the development of inhibitors of the tyrosine kinase (TKI) domain of EGFR. Gefitinib was initially tested in the Phase I setting after promising pre-clinical data showing inhibition of receptor auto phosphorylation and xenograft growth. Doses up to 1000mg were used with the limiting toxicities of rash and diarrhea.[1] The rash management has since become incorporated in lung cancer care, occurring primarily because of the abundant EGFR expression in keratinocytes and sebaceous glands. Interestingly, there appears to be a relationship between rash development and the probability of clinical benefit.[2]

The Iressa Dose Evaluation in Lung Cancer 1 and 2 studies compared 250 and 500mg doses in patients who had progressed on prior chemotherapy. No clear benefit was seen with the higher dose and this led to the incorporation of the 250mg dose in Phase III studies.[3,4]

Meanwhile, erlotinib, a sister molecule with a similar action, was pushed rapidly into Phase III development at 150mg daily. Both agents were combined with concurrent chemotherapy in the TALENT/TRIBUTE studies (erlotinib) and INTACT1/2 (gefitinib). Disappointingly, all studies showed no advantage for the combination.[5-7] It has been questioned whether the addition of an EGFR inhibitor induces cell cycle arrest. A similar effect has been seen in breast cancer when chemotherapy was administered concurrently with the hormonal therapy tamoxifen (which is a known cytostatic agent).

A parallel set of studies however, compared the TKIs with best supportive care (placebo). The BR21 study was a landmark study showing a survival advantage with the use of erlotinib, the first biological or targeted agent to do so in NSCLC. The median survival was 6.7 months and one-year survival 31% with erlotinib, compared with 4.7 months and 22% for placebo.[8]

Interestingly, the Iressa Survival Evaluation in Lung Cancer (ISEL) study comparing gefitinib with placebo only identified an impact on time to treatment failure (three months versus 2.6 months) but no impact on overall survival.[9] The comparative results have questioned the difference in efficacy of the two drugs. It has however, been argued that the population tested in ISEL were refractory to chemotherapy. Another study investigating consolidation gefitinib following chemo-radiotherapy was closed early because the TKI was not adding efficacy (and arguably looked inferior to standard therapy).[10] Somewhat reassuringly, a more recent study comparing gefitinib with docetaxel (the standard of care in second-line treatment in NSCLC) showed equivalent survival, confirming its activity in advanced lung cancer.[11]

Although the agents have shown an overall benefit in NSCLC, it has been apparent from their use that certain patients are more likely to benefit. Clinically, the phenotypes that derive the most benefit are non-smokers, patients with adenocarcinoma, women and Asian patients.[8,12] Assessment of EGFR status has

yielded mixed results. Initial Phase II results, particularly with gefitinib, have not demonstrated EGFR expression (assessed by immunohistochemistry) as a useful predictive marker of benefit. In BR21, immunohistochemistry was significantly predictive of a survival advantage by univariate, but not multivariate analysis. A similar signal was seen for EGFR gene copy analysis through fluorescent in-situ hybridisation. Interestingly, it was decided to use these tests as inclusion criteria in the current adjuvant erlotinib study despite the lack of conclusive evidence.

Unusually impressive responses have been noted in patients with tumours carrying an activated form of the EGFR receptor.[13,14] Mutation analysis of BR21 patient tumours however, has not demonstrated any relationship with survival.[12]

In conclusion, the average patient stands to gain from these therapies, but no particular factors beyond the clinical profile truly assist in treatment decisions, particularly in the cost rationalisation of treatment in NSCLC.

The EGFR pathway can also be blocked with the use of monoclonal antibodies directed against the external domain of the receptor. There are multiple mechanisms of action including blockade of signal transduction, promotion of receptor internalisation and degradation, and antibody-dependent cellular toxicity. Cetuximab is a humanised antibody that has previously demonstrated efficacy in colorectal cancer. It has also recently been assessed in EGFR positive NSCLC. The FLEX (First Line in lung cancer ErbituX) study presented at the American Society of Clinical Oncology showed that the addition of cetuximab to chemotherapy improved median survival from 10.1 months to 11.3 months, with particular benefits seen in caucasians and patients with adenocarcinoma. The toxicities seen are typical of EGFR blockade, namely rash and diarrhoea.[15]

Anti-angiogenic targeted therapy

One of the other key areas of targeted anti-cancer drug development is the area of anti-angiogenesis. The reliance of tumours on the development of new blood vessels (angiogenesis) in order to grow is now an established concept in tumour biology. Furthermore, it is known that angiogenesis in tumours can be switched on, usually by over-expression of pro-angiogenic factors, and that blocking these factors can inhibit tumour growth and metastasis.[16] However, this process is complex and involves interaction with the host micro-environment and extracellular matrix, where vascular sprouting must traverse and many growth factors can reside. In lung cancer, there are a number of studies that have demonstrated that high micro vessel density or over-expression of angiogenic growth factors is associated with a poor prognosis in terms of metastasis development and survival.[17]

A number of angiogenesis inhibitors have been developed and explored in lung cancer. These can be classified into direct inhibitors which target key angiogenic processes (eg. matrix metalloproteinase inhibitors (MMPIs) affecting extracellular matrix protein degradation), or indirect inhibitors targeting key mediators of angiogenesis eg. angiogenic growth factors such as vascular endothelial growth factor (VEGF) or its receptor(s), and platelet derived growth factor among others.[18]

The first generation of clinical trials of angiogenesis inhibitors in lung cancer involved the addition of an MMPI to chemotherapy. Unfortunately several Phase III trials evaluating the addition of an MMPI to first-line standard chemotherapy compared with chemotherapy/placebo failed to demonstrate any advantage, in both NSCLC and small cell lung cancer.[19,20] And these drugs were found to be associated with musculoskeletal toxicity.

The only successful clinical trials of angiogenesis inhibitors have focused on VEGF as the main target. Bevacizumab (Avastin®), a humanised monoclonal antibody, demonstrated tumour growth inhibition and synergy with chemotherapy in pre-clinical models and has demonstrated synergy with chemotherapy in metastatic colorectal cancer, where it is Therapeutic Goods Administration registered.[21] In NSCLC, a pivotal randomised Phase II clinical trial was reported in 2004. Here, 99 patients were randomly assigned to bevacizumab 7.5 or 15mg/kg plus carboplatin and paclitaxel Q 3 weekly or carboplatin paclitaxel alone (n = 32).[22] Compared with control (carboplatin paclitaxel alone), treatment with carboplatin paclitaxel and bevacizumab (15mg/kg) resulted in a higher response rate, longer median time to progression and a modest increase in survival. Bleeding was the most prominent adverse event with minor epistaxis most common (44%), but major haemoptysis was seen in six patients, four of which were fatal. The major haemoptysis was found to be associated with squamous cell cancer histology, tumour necrosis and cavitation and disease location close to major blood vessels.[22] Other unique bevacizumab related toxicity seen was hypertension and asymptomatic proteinuria.

This trial led to a landmark US Phase III clinical trial (ECOG 4599) of first–line paclitaxel carboplatin alone or with bevacizumab in SIIIB/IV NSCLC (n = 878). This trial excluded patients with squamous cell cancer, brain metastases or clinically significant haemoptysis. The primary endpoint was overall survival. Median survival was 12.3 months (paclitaxel carboplatin + bevacizumab arm) compared with 10.3 months (paclitaxel carboplatin alone (Hazard Ratio (HR) 0.79; P=0.003)).[23] The median progression-free survival in the two arms was 6.2 and 4.5 months, respectively (HR 0.66; P<0.001), with corresponding tumour Response Rate (RR) of 35% and 15% (P<0.001). Clinically significant bleeding was seen in 4.4% and 0.7%, respectively (P<0.001). There were 15 treatment related deaths in the paclitaxel carboplatin + bevacizumab arm, including five from pulmonary haemorrhage.

Supporting the results from this study were the findings from a second randomised Phase III study (N = 1043) comparing two doses of bevacizumab plus cisplatin/gemcitabine (CG) versus cisplatin/gemcitabine plus placebo in first line non-squamous cell cancer SIIIB/IV NSCLC, presented in abstract form in 2007.[24] Progression free survival was the primary endpoint and both doses of bevacizumab significantly improved progression free survival (7.5 mg/kg: HR 0.75, P=0.002); 15 mg/kg HR 0.82, P=0.03) and RR (34 and 30%

respectively for bevacizumab arms compared with 20% for CG). Grade III/IV hypertension was seen in < 9% of bevacizumab patients, with GIII/IV haemoptysis in < 1.5%. The safety of bevacizumab is currently under evaluation in an international observational study. Preliminary results in > 1000 NSCLC patients have confirmed the existing well described safety profile without central nervous system haemorrhage.[25]

The other broad class of angiogenesis inhibitors under evaluation are the small molecule receptor TKIs. Several, targeting more than one angiogenesis promoting TK receptor, are in clinical development.[11] Preliminary results from Phase II trials have shown promise for the multi-kinase inhibitors ZD6474, sunitinib and sorafenib amongst others.[26-28] Further Phase II and Phase III trials evaluating anti-angiogenic TKIs are underway and final results are awaited.

Finally, the Phase III efficacy results with bevacizumab and the promising Phase II results from several oral anti-angiogenic TKIs have confirmed the important role that angiogenesis inhibitors may come to have in the future management of lung cancer. It is important to note that patient selection has and will be important in the future use of these agents. Furthermore, the use of angiogenesis inhibitors has identified several broad 'class' side-effects such as hypertension, bleeding and proteinuria, indicating that careful patient monitoring will also be required.

New approaches

A huge array of novel agents is currently under investigation. Another receptor that shows promise as a therapeutic target is the insulin-like growth factor receptor 1 (IGFR1). This transmembrane protein is implicated in oncogenic transformation, cancer cell growth and survival. Molecules such as monoclonal antibodies against IGFR1 are being tested in early phase studies in NSCLC.[29] Downstream cellular kinases such as PI3 Kinase also appear attractive targets for novel therapeutics.

Much of the approach until recently has been directed towards inhibiting uncontrolled growth. The stimulation of apoptosis (programmed cell death) is a different angle of attack. Agonists of so-called 'death receptors', such as the tumour necrosis (TNF) related apoptosis-inducing ligand (TRAIL) receptor family, may promote apoptosis of cancer cells.[30] Downstream manipulation of the caspase pathway may also trigger apoptosis and this is being investigated.

Conclusion

Management of NSCLC is entering a new era, with greater understanding of molecular biology and the resultant development of targeted therapies. Better understanding of factors predicting benefit is needed however, as the cost of these therapies is becoming prohibitive for many individuals and societies. These agents must then be tested in populations enriched by patients bearing these predictive factors and particularly in the early stage lung cancer patients where the chance of cure is more realistic. The mechanism of cancer growth is complex and it is also likely that multiple therapies will be required in concert to achieve a meaningful impact on lung cancer in the future.

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TARGETED THERAPY IN COLORECTAL CANCER

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Abstract

Our understanding of the molecular pathways that mediate cancer cell proliferation has increased significantly and with this comes the rapid development of molecular targeted therapies. The epidermal growth factor receptor and the vascular endothelial growth factor are two such targets that have proven to be important in the treatment of advanced colorectal cancer. Successful inhibition of these targets, utilising monoclonal antibodies bevacizumab, cetuximab and panitumumab, has led to improved patient outcomes. Prolongation of patient survival and improvement in quality of life has been associated with the use of these antibodies. Such therapies are now becoming part of standard management of advanced colorectal malignancy. Predictive biomarkers that allow for a more rational and effective utilisation of these new molecular targeted therapies are being discovered. The number of potential molecular targets seems infinite as new drugs are rapidly processed through new accelerated clinical trial designs and drug development programs. Many challenges remain in the successful development of molecular targeted therapies, including overcoming mechanisms of resistance, optimal drug delivery, the issues of the financial cost of these new drugs and equitable access to the new therapies.

Colorectal carcinoma is the third most common malignancy of both sexes in developed countries.[1] The spread of colorectal cancer to distant sites (Duke's stage D) represents essentially incurable disease, except for selected cases where complete surgical resection can be applied. Chemotherapy for advanced colorectal cancer can prolong survival and provide symptomatic benefit and quality of life improvement.[2-8] Over the last decade new cytotoxics, including irinotecan and oxaliplatin, have produced further survival benefit.[9-13] Therapeutic options for patients with metastatic colorectal cancer who have failed these treatments are limited.

The epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF) represent the two molecular structures and associated pathways that have proven to be successful targets in the development of new drugs. Other targets are being evaluated in ongoing clinical trials. We will outline the results obtained in trials that have evaluated molecular targeted strategies and briefly outline the challenges of successful implementation of such treatment, in the context of advanced colorectal cancer.

Targeted therapy directed against epidermal growth factor and associated pathways

Cetuximab is a chimeric immunoglobulin G1 monoclonal antibody that binds to the EGFR with high affinity.[14] Panitumumab is a humanised monoclonal antibody that has the same effect on EGFR.[15] This association of antibody and receptor competitively inhibits ligand binding and leads to inhibition of phosphorylation and subsequent activation of downstream signalling pathways. These antibodies also stimulate EGFR internalisation, effectively removing the receptor from the cell surface.[14] Blocking EGFR can lead to cell cycle arrest in the G_1 phase,[16] and cell death via apoptosis.[17]

Single-agent therapy with cetuximab or panitumumab has demonstrated activity in patients with refractory, metastatic EGFR-positive colorectal carcinoma. The objective response rates observed in these studies vary between 8 to 12% for single-agent EGFR directed therapy.[18-21] The response rate appears similar (10%) when cetuximab is used as a single agent as first line therapy for previously untreated patients.[22] Two Phase III randomised control trials have confirmed a benefit of EGFR directed therapy when compared to best supportive care. Cetuximab demonstrated an overall survival advantage, and a quality of life benefit.[20] Panitumumab was associated with a progression free survival benefit, but not an overall survival advantage, although the trial design allowed for cross-over from best supportive care to panitumumab on disease progression.[19] An acneiform skin rash is the principal side-effect of such a treatment approach. An increased severity of skin rash has been associated with a greater response rate.[20,23] The problem with using rash as predictive markers is that the drug must first be administered to observe the rash. It is therefore not a predictive factor that can be used prior to therapy, and cannot be used to select patients for initiation of therapy.

Efficacy has also been demonstrated with the combination of either panitumumab or cetuximab and irinotecan in patients with irinotecan-refractory EGFR-positive metastatic colorectal cancer.[23,24] Response rates of 19 to 23% with median duration of response of four to six months have been observed, but the median survival of approximately six to eight months remains similar to that observed in the single agent EGFR antibodies.[20,23,25] The combination of FOLFIRI and cetuximab was associated with a modest prolongation of progression-free survival when used as a first line treatment for advanced colorectal cancer. A trial comparing irinotecan plus cetuximab versus irinotecan alone as second line treatment, showed no overall survival difference between the two arms.[26] The

combination of oxaliplatin, fluoropyrimidines and EGFR directed antibody has also been evaluated, with evidence of higher response rates with the antibody-chemotherapy combination approach.

Targeting the EGFR pathway via the associated tyrosine kinase has been tried, with initial studies suggesting possible efficacy. Single agent tyrosine kinase inhibitor (TKI) therapy was associated with stable disease in almost 40% of patients, but no objective responses.[27] Phase I and II trials combining TKI with chemotherapy initially suggested safety and possible efficacy, but subsequent studies have been disappointing.[28,29] The addition of gefitinib does not overcome fluoropyrimidine

Table 1: *Chemotherapy naive*

	Chemotherapy alone median survival (months)	Bevacizumab with chemotherapy median survival (months)	Absolute benefit (months)	HR	P value
Bevacizumab with Fluoropyrimidine monotherapy					
Kabbinavar et al (Combined analysis)[36]					
PFS	5.6	8.8	+ 3.2	0.63	0.0001
OS	14.6	17.9	+ 3.3	0.74	0.0081
Bevacizumab with Irinotecan based chemotherapy					
Hurwitz et al (AVF2107g)[35]					
PFS	6.2	10.6	+ 4.4	0.54	< 0.001
OS	15.6	20.3	+ 4.7	0.66	< 0.001
Bevacizumab with Oxalipaltin based chemotherapy					
Saltz et al (NO 16966)[37]					
PFS	8.0	9.4	+1.4	0.83	0.0023
OS	19.9	21.3	+1.4	0.89	0.07
Hochster et al (TREE)[38]					
PFS					
mFOLFOX6	8.7	9.9	+ 1.2		
bFLOX	6.9	8.3	+ 1.4		
CapOx	5.9	10.3	+ 4.4		
OS	18.2	23.7	+ 5.5		
mFOLFOX6	19.2	26.1	+ 5.9		
bFLOX	17.9	20.4	+ 2.5		
CapOx	17.2	24.6	+ 4.4		

Table 2: *Previously treated with chemotherapy, bevacizumab naive*

	Chemotherapy alone median survival (months)	Bevacizumab with chemotherapy median survival (months)	Absolute benefit (months)	HR (95% CI)	P value
Bevacizumab with Oxalipaltin based chemotherapy (Irinotecan Refractoy)					
Giantonio et al (E3200)[40]					
PFS	4.8	7.2	+ 2.4	0.64	<0.0001
OS	10.8	12.9	+ 2.1	0.76	0.0018
Bevacizumab with Fluoropyrimidine monotherapy (Irinotecan/Oxaliplatin refractory)					
Chen et al (TRC-0301)[41]					
PFS	–	3.5	–	–	–

OS (Overall survival); PFS (Progression free survival); HR (hazard ratio); FOLFOX6 (bolus and infusion fluorouracil [FU] and leucovorin [LV] with oxaliplatin); bFLOX (bolus FU and low-dose LV with oxaliplatin); CapOx (capecitabine with oxaliplatin).

resistance.[30] In a randomised Phase II trial the addition of gefitinib to FOLFIRI did not provide benefit,[31] and in another Phase II study the combination of irinotecan and gefitinib was associated with increased toxicity.[32]

Targeted therapy directed against the vascular endothelial growth factor and associated pathways

Angiogenesis plays an important role in the growth and progression of cancers like colorectal cancers. VEGF pathways play a key role in this process. The two major players are VEGF receptors (VEGFR) and their ligands, VEGF glycoproteins. There are five major ligands, VEGF-A through E, while the receptors include VEGFR-1, 2 and 3. The binding of VEGF ligands to the receptors triggers a series of events involving endothelial cell proliferation, migration and survival, in addition to altering vascular permeability, thereby controlling the physiological and tumour angiogenesis.

Angiogenesis plays an important role in cancer survival and progression.[33] There are two major anti-angiogenic approaches – monoclonal antibodies or small molecules directed against the VEGF pathways. Other approaches like antisense oligonucleotides and aptamers are still in early research phase. Worldwide, several such drugs like bevacizumb, sunitinib and sorafenib, are approved for routine clinical use to treat patients with colorectal cancer, renal cancers, lung and breast cancers, based on efficacy data from well conducted Phase III trials. In this review, we present the evidence to show how targeting angiogenesis has changed the way we manage colorectal cancer.

Bevacizumab, a recombinant humanised monoclonal antibody against VEGF-A ligand, was the first anti-angiogenic drug to show impressive survival benefit in clinical trials. Most studies indicate that bevacizumab in combination with chemotherapy is better than chemotherapy alone in terms of survival for metastatic colorectal cancer. Bevacizumab acts as a chemo-sensitiser by reducing new blood vessel formation and inducing apoptosis in addition to normalising the tumour vasculature, improving delivery of chemotherapy.[34]

Hurwitz et al compared the benefit of adding bevacizumab to irinotecan and 5-fluorouracil in patients with previously untreated metastatic colorectal cancer.[35] There was a significant difference in response rates, overall survival and progression free survival in favour of the bevacizumab arm.

The consistent survival benefit of adding bevacizumab to other chemotherapy regimens like bolus 5-FU/LV,[36] FOLFOX[37] and capecitabine/oxaliplatin[38] confirmed that the approach of combining anti-angiogenic drugs and chemotherapy is beneficial. The survival advantage ranged from 1.4 to 4.7 months. Interestingly, the NO16966 study showed a progression-free survival benefit, but no significant differences in overall survival and response rates.[37] Early cessation of bevacizumab in this trial has been postulated as a reason for the smaller observed benefit, and has led to recommendations that bevacizumab should be continued beyond the completion of first-line chemotherapy.[39] Results from trials in which bevacizumab has been added to chemotherapy in the first line and second line setting are summarised in tables 1 and 2.

Chen et al studied the efficacy of bevacizumab and 5-FU (bolus or infusion) in heavily pre-treated patients who were refractory to irinotecan and oxaliplatin in a single arm Phase II trial.[41] The progression-free survival was 3.5 months and response rate was just 1%. The Eastern Co-operative Oncology Group trial (E3200) was a Phase III trial comparing FOLFOX with or without bevacizumab in irinotecan refractory patients. A survival benefit was demonstrated in the bevacizumab treated patients.[40]

There are several ongoing studies which evaluate the role of bevacizumab to the standard adjuvant chemotherapy with FOLFOX for Duke's C or high risk Duke's B colorectal cancer. Since bevacizumab is a potent radio-sensitiser through its normalisation of tumour vasculature, it is being evaluated in combination with radiotherapy for rectal cancers. The results of these trials are eagerly awaited before bevacizumab can be recommended in this setting.

Targeting angiogenesis with small molecule TKIs has not met with such success as the antibody-based approach. Vatalinib is one such TKI of multiple targets including VEGFR, platelet derived growth factor and C-KIT. The advantage of this drug is oral administration in addition to multi-targeting activity. Vatalinib has been studied extensively in very large Phase III trials (Colorectal Oral Novel Therapy for the Inhibition of Angiogenesis and Retarding of Metastases – CONFIRM 1 and 2) in combination with chemotherapy in the first line and second line setting.[42,43] There was no benefit in survival or response rates. A subsequent meta-analysis showed that the addition of vatalinib improved the progression-free survival in patients with elevated lactate dehydrogenase.[44] The valuable lessons learnt from these studies indicate the need for better patient selection using validated predictive factors.

There are several ongoing studies with other anti-angiogenic drugs including sunitinib, sorafenib and cediranib in combination with chemotherapy drugs. The results of these trials are still awaited.

There is a well recognised toxicity profile related to anti-angiogenic drugs, including hypertension, proteinuria and bleeding. The trials of bevacizumab have identified proteinuria (28%), hypertension (25%), haemorrhage (2 to 9%), arterial thromboembolism (0 to 3.8%), wound healing complications (2%) and gastrointestinal perforation (1.5 %).[45] Several Phase IV studies of bevacizumab in combination with various chemotherapy agents in community practice have highlighted similar incidence of adverse events.[46-48] Early identification and prompt therapy of these complications cannot be overemphasised.

Combination of bevacizumab and EGFR-directed monoclonal antibodies

Preliminary results from Phase II and III trials have failed to demonstrate a benefit in combining bevacizumab with EGFR-directed monoclonal antibodies.[49-51] These studies raise concerns about increased toxicity and reduced treatment efficacy when combining these

molecular targeted therapies. We have much to learn about the interaction of these drugs and our understanding of 'multi-targeting' remains rudimentary.

Biomarker predictors of benefit to molecular targeted therapy

Colorectal cancer is a multi-step process characterised by a sequence of genetic alterations in cell growth regulator genes, such as K-RAS, p53 and DCC genes.[52] EGFR is a logical potential biomarker, but as measured by immunohistochemistry, is not a useful predictive factor. There is no significant relationship between EGFR expression as determined by immuno-histochemistry and the likelihood of response to cetuximab.[23,25,53,54] K-RAS gene mutations occur early in the stages of carcinogenesis, as the colorectal adenoma progresses to develop into a carcinoma. The RAS/RAF/MAP kinase and the PTEN/PI3K/AKT signalling pathways are activated by ligand binding and activation of EGFR, and these pathways form a network that plays a central role in cancer progression and survival.[55] Mutations in K-RAS can lead to constitutive activation of the pathway, and this may render inhibitors of components of the cascade upstream of EGFR ineffective. K-RAS mutations are found in 30-50% of colorectal cancers with most mutations found in exon 2 of the K-RAS gene.[56,57-64]

Previous studies have compared the efficacy of EGFR-directed monoclonal antibodies across wild-type K-RAS and mutant K-RAS tumours. Median survival was longer and responses were seen almost exclusively in the wild-type K-RAS subsets.[58-60,65] In a randomised control trial, panitumumab benefit when compared to best supportive care was confined to patients with wild-type K-RAS tumours.[56] For patients with K-RAS mutant tumours, there was no difference in progression-free survival between the panitumumab and best supportive care groups, but median progression-free survival for patients with wild-type K-RAS tumours was 12.3 weeks with panitumumab and 7.3 weeks with best supportive care. All of the objective responses occurred in patients with panitumumab treated wild-type K-RAS tumours.[56]

In the first line setting, K-RAS mutation status has a similar predictive significance. Results of the CRYSTAL study demonstrated that benefit through the addition of cetuximab to FOLFIRI chemotherapy is restricted to patients with wild-type K-RAS tumours. Patients with colorectal tumours that contain K-RAS mutations did not obtain a benefit with cetuximab.[66] Similar results were observed in patients receiving the FOLFOX chemotherapy combination as first line therapy, and the progression free survival was trending lower in those patients with K-RAS mutations when treatment included cetuximab versus chemotherapy alone.

Other gene mutations, such as mutations involving the PTEN, BRAF or PI3KCA genes, can also lead to unrestricted cancer cell growth and may also be useful predictive biomarkers. Loss of PTEN activity, for example, has been associated with lack of efficacy as measured by radiological response, with none of 11 patients responding to cetuximab in a recently reported series.[60] Moving upstream in the signalling pathway, high EGFR ligand expression, particularly amphiregulin and epiregulin, has been observed in tumours responding to cetuximab and these ligands represent attractive targets for future biomarker research.[67] So far, there are no reliable biomarkers to predict benefit from bevacizumab.

Real progress but significant challenges

Over the last decade there has been a paradigm shift in the way we manage patients with advanced colorectal cancer. Multi-agent chemotherapy and multiple lines of therapy are now part of optimal treatment strategies. Anti-angiogenic therapy has contributed to improving outcomes, particularly prolonging disease control with an associated prolongation of overall survival. The benefit has been observed when bevacizumab is used as part of either first or second line therapy. EGFR directed therapy, particularly utilising cetuximab or panitumumab, also prolongs survival, but this appears to be restricted to patients with tumours that are have wild-type K-RAS. These new targeted therapies are relatively expensive. In the UK National Health Service review, bevacizumab was not considered to be cost effective in combination with chemotherapy,[68] and in 2008 bevacizumab and the EGFR-directed antibodies are not funded on the Pharmaceutical Benefits Scheme in Australia. The cost effectiveness improves when these treatments can be delivered to patients with a higher chance of benefiting. Avoiding therapy in patients that have little chance of responding can help to eliminate toxicity of ineffective therapy and allow other treatment approaches to be pursued. Accurate and reliable biomarkers that allow selection of patients with advanced colorectal cancer, who will benefit from new therapies, would represent a significant advance in the clinical management of this disease. The K-RAS correlative analyses have identified a biomarker that can effectively exclude a significant proportion of patients, 40% with tumours that have K-RAS mutations, from EGFR monoclonal antibody therapy. Other prognostic and predictive variables, preferably ones that are reliably and easily measured, need to be identified.

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TARGETED THERAPIES IN RENAL CELL CARCINOMA

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Abstract

The landscape of treatment for renal cell carcinoma has changed radically over the last few years. Previously, the most effective treatments were too toxic, too expensive or too ineffective. Careful biological studies have uncovered pathways relevant to the survival, growth and spread of renal cell carcinoma and other cancers, and have highlighted rational targets for therapy. New agents aimed at these targets have been shown to be highly effective, but have brought with them a new range of toxicities and other complexities in the management of our patients. This review describes three drugs recently approved in Australia for use in advanced renal cell carcinoma and other agents of clinical and research interest.

Renal cell carcinoma

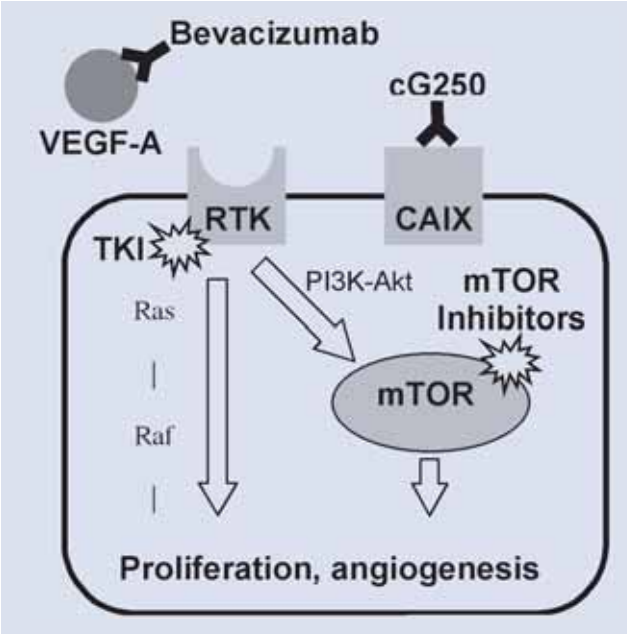
Renal cell carcinoma is diagnosed in over 2000 Australians every year and about 800 die of the disease annually. It makes up 2% of cancer deaths and affects males more than females.[1] Three quarters of renal cell carcinomas are of so-called conventional clear cell histology, 15% are papillary and the remainder are predominantly made up of chromophobe, oncocytoma and collecting duct tumours.[2] Most new cases are found incidentally and outcomes are good if the cancer is resectable. However, until recently few treatment options were available for advanced or metastatic disease and the median survival of metastatic renal cell carcinoma was of the order of one year.[3]

Six prognostic factors that independently predict survival have been derived from studies of patients treated with interferon and have been used in predictive nomograms. These factors are: a Karnofsky Performance Status of less than 80%; an interval from diagnosis to treatment less than one year; anaemia; hypercalcaemia; lactate dehydrogenase elevated to greater than 1.5 the upper limit of normal; and more than two sites of metastatic disease.[4,5]

Many of the pathways driving the growth of renal cell carcinomas are now much better understood and have provided a rational basis for the development of new therapies. The von Hippel-Lindau protein (VHL) degrades hypoxia-inducible factors in renal cells when oxygen levels are adequate, but allows these factors to accumulate and move to the nucleus to promote expression of factors involved in angiogenesis, glucose transport, pH regulation and the prevention of apoptosis.[6] In 80% of renal cell carcinomas this pathway is exploited by inactivation of the VHL protein, allowing HIF accumulation despite normal oxygen tension.[7] This results in expression of growth factors that promote tumour growth and result in many of the characteristics of renal cell carcinoma. These factors include: vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which stimulate angiogenesis resulting in characteristic vascular tumours; transforming growth factor-alpha, which can stimulate tumour growth through activation of the epidermal growth factor receptor (EGFR); adipose differentiation related peptide, that results in lipid accumulation and characteristic clear cells; and interleukin-6, which results in fevers common in patients with the disease.[8]

Until recently, the most effective systemic treatments for advanced disease were the cytokines interleukin-2 and interferon-alpha, however both were limited by potentially severe toxicities. Three agents (sunitinib, sorafenib and temsirolimus) that target the various pathways involved in the growth and spread of renal cell

Figure 1: *Sites of action of targeted agents in renal cell carcinoma cells. The tyrosine kinase inhibitors also act on endothelial cells to reduce proliferation. RTK denotes receptor tyrosine kinase; CAIX denotes carbonic anhydrase IX.*



carcinoma, have been approved in Australia since late 2006 and even more are in development.

Approved agents

Many of the growth factors involved in the growth of renal cell carcinoma act by binding to receptor tyrosine kinases that mediate signals by phosphorylation of tyrosines on proteins downstream of the receptor. Tyrosine kinase inhibitors (TKIs) are small molecules that prevent signal transduction, usually by interfering with binding of ATP (see figure 1). They vary in their affinity for various receptors and consequently have differing spectra of activity and side-effects.

Sunitinib (Sutent®) is an orally bioavailable TKI with activity against a large number of receptors including VEGF receptor-2 and PDGF receptor b, FLT3, C-KIT, RET and CSF-1.[9] When compared with interferon-alpha in previously untreated patients with metastatic clear cell renal cell carcinoma and favourable prognostic features, treatment with sunitinib resulted in a 31% response rate and 11 month progression free survival, compared with 6% and five months with interferon.[10] The main side-effects of treatment were diarrhoea, fatigue, nausea, stomatitis, vomiting, hypertension and hand-foot syndrome, but these were rarely severe. Neutropenia was shown to occur in a small proportion of patients. Hypothyroidism is reported in approximately one third of patients and is similar in pattern to thyroiditis, as half of these patients experience a transient fall in thyroid stimulating hormone (biochemical hyperthyroidism) before becoming hypothyroid.[11] More recently, cardiomyopathy has been reported in patients treated with sunitinib with an incidence estimated to be from 2.7 to 15.5%.[12-14] There appear to be two patterns of cardiotoxicity. The first is a rapid onset of congestive cardiac failure, which has been reported to occur after as few as four days of treatment, with sunitinib and often results in death within months.[13] The second is a gradual decrease in ejection fraction, which occurs over several cycles in about 20% of patients.[12] Regression analysis indicates significant associations with hypertension and coronary artery disease.

Sorafenib (Nexavar®) is an orally bioavailable TKI with affinity for VEGF receptors, PDGF receptors, C-KIT, FLT-3 and RET receptors.[15] It was compared with placebo in a large randomised and double blinded study of patients with clear-cell renal cell carcinoma, who had progressed after one course of systemic therapy, usually cytokines.[16] Patients had a good performance status and did not have poor prognosis of disease. Median progression free survival was 5.5 months compared with 2.8 months on placebo, despite a response rate of only 10%. This observation highlights the fact that conventional response criteria may be less relevant in assessment of clinically meaningful outcomes when this class of agents is being tested. The median overall survival for sorafenib was 19.3 months, but was difficult to compare with placebo as patients were allowed to cross over to sorafenib mid-way through the study. Side-effects included diarrhoea, rash, fatigue, hand-foot syndrome, alopecia and hypertension. Cardiovascular events were six times more common and bleeding events were twice as common in the sorafenib group.

Temsirolimus (Torisel®) is an intravenously administered inhibitor of the mammalian target of rapamycin (mTOR). mTOR forms a multi-protein complex involved in the control of cell proliferation and angiogenesis and which acts downstream of the receptor tyrosine kinases. Temsirolimus was compared with interferon, and with a combination of the two drugs in previously untreated patients with renal cell carcinoma and at least three poor prognostic factors.[17] Notably, in this trial, 20% of patients had non clear-cell histology and 82% had a Karnofsky performance status of ≤70%. Temsirolimus improved overall survival from 7.3 to 10.9 months compared with interferon alone. A survival benefit was not observed in the combination arm, possibly because the doses of both drugs were suboptimal due to the toxicity of the combination. The temsirolimus arms had improved progression free survival of between 1.8 and 2.4 months. Side-effects of treatment with temsirolimus were rash, peripheral oedema, mouth ulcers, hyperglycemia and lipid abnormalities. Despite being less toxic than interferon, two-thirds of patients had to delay temsirolimus treatment as a result of toxicity.

Now that several approved agents are available for use in the clinic, the challenge remains as to when and in which order they should be used. As with all decisions on when to treat, possible side-effects of treatment need to be weighed against the probable benefit to the patient. In patients with good prognosis and slowly progressive disease, we will often delay treatment until the patient develops symptoms related to their disease. Symptomatic patients with good prognostic features will generally be treated with sunitinib or sorafenib, unless they have contra-indications such as cardiac failure, for which we screen prior to treatment. As the agents differ in their specificity for receptor tyrosine kinases, we usually use a second TKI on failure of first line therapy if the patient is well enough. At present, temsirolimus is used as second or third line therapy, or as first line therapy in patients with poor prognosis disease, non-clear-cell histology or contra-indications to TKI therapy.

Agents under investigation

Everolimus is an orally bioavailable mTOR inhibitor that has shown activity in early clinical studies.[18] A recent double-blind placebo control trial in patients who had progressed on or within six months of sunitinib and/or sorafenib demonstrated an improved progression free survival of 4.6 months on everolimus compared with 1.9 months with placebo.[19] Side-effects of treatment were similar to temsirolimus, but also included asthenia, pneumonitis, hypophosphataemia, thrombocytopaenia, anaemia and hepatotoxicity.

Pazopanib is an oral TKI with activity against VEGF receptor, PDGF receptor and C-KIT. In patients previously treated with cytokines or bevacizumab, treatment with pazopanib resulted in a 35% response

rate and a 12 month progression free survival.[20] Side-effects included diarrhoea, hypertension, hair colour changes, fatigue and hepatotoxicity. Similarly, cediranib and axitinib, both VEGF receptor targeted TKIs, induced responses in 38% and 20% of patients and progression free survival of 8.7 and 7.7 months respectively, with side-effects including hypertension, fatigue and dyspnoea.[21,22]

Erlotinib is a TKI that targets EGFR and is registered for treatment of lung cancer. A small study showed a long progression free survival of 27 months in untreated papillary renal cell carcinoma despite a response rate of only 11%.[23]

Bevacizumab is a humanised monoclonal antibody against the ligand VEGF-A rather than the VEGF receptor. It has activity in various cancers when combined with chemotherapy and modest activity against renal cell carcinoma as a single agent.[24] When compared with interferon in previously untreated patients, a combination of interferon and bevacizumab improved progression free survival from 5.4 to 10.2 months.[25] Toxicities such as fatigue and weakness were mainly related to interferon, however treatment with bevacizumab resulted in proteinuria, hypertension, bleeding and a small incidence of gastrointestinal perforation and arterial and venous thrombotic events.

G250 or carbonic anhydrase IX is a membrane protein found on 85% of renal cell carcinoma, but in normal tissues is only found on gastric epithelium, biliary ducts and some pancreatic acini.[26] A chimeric monoclonal antibody to this protein (cG250) is able to target radioisotopes to renal cell carcinoma effectively in order to deliver radiotherapy to the site of the tumour.[27] Studies of cG250, bound to different radioisotopes and in combination with chemotherapy or cytokines, are ongoing to determine whether its efficacy can be improved.[28,29]

Conclusions

Options for treatment of advanced renal cell carcinoma have increased rapidly over the last few years, with agents targeting different aspects of the pathways involved in cancer growth, as well as targeting the cancer cells themselves. Substantial improvements in cancer outcomes such as progression free survival and overall survival have been seen, although these do not always correlate with radiological response rates. However, despite significant activity, none of these agents have been shown to cure renal cell carcinoma, complete remissions are uncommon and each causes side-effects that must be weighed against benefit. More work needs to be done to characterise the optimal sequence and combinations of the various drugs now available and to determine whether there may be benefit of their use in the adjuvant setting. Nevertheless, it is now possible to say that renal cell carcinoma is a highly treatable cancer.

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SEARCH FOR THE HOLY GRAIL: EVOLVING TARGETED THERAPIES IN BREAST CANCER

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Abstract

Understanding growth factor pathways overactive in subsets of women with breast cancer has enabled the development of agents which target these more precisely, enhancing efficacy of standard therapies and reducing side-effects. The first proof of this principle was the monoclonal antibody trastuzumab, which targets the HER2 receptor, over-expressed in approximately 20% of patients. Its efficacy has been established across the spectrum of clinical settings over the last decade, improving outcomes and synergising with chemotherapy and endocrine therapy. The intracellular HER2 tyrosine kinase inhibitor lapatinib extends this concept and clinical development is progressing rapidly, with adjuvant trials now open. Agents targeting angiogenesis have also found a role in the treatment of metastatic disease, although lack of specific diagnostic tests to identify a subgroup most likely to respond has hampered patient selection. Toxicities of these agents can be predicted by an understanding of their effects on normal cells expressing these pathways, and have generally been reversible. Their economic toxicity has proven more of a challenge and innovative trial designs will be required in future to reduce the cost of bringing them from bench to clinic.

The 'Holy Grail' of anti-cancer therapies is the mythical agent that affects only cancer cells which are marked out by a characteristic inscription, leaving normal tissues unharmed. Such an agent would ideally be oral, active at all sites in the body and able to be individualised in dosing for patients with different metabolic capabilities. Its use would ideally be triggered by a diagnostic test of high reliability, and its efficacy should be able to be monitored by serial testing, allowing individualised discontinuation when the cancer is cured. And it should be inexpensive.

Impossible? The haematologists might say "We've already got one!" as imatinib (Glivec®) in chronic myeloid leukaemia comes close to these specifications, with the exception of its cost and the need for chronic use.[1,2] In breast cancer the quest continues, however progress is being made and will be reviewed here.

There are important factors to consider in assessing the usefulness of targeted therapies.

What makes a good targeted therapy?

- Target molecule is present only in cancer tissues, or is significantly more active in cancer than in normal tissues.
- Frequency of the target is high in the population of patients.
- Target can be measured in histological samples in a reliable manner.
- Target occurs in an important growth pathway to which the cell is "addicted".
- Target is present in early "stem cell like" populations which tend to be resistant to other therapies.
- Targeted therapy can be safely combined with other anti-cancer therapies eg. chemotherapy and endocrine therapy, with synergistic efficacy.
- Oral bioavailability, to allow extended use and reduced administration costs.
- Therapy can reach all body tissues ie. not blocked by blood brain barrier.
- "Off target" toxicities are low and reversible.

Breast cancer targets

Much progress has been made in breast cancer treatment by recognising the responsiveness of the disease in many patients to oestrogen deprivation and the development of endocrine therapies to exploit this vulnerability (reviewed elsewhere in this issue of *Cancer Forum*).[3]

Oestrogen is not the only growth factor for breast cells and a number of other growth pathways are active at different phases of life, and provide potential targets for anti-cancer agents.

Epidermal growth factor family

This family of receptors (HER1,2,3,4 and their dimmers and heterodimers) are transmembrane glycoproteins which trigger tyrosine kinase activation, triggering cell growth and survival, and is important in both growth and repair from injury in many epithelial tissues.

In approximately 20% of women with breast cancer, overactivity of the pathway is conferred by amplification of the HER2 oncogene, leading to over-expression of the HER2 receptor.[4] The trigger of amplification is not known. It appears to occur early in oncogenesis and is often found in high-grade ductal carcinoma in situ. Detection is by immunohistochemistry or in situ hybridisation (summarised in recent American Society of Clinical Oncology guidelines).[5] This form of breast cancer is more likely to be high grade, invasive and associated with neovascularisation. It may be hormone receptor positive or negative, and if positive, may be

associated with poorer responsiveness to endocrine therapies. It may be more responsive to anthracycline based chemotherapy if there is co-amplification of the topoisomerase II gene, which is collocated on chromosome 17.[6] HER2 receptors are present in many normal tissues, including the skin, gut and heart, although the pathway is not usually active in these tissues in adults unless there is tissue injury.

Trastuzumab

The development of mouse monoclonal antibodies to the HER2 receptor allowed diagnostic identification of this subset. These were able to be crafted into therapeutic agents by humanising the antibody, known as trastuzumab (Herceptin). This agent has been widely studied in breast cancer over the past decade, and has activity against both stem and non-stem cell populations, which may account for its better than expected efficacy.[7] It has established roles in the following settings.

Adjuvant trials over the past decade included a variety of strategies (summarised in table 1), all of which appear to improve disease free survival (DFS), and the extended therapies also improve overall survival (OS). Concurrent administration with chemotherapy might theoretically provide greater synergy, particularly in high risk patients. The sequential approach also performed well in the HERA study with lower overall toxicity, however the smaller sequential study PACS-04 failed to achieve statistical significance.

Recent meta-analyses have confirmed benefits in disease free and overall survival, local recurrence and distant disease free survival.[13] A higher rate of brain metastases as first site of relapse was also noted (RR1.6, CI 1.06-2.40), consistent with poor penetration of the blood brain barrier.

Trastuzumab has a low but important incidence of cardiac toxicity, manifest as asymptomatic falls in left ventricular ejection fraction, and rarely, symptomatic left ventricular failure and cardiac death (total events <4.0%). It is more common in women who also receive anthracycline chemotherapy, and is due to the activation of epidermal growth factor receptor (EGFR) pathways in myocardium recovering from anthracycline damage. Other predisposing factors include concurrent use with chemotherapy versus sequential use, increased age and hypertension. Women with more serious underlying cardiac defects were excluded from all of the adjuvant studies, so the safety of Herceptin in such women is unknown. Use of a non-anthracycline chemotherapy, such as Carboplatin and Docetaxel (as in BCIRG 006), with close monitoring and tight blood pressure control, might be the safest approach in such women.[9]

Non cardiac toxicities include allergic reactions and anaphylaxis (usually with the first infusion), diarrhoea, rash, fatigue, nausea and headache. When used in combination with chemotherapy, rates of febrile neutropaenia are higher.

Optimal duration in the adjuvant setting remains a subject of investigation. A further arm of HERA, utilising two years of trastuzumab therapy, is yet to report. A number of other studies are underway investigating shorter durations of therapy, such as six months and nine weeks. Further follow-up data will emerge from the studies noted above, however it will be influenced by crossover of some patients on control arms to delayed trastuzumab. The use of 12 months of adjuvant trastuzumab is now recommended by the National Breast and Ovarian Cancer Centre guidelines and has been subsidised in Australia (if commenced concurrently with chemotherapy post-operatively) since October 2006.[14] This potentially curative approach should pay dividends with falling death rates in the next

Table 1: *Adjuvant trastruzumab trials in operable breast cancer.*

Study	Number analysed	Duration of trastuzumab	Chemotherapy backbone	Strategy	Hazard ratio DFS (CI)	Hazard ratio OS (CI)
N9831 NSABP B31[8]	3351	52 weeks	AC x 4, weekly paclitaxel x 12 or 3 weekly x 4	concurrent paclitaxel	0.48 (0.39-0.59)	0.65 (0.51-0.84)
BCIRG 006[9]	3222	52 weeks	AC Docetaxel or Carboplatin Docetaxel	concurrent	0.61 ACTH (0.48-0.76) 0.67TCH (0.54-0.83)	0.59 ACTH (0.42-0.85) 0.66 TCH (0.47-0.93)
HERA[10]	3401	1 year 3 weekly	Sequential	various	0.64 (0.54- 0.76)	0.66 (0.47-0.91)
FinHer[11]	232	9 weeks	Docetaxel before anthracycline	concurrent	0.42 (0.21-0.83)	Not sig at 3 yrs
PACS 04[12]	528	I year 3 weekly	FEC-Docetaxel or Epirubicin Docetaxel	sequential	0.86 NS (0.61-1.22)	1.27 NS (0.68-2.38)

AC = Adriamycin and cyclophosphamide FEC = 5-Flurouracil, Epirubicin, and cyclophosphamide

decade. As Dennis Slamon has observed: "This is proof of the principle that we can identify what's wrong in a cancer cell and fix it".[15]

A randomised Phase III study showed that adding trastuzumab to neoadjuvant chemotherapy increased the proportion of women obtaining a pathological complete response.[16] This effect does not appear to be influenced by hormone receptor status. This approach is not funded in Australia, and is being evaluated in further Phase II studies (including ANZ 0502 – Neo Gem) in Australia.

Targeted therapy might be of particular benefit in women with locally advanced or inflammatory breast cancer, which has a high rate of HER2 positivity. A Phase II study showed feasibility of combination with non-anthracycline based chemotherapy in this setting.[17]

Of great interest when first presented, this study was a collaborative effort of researchers and advocates, who worked to improve recruitment in the US, proving many principles along the way.

The original study identified additive benefit for DFS and OS (25.1 versus 20.3 months) combining trastuzumab with either anthracycline or paclitaxel chemotherapy.[18] The unacceptable incidence of cardiac toxicity has led to the avoidance of anthracycline combinations in subsequent usage.

Efficacy of trastuzumab in improving DFS and OS (31.2 versus 22.7 months) in combination with docetaxel given three weekly was subsequently reported.[19] Concurrent use of either weekly or three weekly trastuzumab with either taxane has been funded in Australia since 2001 via a separate Health Insurance Comission scheme after repeated Pharmaceutical Benefits Scheme (PBS) rejection.

Trastuzumab is also effective in combination with Vinorelbine in the metastatic setting, although this combination has never been approved in Australia.[20] This study also identified that lack of an early fall in serum levels of HER2 extracellular domain predicted for lack of response. Given the number of women who now receive a taxane as part of their adjuvant therapy, those who relapse would benefit from greater availability of this approach. In vitro synergy is observed with many cytotoxic agents and other combinations are under investigation.[21]

Combination with the aromatase inhibitor anastrazole also improved DFS compared with AI alone, and for patients with ER positive and lower risk metastatic disease, this offers a low toxicity approach to therapy.[22]

Controversy surrounds the issue of whether progression while on trastuzumab therapy should lead to the reintroduction of chemotherapy with maintained trastuzumab, or a switch to other agents. A German breast group study with capecitabine as a second line agent showed additional benefit to continuing trastuzumab.[23] The higher incidence of central nervous system metastases in these women has also been noted, leading to therapy with radiotherapy and/or surgery. A search for targeted agents with the potential to cross the blood brain barrier has emerged as a clear priority.

Lapatinib

The orally active tyrosine kinase inhibitor lapatinib (Tykerb) binds to the intracellular portion of the HER2 receptor and blocks signal transduction.[24] It has the potential to overcome trastuzumab resistance due to loss of the extracellular binding site (truncated p95 receptor).[25] To date it has been associated with lower levels of cardiotoxicity, although most patients studied have not had recent anthracyclines.[26] Some other common side-effects relate to its blockade of the EGF receptor (which does not correlate with clinical activity), including rash and diarrhoea.[27,28] It has established use in the second line metastatic setting in combination with capecitabine and is under investigation in a number of other clinical settings.

The pivotal study EGF 100151 compared capecitabine alone with capecitabine plus lapatinib in women whose disease had progressed after chemotherapy and trastuzumab. Improved progression free survival was demonstrated of 27.1 versus 18.6 weeks (CI 0.43-0.77). There was a higher response rate in the combination arm, and a 22% reduction in the risk of death.[29] Lapatinib was approved for PBS subsidy in this patient population in May 2008.

Lapatinib has the potential to cross the blood brain barrier and has demonstrated activity in animal models of brain metastases. Clinical responses with monotherapy lapatinib were observed in patients progressing after trastuzumab, radiotherapy +/- surgery.[30]

The head to head comparison study of trastuzumab versus lapatinib in combination with taxane chemotherapy has just opened internationally (Promise, MA31, NCIC). Translational studies will attempt to identify subgroups with higher responsiveness to either agent.

High response rates as monotherapy have been reported with lapatinib in inflammatory breast cancer, and combination studies are underway with taxanes and the antiangiogenic tyrosine kinase inhibitor pazopanib.[31]

Combination studies in metastatic disease with aromatase inhibitors are due to report in the next year. This offers an all oral approach to restoring endocrine sensitivity in dual positive breast cancer.

The ALTTO clinical trial is underway as a global cooperation to evaluate lapatinib alone, in combination or in sequence after trastuzumab in the adjuvant setting. Predetermined translational studies assessing Topo II, c myc, and the presence of p95 receptor will also be relevant to treatment choice in the future.

Many HER2 positive women worldwide have not had access to adjuvant trastuzumab, yet remain at increased risk of relapse for up to 10 years. The TEACH study has accrued 3165 patients to investigate the role of one year of lapatinib given at some distance from original treatment. Results are anticipated in 2010.

Angiogenesis inhibitors

Growth of tumours beyond approximately 4mm requires the development of new blood vessels to

supply nutrients. The process of new vessel formation, angiogenesis, is triggered by tumour hypoxia. Growth factors including vascular endothelial growth factor (VEGF) are released to stimulate endothelial proliferation and migration.[32] Targeting of this pathway has the potential to interrupt tumour growth, reduce metastatic potential, enhance penetration of chemotherapy and reduce recovery from sublethal damage.

Bevacizumab

This monoclonal antibody to VEGF reduces available ligand for binding to the VEGF receptor and inhibits angiogenesis.[33] It is administered intravenously on a variety of schedules.[34] Its related toxicities include impaired wound healing and renal impairment, proteinuria and hypertension. Anaphylactic reactions have also been described.

Two trials have addressed bevacizumab's combination with first line chemotherapy in metastatic breast cancer. The E2100 study investigated combining bevacizumab 10mg/kg 2nd weekly with weekly paclitaxel, showing significantly improved progression free survival (PFS) from 5.9 to 11.8 months (HR 0.60).[35] Overall survival was similar in the two groups. More recently, the AVADO study utilised three weekly docetaxel and two doses of bevacizumab (7.5 and 15 mg/kg 3 weekly) and showed a modest increase in PFS with both doses.[36] Overall survival data is not yet mature. Hypertension rates were lower and infection rates higher than E2100. It is possible that the anti-angiogenic activity of paclitaxel itself is a factor in the results of E2100, and the optimal chemotherapy backbone remains a subject for investigation. There is also cross-talk between HER2 and VEGF pathways, and double targeting approaches are under investigation in HER2 positive patients.

Pharmaceutical Benefits Scheme funding for this approach has not been secured in Australia to date and although bevacizumab has Therapeutic Goods Administration approval, the significant expense has inhibited implementation. The lack of a diagnostic test to identify patients most likely to respond prevents optimal targeting.

Global clinical trials have opened in 2008 (B020289: BEATRICE) focused on this high risk group, and will explore the benefits of adding 12 months of bevacizumab to standard adjuvant chemotherapy (including anthracyclines and taxanes).

Other angiogenesis and growth factor inhibitors

Multikinase inhibitors including pazopanib (which targets VEGF receptor signalling along with PDGF and C-KIT)[37] and sunitinib[38] are under investigation, and other monoclonal antibodies targeting the VEGF receptor-2 will enter trial in the next year.

Other important receptor mediated pathways active in some breast cancer patients include insulin-like growth factor and growth hormone. Many of these pathways are engaged in cross-talk with each other, with HER2, VEGF and ER. Many agents targeting ligands, receptors and downstream signalling molecules are in development.

Further development of the plethora of targeted agents will require changes to clinical trial design, perhaps to greater use of short periods of pre-operative therapy, with serial analysis of biomarkers of response and genetic predictors. More rapid progress should be able to be made as side-effects are often able to be predicted by understanding of pathway interruption. There is hope that this will reduce the overall cost of bringing these agents to the clinic and allow the identification of patients most likely to benefit. The search for the Holy Grail continues…and it won't be inexpensive.

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TARGETED THERAPIES IN HAEMATOLOGICAL MALIGNANCIES

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Abstract

By delivering major improvements in patient outcomes, targeted therapies have revolutionised treatment paradigms for many haematological malignancies, particularly chronic myeloid leukaemia, acute promyelocytic leukaemia and diffuse large B-cell lymphoma. They promise even greater benefits in the future.

As defined by others, truly targeted therapy should attack a biologically important process, preferably one central to a hallmark of cancer.[1] Such therapy involves a drug with a focused mechanism that specifically acts on a defined target or biologic pathway that, when inactivated, causes regression or destruction of the malignant process.[2] The target should be measurable in the clinic and measurement of the target should correlate with clinical outcome when the targeted therapy is administered.[1] The ideal target should be specific and crucial to the malignant clone and not be expressed in normal tissues to avoid toxicity seen in traditional cytotoxic chemotherapy.

Recent advances in understanding of molecular mechanisms and identification of immunophenotypic signatures specific to haematological malignancies, have led to the discovery of many novel therapeutic strategies, some of which fulfil all the above listed criteria for targeted therapy. These targeted therapies for haematological malignancies can be broadly divided into therapeutic monoclonal antibodies or small molecule inhibitors. This review will highlight some of the major advances in haematological malignancies using these smarter approaches. These drugs have already changed the landscape of care for patients.

Tyrosine kinase inhibitors in chronic myeloid leukaemia and other chronic myeloproliferative disorders

Tyrosine kinase inhibitors for chronic myeloid leukaemia are perhaps the most convincing examples of the utility of targeted therapy. They fulfil all of the criteria that define targeted therapy and have resulted in a revolution in the management of chronic myeloid leukaemia and a fundamental beneficial change in the natural history of the disease.

Chronic myeloid leukaemia is a myeloproliferative disorder with an incidence of one to two cases per 100,000 people per year.[3] Approximately 300 to 400 patients are diagnosed each year in Australia. The pathophysiology of chronic myeloid leukaemia is characterised by a clonal expansion of haematopoietic stem cells carrying the Philadelphia chromosome, a reciprocal translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34;q11).[4] This balanced translocation creates a unique hybrid gene known as BCR-ABL. Expression of BCR-ABL transcript is the hallmark of chronic myeloid leukaemia. It encodes the aberrant BCR-ABL protein that contains a constitutively active ABL tyrosine kinase, capable of producing a 'switch-on' proliferative signal affecting a number of downstream intracellular pathways. Murine models using retroviral transfection with BCR-ABL have elegantly demonstrated the ability of aberrant expression of this protein to produce a phenotype resembling that of a chronic myeloproliferative disease, providing compelling evidence that this target is essential to the development of the disease.[5]

The search for specific inhibitors of ABL tyrosine kinase led to the development of the first generation of tyrosine kinase inhibitor, imatinib mesylate and its phenomenal success in the treatment of chronic myeloid leukaemia in chronic phase. Prior to the imatinib era, interferon alpha plus cytarabine was the treatment of choice for most patients with chronic myeloid leukaemia who were not candidates for curative haematopoietic stem cell transplantation. This poorly tolerated therapy delivered a three year overall survival of 86% with few patients surviving greater than 10 years, due to progression to highly malignant blast phase chronic myeloid leukaemia.[6]

Imatinib is a potent tyrosine kinase inhibitor that binds to the inactive configuration of ABL kinase and functions as a competitive inhibitor of the ATP binding site of BCR-ABL.[7] The key effect of imatinib binding is to block the autophosphorylation of the kinase, a critical event leading to downstream signal transduction.[8] Inhibition of this signal transduction can be readily observed in cells from patients treated with imatinib. The cellular responses to this targeted therapy can be measured by its impact on tumour burden, using either conventional cytogenetics, or fluorescence in situ hybridisation to indicate what proportion of blood cells are from the malignant clone, and molecular techniques to quantify BCR-ABL transcripts.

The landmark International Randomised Study of IFN versus STI571 study investigated the role of imatinib in first line therapy for patients with chronic myeloid leukaemia in chronic phase. Impressive and durable responses were confirmed after a median five year follow-up; the estimated disease-specific overall and progression-free survivals of patients who received imatinib as initial therapy were 95% and 93% respectively.[9] The annual rate of progression to accelerated phase or blast crisis declined remarkably to zero in the sixth year of therapy (annual rate during the first five years was 1.5, 2.8, 1.6, 0.9 and 0.6% respectively).[10]

400mg imatinib is now the standard of care in newly diagnosed chronic myeloid leukaemia in chronic phase. Long-term follow-up has also shown improved responses to imatinib over time: the complete cytogenetic response (CCyR) was 69% after one year and 87% after five years of therapy.[9] There was a significant correlation with better overall survival for those patients obtaining a CCyR response by 12 months; furthermore, no patient progressed to the accelerated or blast crisis during a five year follow-up if a major molecular response together with a CCyR at 12 months was attained. Imatinib is generally well tolerated. Inhibition of normal ABL kinase activity does not limit the use of this drug in most patients. For the great majority of newly diagnosed patients with chronic myeloid leukaemia, this is no longer a devastating disease with a poor long-term prognosis. Rather, it is a chronic disease, more akin to chronic non-malignant disorders.

Nevertheless, resistance is one of the emerging challenges in the imatinib era. Over five years, approximately 17% of patients initially treated with imatinib will fail due to the outgrowth of a clone with a mutated BCR-ABL that has diminished binding to imatinib.[9] Second generation tyrosine kinase inhibitors (dasatinib and nilotinib) have different binding characteristics, are more potent than imatinib and are generally highly effective in the setting of imatinib intolerance or failure.[10] However, one particular mutant form of BCR-ABL, the T351I mutation, is resistant to all approved agents and is a major hurdle yet to be overcome.

Tyrosine kinase inhibitors like imatinib are also effective in several rare myeloproliferative diseases driven by the expression of other aberrant tyrosine kinases. Serendipitously, it was empirically observed that imatinib was highly effective for patients with chronic eosinophilic leukaemia.[11] Subsequent investigation revealed that the cryptic fusion oncogene, FIL1L1-PDGFRa, was not only causative of the condition, but exquisitely sensitive to inhibition by imatinib. Another imatinib-sensitive blood disease is the myelodysplastic/myeloproliferative disorder driven by constitutive activity of the PDGFRb kinase. For both conditions which generally fail to respond to conventional therapies, complete responses are now commonly seen, including complete molecular responses.

Targeted immunotherapy in B cell lymphoproliferative disorders

The identification of surface-specific markers on B cell malignancies has led to the development of monoclonal antibodies that target these antigens. The most widely studied therapeutic antibody, rituximab, is directed against CD20, a pan-B cell surface antigen that is also widely expressed in normal B cells. Rituximab is a chimeric monoclonal antibody of IgG1 subtype and was the first antibody approved for cancer therapy in history. Its proposed mechanism of action is mediated by antibody-dependent cell-mediated cytotoxicity and complement dependent cytotoxicity. Despite the fact that the cellular target is not specific for malignant B cells, depletion of normal B cells does not appear to be a major clinical problem with early non-malignant B cell recovery observed at 24 weeks after a single infusion of 375mg/m2 (unpublished data). Rituximab was initially approved in refractory CD20+ low grade or follicular lymphoma with an overall response rate of 50% and a median duration of response of 12 months.[12] As a single agent in newly diagnosed follicular lymphoma, the overall response rate approaches 80% with median duration of responses of 18-26 months.[13] Of greatest importance is the synergy observed between rituximab and cytotoxic chemotherapy. Rituximab containing chemotherapy regimens have become the standard of care in first line and relapsed follicular lymphoma.

Among the lymphoproliferative disorders, diffuse large B-cell lymphoma is the most common aggressive lymphoma despite refinements in chemotherapy. No improvement in the cure rate had been achieved in the last 20 years. In a landmark Phase III trial in elderly patients (aged between 60 to 80) with previously untreated diffuse large B-cell lymphoma, addition of rituximab to standard chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone) ie. R-CHOP showed superior progression-free and overall survivals compared to CHOP alone. The seven year progression free survival was 52% for R-CHOP and 29% for CHOP ($p<0.0001$), and the overall survival was 53% for R-CHOP and 36% for CHOP ($p=0.0004$).[14] Superiority in event free survival and overall survival of rituximab plus CHOP like regimens has also been demonstrated in younger patients with untreated diffuse large B-cell lymphoma.[15] R-CHOP is now the gold standard for newly diagnosed diffuse large B-cell lymphoma.

Anti-CD20 based radioimmunoconjugate therapy is another approach to targeted therapy, enhancing cytotoxic potential of a monoclonal antibody by attaching to a radionuclide. Radioimmunoconjugate therapy targets the cells to which the antibody is bound, the surrounding lymphoma cells and the local micro-environment. Ibritumomab tiuxetan is an example of radioimmunoconjugate therapy and consists of a murine anti-CD20 antibody linked covalently to a metal chelator (MD-DTPA), permitting stable binding of 90Y to produce enhanced targeted cytotoxicity.[16] It is currently indicated for relapsed, refractory or transformed low-grade lymphoma, but is not widely used in Australia. Experience with radioimmunoconjugate therapy in intermediate to high grade diffuse large B-cell lymphoma is limited to patients with refractory or relapsed disease.

Encouraged by the success of rituximab, many new agents targeting surface antigens are in development for

B cell lymphoproliferative disorders. SGN-40 is a humanised antibody against CD40 (a member of the tumour necrosis factor receptor family). Epratuzumab is directed at CD22, a specific antigen expressed by pre-B cells and mature normal B cells. Apolizumab and lumiliximab target HLA-DR and CD23 respectively.[17] The prospects for further major improvements in outcome for patients with lymphoproliferative disorders are excellent.

Targeted therapy in acute myeloid leukaemia

The use of all *trans* retinoic acid (ATRA) as part of frontline therapy for newly diagnosed patients with acute promyelocytic leukaemia, is one of the best examples of how targeting specific genetic lesions within leukaemic cells can result in a remarkable advance in cure rates. Interestingly, it is also an illuminating example of how the molecular mechanism of action was discovered only after empirical proof of its efficacy against the disease. The hallmark of classic acute promyelocytic leukaemia is t(15;17), which results in the production of a PML-RARa aberrant fusion gene leading to a blockade in differentiation at the promyelocyte stage. Retinoic acid is a critical regulator of the balance between cellular differentiation and self-renewal, and works by binding to a retinoic acid receptor (RAR). Wild-type RARa is a ligand-dependent transcription factor expressed primarily in haemato-poietic cells and normally induces transcriptional repression in the absence of retinoic acid. Like wild-type RARa, the PML-RARa fusion protein is a dominant negative inhibitor of retinoid-induced transactivation.[18] Treatment with ATRA reverses the inhibitory activity and induces terminal differentiation of malignant promyelocytes.[19]

The incorporation of ATRA in induction therapy results in a high complete remission rate, leads to rapid resolution of the characteristic life-threatening coagulopathy and most importantly, decreases the relapse rate compared with treatment with chemotherapy alone. In the Australian trial of ATRA plus anthracycline chemotherapy, followed by ATRA maintenance, an overall survival of 88% was observed after five years.[20] Acute promyelocytic leukaemia is now the most curable subtype of acute myeloid leukaemia in adults. Sensitive and specific polymerase chain reaction techniques to detect PML-RARa are available to monitor response and survey for early signs of molecular relapse.

The surface antigen CD33 has been extensively evaluated as a therapeutic target in acute myeloid leukaemia. CD33 antigen is a surface glycoprotein of unclear biological function that is expressed on leukaemic blasts in up to 90% of acute myeloid leukaemia, hence its attraction.[21] The expression of this cell surface marker is normally restricted to mature myeloid cells and not in normal haematopoietic stem cells. However, expression of CD33 antigen by leukaemic stem cells capable of repopulating human acute myeloid leukaemia cells in xenograft model using immunodeficient mice has been demonstrated.[22] The differential expression between acute myeloid leukaemia and normal myelopoiesis serves as the basis for the desired selective anti-leukaemic effect. Gemtuzumab ozogamicin is a novel conjugated humanised monoclonal antibody of IgG4 subtype directed against CD33, that is covalently attached to a powerful anti-tumour antibiotic, calicheamicin, which in turn is too toxic to be administered as a free drug. The binding of the anti-CD33 antibody portion of gemtuzumab ozogamicin with CD33 antigen on myeloblasts results in the formation of a complex that is rapidly internalised. After entering the leukaemic cells, the calicheamicin derivative is released from the antibody in the acidic environment of the lysosome and subsequently exerts its leukaemia killing effect. In a Phase II clinical trial involving 277 patients over the age of 60 with acute myeloid leukaemia in first relapse, gemtuzumab ozogamicin has been reported to have significant single-agent activity with an overall remission rate of 26%, including 13% complete responders and median relapse-free survival of 6.4 months.[23] Gemtuzumab ozogamicin has been approved for relapsed or refractory CD33+ acute myeloid leukaemia in patients over the age of 60 years. A number of prospective trials exploring the potential benefits of gemtuzumab ozogamicin when combined with cytotoxic chemotherapy, in different settings in acute myeloid leukaemia, are underway.

Lintuzumab (SGN-33) is a humanised recombinant monoclonal antibody of IgG1 directed against CD33. Lintuzumab is thought to stimulate antibody dependant cellular cytotoxicity against leukaemic cells expressing CD33. In a dose-finding study, lintuzumab was shown to be well tolerated and have active anti-leukaemic effect with overall objective responses seen in seven of 17 elderly patients with relapsed or untreated advanced acute myeloid leukaemia, including four patients achieving complete remission.[24]

Potential new targets

A number of new exciting targeted therapies are under active evaluation in various haematological malignancies.

FLT3 is a receptor tyrosine kinase that activates a number of signalling proteins involved in the regulation of growth and apoptosis. When constitutively activated by mutation or internal tandem duplication, FLT3 is an oncogene implicated in approximately 25% of acute myeloid leukaemia. The presence of an FLT3 mutation is a powerful predictor of relapse in acute myeloid leukaemia. Lestaurtinib (CEP-701) is an example of a potent inhibitor against FLT3-mutant primary acute myeloid leukaemia samples.[25] In vitro studies suggest that clinical benefit may be maximised when lestaurtinib is given immediately following chemotherapy. This concept is now being investigated in randomised clinical trials of FLT3-mutated acute myeloid leukaemia patients. A plasma inhibitory activity assay has proven useful in monitoring the extent of FLT3 inhibition in these trials.

Leukaemic stem cells represent another potential target in acute myeloid leukaemia. CD123 (a sub-unit of the interleukin-3 receptor) is one of few unique markers consistently expressed in leukaemic stem cell compartment (CD34+ CD38-) capable of repopulating

human acute myeloid leukaemia cells in an immunodeficient mouse model.[26] A fusion protein using anti-CD123 monoclonal antibody with a diphtheria toxin (DR383 IL-3) has been shown to have modest activity in acute myeloid leukaemia in early phase trial.[27] A neutralising monoclonal anti-CD123 antibody (CSL360) is currently undergoing Phase I trial in Australia (clinicaltrials.gov).

BCL-2 over-expression is the hallmark of chronic B cell lymphoproliferative disorders. While initial attempts to target BCL-2 through anti-sense therapy (oblimerson) have proved disappointing, a new class of agents, the BH3 mimetics, is emerging as a highly effective way to inhibit BCL-2 and trigger tumour cell death in these diseases. ABT-263 is a novel BH3 mimetic that binds with high affinity and inhibits multiple anti-apoptotic BCL-2 family proteins.[28] A recent Phase I study reported impressive early evidence of efficacy with good partial responses observed in patients with advanced and refractory lymphoid malignancies, such as chronic lymphocytic leukaemia.

Given the wealth of new potential agents, the ongoing challenges for developing truly targeted therapies for haematological malignancies are prioritisation according to potential clinical impacts, rationalisation of combination therapies and study designs, minimisation of potential side-effects and the associated financial burden on patients and the health care system.

Conclusion

Targeted therapies have revolutionised care for patients with many haematological malignancies over the last 10 years. However, with the exception of tyrosine kinase inhibitors for chronic myeloid leukaemia, monotherapy with these agents is unlikely curative in the majority of patients. The most promising future approach is to combine these novel agents with conventional cytotoxic chemotherapy to improve clinical outcomes.

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TARGETED THERAPIES FOR SARCOMAS (INCLUDING GASTROINTESTINAL STROMAL TUMOURS)

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Abstract

Sarcomas represent an extraordinarily complex set of diseases derived from mesenchymal cells, which have the potential to differentiate along the lineages of various 'connective tissues' in the body. In recent years, important insights into understanding their molecular biology have lead to not only a better ability to subtype these diseases for the purposes of an accurate diagnosis, but more importantly into the development of highly effective new drugs targeting some of these specifically implicated pathways. This review will outline some of these recent developments and potential new therapies for the future.

The management of sarcoma encompasses a broad range of malignancies, arising from bone, soft tissue and gastro-intestinal sources, with unique pathologic and cellular pathways. Although sarcomas are rare – approximately 800 new sarcoma cases reported in Australia per year – the incidence has increased by 40% in 10 years.[1] With an overall mortality of 50%, in a disease that predominantly affects the young, the community impact of this is significantly greater. It has been estimated that 17 years of life are lost per sarcoma patient, three times the rate of bowel or breast cancer.

In recent years, a number of critical biological and molecular factors driving the growth and progression of sarcomas have been identified. These insights have not only assisted in better characterising sarcoma subtypes, but have also helped identify potential therapeutic targets, enabling a rapid translation into proof of concept trials and effective new therapies. The impact of these breakthroughs has extended far beyond this smaller patient population, providing important insights into treating more common cancers with rationally developed molecularly targeted therapies.

This review will outline some of the advances in targeted therapies for sarcoma in recent years, as well as agents and therapies in development for treating this spectrum of diseases in the future.

Gastrointestinal stromal tumours

Gastrointestinal stromal tumours are the most common mesenchymal tumour of the gastrointestinal tract, most frequently arising in the stomach or small intestine.[2] The incidence of gastrointestinal stromal tumours has been reported to be approximately 10-20 per million.[3]

The majority (around 80%) of gastrointestinal stromal tumours have a gain-of-function mutation in the proto-oncogene C-KIT, which renders KIT tyrosine kinase signalling constitutively active.[4] Imatinib mesylate (Glivec®), a protein tyrosine kinase inhibitor (TKI) specifically developed to inhibit the BCR-ABL kinase in chronic myeloid leukaemia, also effectively inhibits the KIT and platelet derived growth factor receptor (PDGFR) tyrosine kinases. Insights into the understanding of the underlying molecular biology of gastrointestinal stromal tumours, first made in 1998, have been translated rapidly into the development of highly effective therapies for a disease that was essentially resistant to conventional cytotoxic chemotherapies.[4] Imatinib was first used for gastrointestinal stromal tumours in 2000 and since then there have been multiple trials confirming its activity in metastatic gastrointestinal stromal tumour (figure 1).[5-8]

The exon at which the mutation occurs in KIT has been demonstrated to carry both prognostic and predictive significance (table 1).[9] KIT mutational analysis can help predict response to imatinib; patients with an exon 11 mutation have a significantly better response than those with an exon 9 mutation or no detectable (wild-type) KIT mutation.[19] Interestingly, in patients with exon 9 mutations, recent data has emerged suggesting imatinib dose can affect the quality of response. Those starting on a higher dose of imatinib (800mg/day) had significantly longer disease control than those starting on 400mg/day.[9]

Gastrointestinal stromal tumours can develop secondary resistance to imatinib therapy, most commonly due to the acquisition of a new mutation in the kinase domain of KIT.[20] This changes the conformational state of the KIT protein, and thereby affects the ability of imatinib to bind to it and stop KIT-directed downstream signalling. Although less well understood, other mechanisms of resistance to imatinib and other kinase inhibitors can occur, including: KIT genomic amplification; activation of alternate signalling

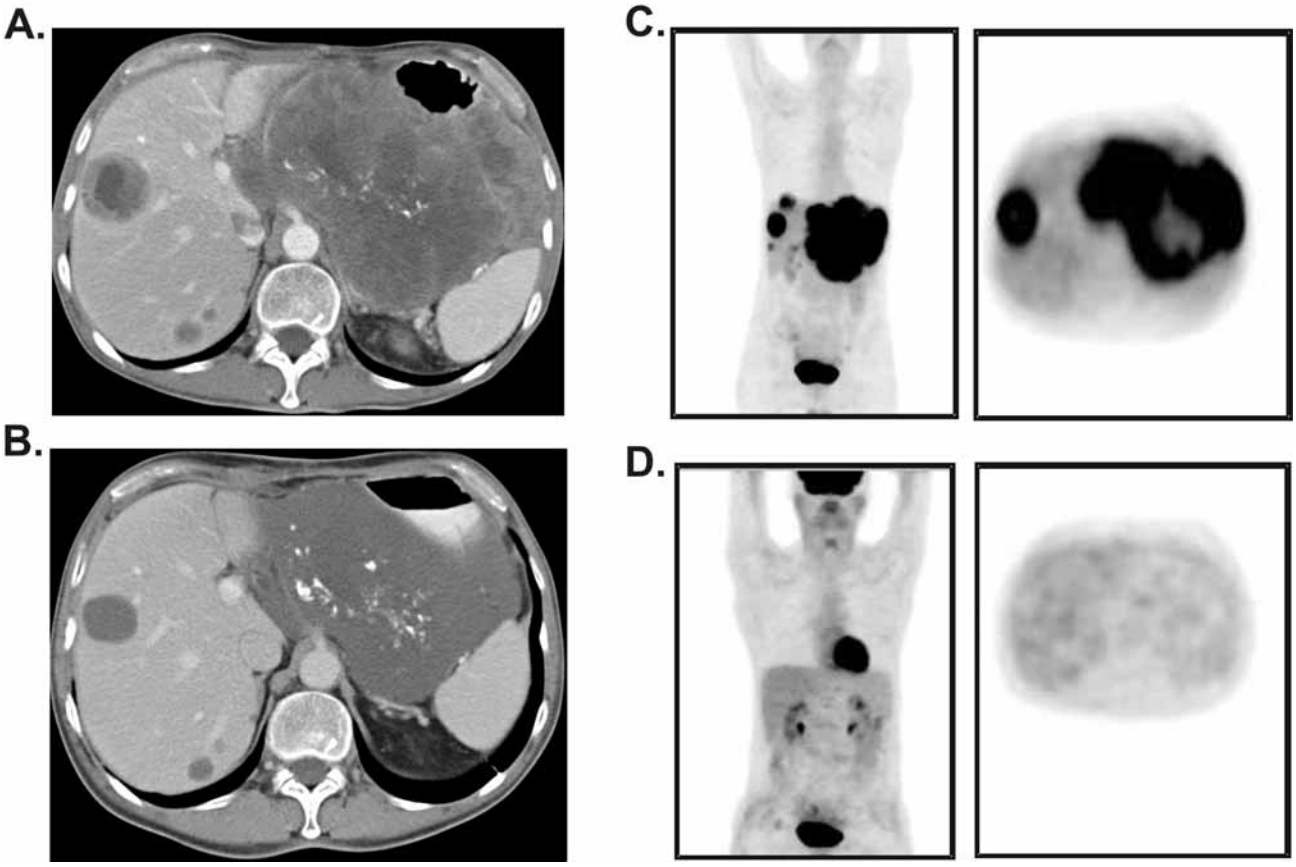
Figure 1: *CT and FDG-PET scans of a patient with a metastatic GIST treated with imatinib mesylate.*

1a: CT scan at baseline. Note large, heterogenous abdominal mass with areas of necrosis. Multiple liver metastases present.

1b: CT scan after four months of treatment. Note that although there has been no reduction in overall external tumour dimensions, there is a clear change in the characteristics of the tumour matrix, with a reduction in tumour density and more homogenous appearance. This is a classic response seen with treatment of GIST with imatinib and other kinase inhibitors.

1c: FDG-PET scan at baseline. Note the increased uptake of tracer in the sites of disease.

1d: FDG-PET scan after four weeks of imatinib. Note the complete resolution of FDG-avid disease.



pathways independent of KIT; or increased action of drug efflux pumps such as MDR1.[21] These molecular changes can lead to unique clinical changes in gastrointestinal stromal tumours, with the development of a resistant clonal nodule, an intra-tumoural nodule which grows despite clinical and radiologic control of the remainder of the disease.[22] In the setting of imatinib failure or intolerance, sunitinib, an oral multi-TKI which inhibits KIT, PDGFB and vascular endothelial growth factor (VEGF) among others, has been shown in a Phase III study to increase time to progression and overall survival.[23] Other KIT-directed TKIs including sorafenib, nilotinib and dasatinib, are currently undergoing clinical evaluation (table 2). Secondary mutations in the kinase domain in KIT have proven resistant to most KIT inhibitors. Alternate approaches to circumventing this, currently being assessed in clinical trials, include targeting kinases downstream of KIT (eg. mTOR), or with agents targeting the protein chaperones that are important in helping to stabilise the KIT-oncoprotein (eg. HSP90). For further reading, there are several recent excellent overviews of gastrointestinal stromal tumours and their management.[3,21,45-50]

Dermatofibrosarcoma protruberans

Dermatofibrosarcoma protruberans is a cutaneous fibroblast-derived soft tissue sarcoma. This rare tumour is an excellent example of the role of autocrine and paracrine loops involving growth factors – in this instance, PDGF – in driving malignancy and the ability to target the loop based on knowledge of this underlying biological mechanism.

The characteristic translocation seen in dermatofibrosarcoma protruberans is t(17;22) which leads to the formation of a fused proto-oncogene, resulting in upregulation of the the PDGFB gene. Mature PDGF production facilitates tumour growth by interacting in an autocrine fashion with PDGF receptor. This is the principal driving mechanism behind the tumour. Imatinib, with its ability to inhibit the PDGF receptor, has proven very effective in managing metastatic and locally advanced dermatofibrosarcoma protruberans that are not amenable to surgical resection. A number of published case reports and series have documented complete and partial responses to imatinib.[29,30] Surgery for dermato-fibrosarcoma protruberans can be particularly

challenging, with significant morbidity and high local recurrence rates, due to the highly infiltrative nature of this tumour. Neoadjuvant imatinib should therefore be considered in the multidisciplinary treatment of this disease. There has been a recent review on the management and background behind this effective treatment of dermatofibrosarcoma protruberans based on the sound understanding of its biology.[51]

Ewing's family tumours (EFTs)

Ewing's sarcomas are rare, highly malignant tumours, thought to derive from neural crest cells and most commonly originate in bone. The median age at diagnosis is only 15 years.[52] Despite aggressive first line management with surgery, chemotherapy +/- radiotherapy, 30-40% of Ewing's family tumours recur.

Translocations are common: t(11;22) and a related translocation occurs in over 80-90% of Ewing's family tumours (table 3).[53] This translocation creates a fusion protein (EWS-FL1), which acts as an aberrant transcription factor, hence driving the process of malignancy. EWS gene translocations are also seen (EWS-WT1) in desmoplastic small round cell tumours, a rare, aggressive, primitive sarcoma. The malignant growth of EFTs is reliant on the development of growth factor-mediated autocrine loops through which signalling occurs.[54] These autocrine loops involve the insulin-like growth factor-1 (IGF-1) and its receptor. The IGF signalling pathway plays a key role in the pathogenesis of EFT and other tumours. The presence of the fusion gene results in a significant increase in secretion of IGF-1 or expression of its receptor.[55] Autocrine IGF-1 signalling, increased significantly by these translocations, is known to contribute to tumour cell survival and maintenance of the malignant phenotype.[56] Thus, there is compelling biologic rationale for targeting IGF-1 and its receptor.

The type 1 IGF receptor (IGF-1R) is a receptor tyrosine kinase which activates the PI3K/AKT/mTOR, Ras/MAP kinase and JAK/STAT signalling pathways. Either IGF-1 itself or its receptor can be targeted by monoclonal antibodies, or small molecule tyrosine kinase inhibitors. Pre-clinical studies of small molecule inhibitors of antibodies to the IGF-1 receptor have demonstrated inhibition of Ewing tumour cell proliferation.[57-59] Phase II trials are currently underway investigating the activity of monoclonal antibodies to IGF-1 receptor, based both on a strong pre-clinical rationale, and on promising results from Phase I studies, where a number of sustained responses have been seen, particularly in patients with Ewing's sarcoma.[32]

It is also known from preclinical studies that Ewing's sarcoma cell lines carrying the EWS-FL1 fusion protein express varying levels of mTOR cell signalling protein. mTOR is a downstream signalling pathway of the IGF-1 receptor and PI3K/AKT pathways, which are activated in numerous cancers.[60] Dysregulation of the mTOR pathway can result from numerous alterations, both

Table 1: *Adjuvant trastruzumab trials in operable breast cancer.*

Mutation	Frequency	Consequence	Targeted agent	Comments	References
KIT exon 11 (juxtamembrane domain)	57-70%	Constitutively active KIT TK signalling	Single best predictor for favourable response to imatinib. Higher RR and PFS on imatinib than exon 9.	More likely to develop 2° mutations (compared with exon 9 mutations).	4,9,10,19
KIT exon 9 (extracellular domain)	5-18%		Intermediate response to imatinib. Better outcomes with high dose (800mg) than low dose (400mg). Appear sensitive to sunitinib.	Uncommon to develop 2° mutations.	9,11
KIT exon 13,14, 17 (exon 17 = activation loop)	0.6-1.4%		Imatinib less effective in most exon 17 mutations. Sunitinib: lower efficacy for 2° KIT mutations in exon 17/18 compared with exon 13/14.	2° mutations can cause imatinib resistance.	11-13
PDGFRA Exon 12 (juxtamembrane) or 18 (activation loop)	5-10%	Constitutively active PDGFRA TK signalling	Less responsive to imatinib.		14,15
Wild type	10-15%	Mechanisms unclear	Less responsive to imatinib. Appear sensitive to sunitinib. Tumours express cKIT with IHC but no mutations.	Majority of GISTs in children/adolescents.	16-18

TK= tyrosine kinase IHC = immunohistochemistry RR= response rate PFS = progression-free survival

Table 2: *Targeted agents in development for GIST and other sarcomas.*

Tumour type	Potential molecular target	Therapeutic agent	Phase of development	References
GIST	cKIT, PDGFR	Imatinib	Registered	5,20
		Sunitinib	Registered	23
		Nilotinib	Phase III	24,25
		Dasatinib	Phase I	26
		Sorafenib	Phase II	27
	HSP90	HSP90 inhibitor (IPI-504)	Phase III	28
DFSP	PDGFR	Imatinib	Phase II Registered in some countries	29,30
Ewing's family tumours	IGF-1R	IGFR1 mAb	Phase II	31,32
	mTOR	mTOR inhibitor	Phase II	33
Rhabdomyosarcoma	IGF-1R	IGFR1 mAb	Phase II	32
	mTOR	mTOR inhibitor	Phase II	
Desmoplastic small blue round cell tumour	IGF-1R	IGFR1 mAb	Phase II	32
Angiosarcoma	VEGF	Bevacizumab	Phase II	34
		Sorafenib	Phase II	35,36
Synovial sarcoma	HER-2	Trastuzumab	Phase II	37
Soft tissue sarcomas	IGF-1R	Multiple	Phase II	32
	Multi-TKI	Sunitinib	Phase II	38
	VEGF	Bevacizumab	Phase I/II	39
	Multi-TKI	Sorafenib	Phase II	40,41
	Multi-TKI	Pazopanib	Phase II	42
	mTOR	mTOR inhibitors	Phase III	40
Haemangiopericytoma	VEGF	Bevacizumab	Phase I	43
Giant cell tumor	RANK-RANKL	Denosumab	Phase II	44

mAb = monoclonal Ab

upstream and downstream from mTOR itself. As potential therapeutic agents, mTOR inhibitors such as rapamycin, temsirolimus (CCI-779), everolimus (RAD-001) and deferolimus (AP23573) are being evaluated in various clinical trials. A pre-clinical study demonstrated that rapamycin blocked the proliferation of Ewing's sarcoma cell lines, indicating that mTOR signalling is central to the biologic mechanisms of Ewing's sarcoma growth.[54] Early clinical studies have demonstrated promising results in refractory sarcomas (table 2). There has been a recent comprehensive review about mTOR inhibition in sarcoma.[61] Plans are also underway to evaluate the efficacy of combining an mTOR and IGF1 receptor inhibitor in refractory EFT.

Rhabdomyosarcoma

Rhadmomyosarcomas, thought to be derived from primitive skeletal mesenchymal cells, are the most common soft tissue sarcomas in children.[62] Subtypes include embryonal (60%, better prognosis) and alveolar (20%, worse prognosis). IGF-2 is known to be overexpressed in rhadmomyosarcomas; this autocrine IGF-2 loop involves mTOR as a downstream signalling pathway.[63] A rhabdomyosarcoma xenograft model has demonstrated anti-tumour activity by the inhibition of the IGF-1R signalling pathway using the mTOR inhibitor temsirolimus.[64] The effect of monoclonal antibodies to IGF1R on the growth of rhadmomyosarcomas will be evaluated in a current international Phase II co-operative group trial being co-ordinated by the Sarcoma Alliance for Research through Collaboration.

Way forward

In clinical practice there has been an escalation of the use of targeted agents in trials and routine practice in the 21st century. Many new drugs are promiscuous in that they inhibit multiple kinase pathways, rather than specifically blocking a particular biological pathway. Some agents which are currently undergoing clinical trials for sarcoma therapy are outlined in table 2.

Awareness of the relevance of a specific pathway which predominantly drives tumour growth allows targeting of that pathway. In the broader world of oncology, growth factors such as EGFR, VEGF and PDGF and their receptors are involved in the activity of many tumours. However, outcomes as impressive as those seen for gastrointestinal stromal tumours and dermato-fibrosarcoma protruberans are not always seen, often

Table 3: *Selected chromosomal translocations in sarcomas*

Sarcoma type	Translocation	Effect of translocation
Ewing's/PNET	t(11;22) (80-85%) t(21;22) t(7;22) t(2;22) t(17;22)	EWS-FL1 translocation: some variants associated with more favourable prognosis. FL1 acts as transcription factor.
Rhabdomyosarcoma (alveolar)	t(2;13) t(1;13)	PAX-FOX01a gene fusion. Encodes chimeric transcription factor. Fusion status correlates with clinical outcome.
DFSP	t(17;22)	Fusion of collagen 1 type 1a and PDGFb.
Synovial sarcoma	t(X;18)	Biology of fusion product not well known –?transcription co-factor.
Clear cell sarcoma	t(12;22)	EWS-ATF1
Myxoid liposarcoma	t(12;16) t(12;22)	CHOP-EWS/CHOP-TLS fusion product.
Desmoplastic small round-cell tumour	t(11;22)	EWS-WT1

because in most solid tumours, multiple pathways involved in tumour growth are likely to exist. The inhibition of only one of these pathways may therefore not be adequate in stopping that tumour's most critical mechanisms for growth. Perhaps this is because in some circumstances we are yet to find the unique 'switch' that is the key driver of the oncogenic process. Alternatively, the stroma or micro-environment of the tumour may also need to be considered, given the important role they play, as the milieu that tumour cells exist within; targeting these as well may prove to be particularly important.

It can be particularly difficult when pre-clinical evidence demonstrates the likely utility of targeting a particular pathway, to move to 'proof-of-concept' trials where a tumour is rare. Although the Phase III clinical trial remains the 'gold standard' for proving efficacy, this may be difficult to perform for tumours such as rhabdomyosarcoma or desmoplastic small blue round cell tumours, where the incidence is low. More realistically, the efficacy of targeted agents for these tumours may need to be shown in carefully selected cohorts of patients from international collaborations. This highlights the need for collaboration between expert centres in the development of novel agents for many sarcoma subtypes.

Since imatinib was first used on compassionate grounds in 2000, the potential for developing effective new targeted therapies for other sarcoma subtypes has been successful. Further progress will now largely depend on ongoing collaborative efforts to better define sarcomas based on their molecular subtypes, with clinical trials adapted to deal with both the complexities and subtleties of assessing responses to modern biological therapies.

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TARGETED THERAPIES IN OVARIAN CANCER

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Abstract

Epithelial ovarian cancer is a challenging disease to treat, with the majority of patients presenting with advanced disease. Despite aggressive surgical debulking and platinum-based chemotherapy, many patients ultimately relapse and die of their disease. There is a real clinical need to improve outcomes in ovarian cancer. The last decade has seen the emergence of a number of targeted therapies that have been incorporated into the management of common malignancies such as breast, colon and lung cancer. Recently, Phase III trials of targeted therapies, including bevacizumab, cediranib and erlotinib, have commenced in ovarian cancer following encouraging Phase II results. The potential role of targeted therapies will be established in this disease over the coming years.

Ovarian cancer is the most common cause of death from gynaecological malignancies in Australia.[1] The majority of patients with epithelial ovarian cancer have advanced disease at presentation, with spread throughout the peritoneal cavity. Despite aggressive surgical debulking and platinum-based chemotherapy, the five year disease free survival rate is approximately 20-25% for these patients.[2-4] In an effort to improve outcomes several strategies have been tested.

The addition of a third non-cross resistant chemotherapy with either an anthracycline, gemcitabine or topotecan has not improved outcomes compared to standard treatment with carboplatin and paclitaxel.[5,6] Maintenance chemotherapy involves extending treatment, generally with a less intense regimen after a favourable response to chemotherapy. Although one trial (SWOG9701/GOG178) found an improved progression-free survival with paclitaxel given monthly for 12 months, compared with three months after standard chemotherapy, other maintenance/ consolidation trials failed to confirm this benefit.[7-10] Intensifying treatment with high-dose chemotherapy and peripheral stem cell support did not result in a progression-free or overall survival advantage compared with standard treatment.[11]

The preliminary results of the JCOG3016 trial were presented at the 2008 American Society of Clinical Oncology (ASCO) meeting. This compared standard chemotherapy with conventional dose carboplatin and paclitaxel versus carboplatin and weekly paclitaxel. There was a significant improvement in progression-free survival. Overall survival data is immature with median survival not yet reached in either arm.[12]

The three largest randomised Phase III trials of intraperitoneal chemotherapy for patients with optimally debulked disease have suggested an additional benefit for the inclusion of an intraperitoneal component of delivery.[4,13,14] One of the main concerns associated with intraperitoneal chemotherapy is the associated toxicity, with over half of patients unable to complete planned treatment. Based on current data, there is considerable controversy as to whether this should constitute standard therapy.[15] An intraperitoneal regimen with more acceptable toxicity profile is needed.

Recently there has been considerable interest in exploring targeted therapies in epithelial ovarian cancer. The most promising agents to emerge include the anti-angiogenic agents and Poly ADP-ribose polymerase (PARP) inhibitors. This review will focus on agents that have entered Phase II and III clinical trials (see tables 1 and 2).

Anti-angiogenic agents

Vascular endothelial growth factor (VEGF) has been shown to be associated with tumour progression and ascites formation in ovarian cancer. The majority of invasive ovarian cancers express VEGF.[36] Several studies have correlated high intratumoural microvascular density and elevated VEGF expression with poor prognosis in ovarian cancers.[37-40] In animal models, blocking VEGF has been found to inhibit ascites formation.[41] Thus there is a strong rationale for targeting VEGF and its receptors in ovarian cancer.

Bevacizumab

Bevacizumab is a humanised anti-VEGF monoclonal antibody. Two Phase II trials in recurrent epithelial ovarian cancer and primary peritoneal cancer have confirmed the single-agent activity of bevacizumab. The response rates seen compare favourably to other malignancies such as colon and breast cancer which have Therapeutic Goods Administration approval.

A study by the Gynecology Oncology Group (GOG170-D) treated 62 patients with bevacizumab 15mg/kg IV every three weeks. The majority of patients (66.1%) had received two prior chemotherapy regimens and 41.9% were platinum resistant. The overall response rate was 21% (including two patients with a complete response). The progression-free survival rate at six months was 40.3%.[16]

Cannistra and colleagues also used this schedule.[17] They treated 44 patients, all of whom were platinum-resistant. Additionally, all patients had progressed during or within three months of receiving either topotecan or liposomal doxorubicin. Patients were heavily pre-treated, with 47.7% having received three prior chemotherapy regimens. This trial initially planned to enrol 120 patients, but was discontinued early due to safety concerns, with 11.4% of patients experiencing

Table 1: *Adjuvant trastruzumab trials in operable breast cancer.*

Study	N	Schedule	Patient population	Response
Bevacizumab				
Burger MA et al.[16] (2007)	62	15 mg/kg every 3 weeks	Platinum sensitive and resistant. 1-2 prior chemotherapy lines.	21%
Cannistra SA et al.[17] (2007)	44	15 mg/kg every 3 weeks	Platinum resistant. Up to 3 prior chemotherapy lines.	15.9%
Aflibercept (AVE0005)				
Tew WP et al.[18] (2007)	162	2 mg/kg or 4 mg/kg every 2 weeks	Platinum resistant. Liposomal doxorubicin or topotecan resistant. 3-4 prior chemotherapy lines.	8% †
Cediranib (AZD2171)				
Hirte HW et al.[19] (2008)	60	45 mg daily (reduced to 30 mg)	Platinum sensitive and resistant. 1 prior chemotherapy.	NR †
Matulonis UA et al.[20] (2008)	29	45 mg daily (reduced to 30 mg)	Platinum sensitive and resistant. Up to 3 prior chemotherapy lines.	18.5% †
Sunitinib (SU11248)				
Biagi JJ et al.[21] (2008)	17	50 mg daily for 4 of 6 weeks	Platinum sensitive and resistant. 1-2 prior chemotherapy lines.	11.8% †
Sorafenib (BAY 43-9006)				
Matei D et al.[22] (2008)	73	400 mg bd daily	Platinum sensitive and resistant. 1-2 prior chemotherapy lines.	3.4% †
Pazopanib (GW786034)				
Friedlander M et al.[23] (2007)	17	800 mg daily	Platinum sensitive and resistant. 1-2 prior chemotherapy lines.	47% Ca125 response †
Erlotinib (OSI-774)				
Gordon AN et al.[24] (2005)	34	150 mg daily	EGFR +ve tumours.	6%
Gefitinib (ZD 1839)				
Posades EM et al.[25] (2007)	24	500 mg daily	No limit on prior chemotherapy.	0%
Schilder RJ et al.[26] (2005)	27	500 mg daily	Platinum sensitive and resistant. 1-2 prior chemotherapy lines.	4%
Cetuximab (C225)				
Schilder RJ et al.[27] (2007)	25	400 mg/m2 bolus then 250 mg/m2 for two 3 week cycles	EFGR +ve tumours. 1-2 prior chemotherapy lines.	4%
Matuzumab (EMD72000)				
Seiden MV et al.[28] (2007)	37	800 mg weekly	EFGR +ve tumours. No limit on prior chemotherapy.	0%
Pertuzumab (rhuMAb 2C4)				
Gordon MS et al.[29] (2006)	123	840 mg loading then 420 mg or 1050 mg every 3 weeks	28.6% HER2 +ve ELISA. Platinum sensitive and resistant. No limit on prior chemotherapy.	4.3%
Trastuzmab				
Bookman MA et al.[30] (2003)	41	4 mg/kg loading then 2 mg/kg weekly	HER 2 IHC 2+ or 3+. No limit on prior chemotherapy.	7.3%
Imatinib				
Posades EM et al.[31] (2007)	23	400 mg daily bd (reduced to 600mg daily)	Up to 4 prior chemotherapy lines.	0%
Alberts DS et al.[32] (2007)	19	400 mg daily	Expressed kit (CD117) or PDGFR. Platinum resistant. 1 prior line of chemotherapy.	0%
Coleman RL et al.[33] (2006)	16	600 mg daily	Over-expressed one of c-kit, PDGFR of c-Abl. Platinum resistant.	0%
Ovegovomab				
Ehlen TG et al.[34] (2005)	13	2 mg weeks 0,2,4,8,12 then 3 monthly	1 or more prior chemotherapy lines.	0%
CGP 69846A				
Oza AM et al.[35] (2003)	22	4mg/kg/day for 21 days every 28 days	1-2 prior chemotherapy lines.	0%

† Preliminary results reported only for patients evaluable for response.

gastrointestinal perforations. The overall response rate was 15.9%. A further 25% achieved stable disease for greater than three months. On review, all five patients with perforations had received three prior regimens and had radiological evidence of bowel involvement.[17]

Bevacizumab 10mg/kg every two weeks and cyclophosphamide 50mg daily were evaluated in 70 patients with recurrent epithelial ovarian cancer. Patients may have received up to three prior regimens and 60% were platinum-sensitive. The overall response rate was 24%. Progression-free survival at six months was 56%. The incidence of gastrointestinal perforation was 6%.[42]

Ongoing Phase II studies are investigating bevacizumab in combination with chemotherapy and other targeted agents. There are currently three large Phase III trials underway incorporating bevacizumab into first and second-line treatment: GOG 218, ICON 7 and GOG 213 (table 2). Each of these trials is studying bevacizumab in combination with chemotherapy, including carboplatin and a taxane followed by maintenance. If these trials are positive, the relative benefit of bevacizumab with chemotherapy, or as maintenance, will be difficult to separate. The GOG 218 trial has a third arm, which will provide some information on the relative benefit of the maintenance component of therapy.

Aflibercept (AVE0005) VEGF Trap

VEGF Trap is a fusion protein composed of the extracellular domains of human VEGFR1 (domain 2) and VEGFR2 (domain 3) fused to IgG1 Fc molecule. This binds to all VEGF-A isoforms and placental growth factor. This antibody binds VEGF with high affinity, interfering with binding and subsequent activation of native receptors.

The preliminary results of a double-blinded randomised Phase II trial evaluating aflibercept at 2mg/kg every two weeks, or 4mg/kg every two weeks in recurrent epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer, were presented at the 2007 ASCO meeting. Efficacy data was available on the 162 patients. All received three to four prior chemotherapy regimens and were platinum resistant. Additionally, patients had documented resistance to either liposomal doxorubicin or topotecan. The pooled blinded data demonstrated a response rate of 8% by Response Evaluation Criteria in Solid Tumours (RECIST) criteria and 13% with Ca125 declines. Forty-one per cent had maintained either partial response or stable disease at 14 weeks. Ascites was present at baseline in 23 patients, of whom 29% had complete disappearance of ascites and in a further 54% there was no increase. The most common toxicity was hypertension (18%, grade 3/4). Two patients have had bowel perforation.[18]

Phase II studies in ovarian cancer are ongoing, including one trial which is comparing aflibercept versus placebo in patients with recurrent symptomatic ascites.

Cediranib (AZD2171)

Cediranib is a highly potent inhibitor of VEGFR2, VEFGR1, VEGFR3, platelet derived growth factor receptor (PDGFR) and C-KIT. The preliminary Phase II results for two trials were presented at the 2008 ASCO meeting. Both trials are now closed to recruitment and final data is awaited. Patients included both platinum-sensitive and platinum-resistant. In both trials the initial dose of 45mg daily was subsequently reduced to 30mg daily due to cardiovascular toxicity and hypertension. The most common grade 3 or 4 toxicity included

Table 2: *Ongoing Phase III trials.*

Study	N	Patient population	Study Arms	Endpoint	Status
GOG 218	2000	First line Stage III and IV Sub-optimal debulking	I. Paclitaxel, carboplatin and placebo x 6 then placebo for up to 22 cycles. II. Paclitaxel, carboplatin and bevacizumab x 6 then placebo for up to 22 cycles. III. Paclitaxel, carboplatin and bevacizumab x 6 then bevacizumab for up to 22 cycles.	OS	Open
ICON 7	1520	First line High risk Stage I and II-IV	I. Paclitaxel and carboplatin x 6. II. Paclitaxel and carboplatin and bevacizumab x 6 then bevacizumab for up to 12 cycles.	PFS	Open
GOG 213	660	First relapse Platinum-sensitive Secondary cryoreduction	I. Paclitaxel (or docetaxel) and carboplatin x 6 – 8. II. Paclitaxel (or docetaxel) and carboplatin and bevacizumab x 6 - 8 then bevacizumab until PD.	OS	Open
ICON 6	2000	First relapse Platinum-sensitive	I. Paclitaxel, carboplatin and placebo (daily) x 6 then placebo (daily) for up to 18 months. II. Paclitaxel, carboplatin and cediranib (daily) x 6 then placebo (daily) for up to 18 months. III. Paclitaxel, carboplatin and cediranib (daily) x 6 then cediranib (daily) for up to 18 months.	OS	Stage I Open
EORTC 555041	830	Following first line platinum-based chemotherapy High risk Stage I and II-IV	I. Erlotinib (daily) for up to 2 years. II. Observation.	PFS	Closed to recruitment

OS Overall survival; PFS Progression-free survival

hypertension and fatigue. No bowel perforations have been seen in either study.[19,20]

ICON 6 is a placebo-controlled trial randomising patients with platinum-sensitive ovarian cancer at first relapse to one of three arms (table 2). This trial will be conducted in three stages and has opened with an interim safety analysis planned after the first 50 patients.

Other small molecule multi-targeted tyrosine kinase inhibitors

The preliminary Phase II results have been presented for three agents, sorafenib, sunitinib and pazopanib, as summarised in table 1. Each trial included patients with platinum-sensitive and platinum-resistant disease and one or two prior treatments were permitted. Activity for each of these agents appears promising, however it is too early for meaningful comparison between these agents or with the other VEGF inhibitors.[21-23] Ongoing Phase II trials are also investigating these agents in combination with chemotherapy.

Other drugs with anti-angiogenic activity that have entered Phase II clinical trials in ovarian cancer include: the multi-targeted tyrosine kinase inhibitors AMG 706, Vandetanib (ZD 6474), XL999 and BIBF1120; a VEGFR-2 inhibitor, CP-547632; and a protein kinase Cß inhibitor Enzastaurin (LY317615).

Poly ADP-ribose polymerase inhibitors

Germline mutations in BRCA1 and BRCA2 are associated with an increased risk of developing ovarian cancer. A Canadian study found BRCA mutations in 13.2% of 1171 unselected patents with an incident ovarian cancer diagnosis. For patients with serous pathology this increased to 18%.[43]

BRCA deficient cells are unable to repair endogenous DNA damage via homologous recombination and rely on base excision repair. PARP inhibitors inhibit base excision repair, thereby leaving BRCA1 and BRCA2 deficient cells susceptible to apoptosis from increased DNA damage.

AZD2281 (KU-0059436)

The first Phase I trial of this agent was reported at the 2007 ASCO meeting. Updated results for 50 patients with ovarian cancer and BRCA mutations were presented in 2008. This analysis included 11 patients in the dose escalation stage and 39 patients in the second expansion phase treated at 200 mg bd. Patients were platinum-sensitive (n=10), platinum-resistant (n=27) or platinum-refractory (n=13). The medium number of prior treatments was three (range 1-8). The combined results found a 28% response rate by RECIST criteria and 39% by GCIG Ca125 criteria. There were increased responses seen in the platinum sensitive group, however responses were seen across each category.[44]

Phase I and II trials are ongoing, including combining AZD2281 with chemotherapy. Two other PARP inhibitors, AG014699 and BSI-201, have recently commenced Phase II studies in patients with BRCA mutations and ovarian cancer.

Epidermal growth factor receptor inhibitors

Epidermal growth factor receptor (EGFR) over-expression has been documented in ovarian cancer, however there is wide variability in the frequency this is reported. Activating mutations of EGFR are rarely identified in ovarian cancer.[45,26]

Erlotinib and gefitinib are small molecular inhibitors of EGFR (HER 1). Small Phase II trials in patients with recurrent ovarian cancer have not documented significant activity.[24-26] One study with erlotinib in heavily pre-treated platinum-refractory patients, found that patients who developed a rash survived significantly longer than patients who did not.[24] Ongoing Phase II studies are combining these agents with chemotherapy and other target therapies.

EORTC 55041 is a randomised trial of maintenance erlotinib for up to two years versus observation in patients with high risk stage I and stage II-IV epithelial ovarian cancer, fallopian tube and primary peritoneal cancer, who either responded or had stable disease after first line platinum-based chemotherapy. This trial completed accrual in February 2008.

Cetuximab and matuzumab are humanised anti-EGFR (HER 1) monoclonal antibodies. Eligibility for these Phase II studies included EGFR-positive tumours. Each of these agents as monotherapy has failed to demonstrate significant activity.[27,28] Two Phase II trials of cetuximab with platinum-based chemotherapy have shown that although combination therapy is tolerable, compared to historical data there was no increase in progression-free survival.[46,47]

Human epidermal growth factor receptor 2 (HER2) inhibitors

Pertuzumab and trastuzumab are monoclonal antibodies that bind the HER2 preventing dimerisation with other HER molecules, thereby preventing activation and blocking downstream signals. In the trial of trastuzumab that included only patients with HER 2 positive tumours, of 837 patients screened, 11.5% were found to have HER 2+ and 3+ tumours as assessed by immunohistochemistry. Phase II trials have shown minimal activity.[29,30] Trials of pertuzumab with chemotherapy continue, with preliminary reports confirming such combinations are well tolerated.[48,49]

Several Phase II studies of the agent lapatinib, which is a dual inhibitor of EGFR and HER2, either as a single agent or in combination with chemotherapy are ongoing.

Platelet derived growth factor receptor inhibitors

Imatinib is an inhibitor of C-KIT and PDGFR. Three small phase II trials, two of which enrolled patients with documented over-expression of either C-KIT of PDGFR, did not demonstrate activity in patients with relapsed disease.[31-33]

Ca125

Oregovomab is a fully murine antibody specific for the Ca125 antigen. Two Phase II studies demonstrated that

patients who mounted an immune response after infusion of oregovomab, may experience prolonged disease stabilisation or an improved survival.[34,50]

A Phase III trial of oregovomab in patients with stage III/IV ovarian cancer, who have had a favourable response to chemotherapy, was presented at the 2008 ASCO meeting. Oregovomab was used as maintenance after chemotherapy with a 2:1 randomisation of oregovomab placebo (249:118). The primary endpoint was progression-free survival. There was no difference in progression-free survival between the two treatment arms. Patients who failed to mount an immune response had a worse prognosis.[51] Ongoing trials of this agent have been discontinued.

Folate receptor alpha inhibitor

Folate receptor alpha is over-expressed on the majority of patents with epithelial ovarian cancer.

MORAb-003 is a humanised monoclonal antibody against folate receptor alpha. An ongoing Phase II trial is evaluating the efficacy of MORAb-003 at first relapse with platinum sensitive ovarian cancer. Patients with symptomatic relapse also received concurrent chemotherapy with a platinum and taxane. The preliminary results from 52 patients have suggested activity with 100% normalisation of Ca125 in patients who received chemotherapy and three of eight patients with a second remission greater than the first.[52]

c-raf kinase inhibitor

One Phase II trial of a c-raf kinase inhibitor failed to demonstrate clinical activity.[35]

Other potential targets

There are a number of other targeted therapies that have commenced Phase II trials in ovarian cancer. These include: temsirolimus (CCI-779), a mammalian target of rapamycin (mTOR) inhibitor; ionafanib, a farnesyl transferase inhibitor; AZD6244, a mitogen-activated extracellular signal regulated protein kinase (MEK) inhibitor; AZD0530, dual inhibitor of SRC and ABL protein tyrosine kinases; and catumaxomab, an antibody to human CD3 and human epithelial cell adhesion molecule (EpCAM).

Conclusion

The potential role for targeted therapies in ovarian cancer will be established over the next five to 10 years and already there are a number of Phase III clinical trials underway.

Bevacizumab and other agents that target VEGF or its receptor have demonstrated activity in both platinum-sensitive and platinum-resistant disease. It remains to be determined whether there is an additional benefit for combining bevacizumab or cediranib with chemotherapy, above chemotherapy alone, for first or second line therapy.

At present, there is no effective maintenance strategy for patients following chemotherapy. With the exception of one trial with paclitaxel, other maintenance trials have not demonstrated an improvement in progression-free survival nor overall survival, and increased toxicity has been reported. Ongoing Phase III trials are testing three agents, bevacizumab, cediranib and erlotinib in this setting. With the exception of the EORTC 00541 trial, maintenance treatment will follow the combination of chemotherapy with the investigational agent. The GOG 218 will provide some information as to the relative effect of bevacizumab in combination with chemotherapy, and then as a maintenance therapy.

Each of these trials has a quality of life component incorporated. This is extremely important when we consider that patients who may have few or no disease related symptoms after chemotherapy, may remain on maintenance therapy for extended periods.

Early results with PARP inhibitors are promising and have entered Phase II trials. At present these trials are recruiting an enriched population with known mutation in BRCA1 or BRCA2. In addition, these agents theoretically have the potential to have a synergistic effect with chemotherapy by inhibiting mechanisms of DNA repair. If efficacy is confirmed in mutation-positive patients, then testing on a wider ovarian cancer population would be worthy of evaluation.

Ongoing translational research projects should continue to be incorporated into clinical trials to further our understanding of the mechanisms that drive tumour growth, as well as identify potential predictive factors for response to new investigational agents.

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ARTICLES

CANCER COUNCIL AUSTRALIA'S STUDENT ESSAY COMPETITION

Cancer Council Australia's annual essay competition is open to Australian residents enrolled in a medical course in an Australian university. Students are required to submit an essay on an issue related to cancer control. In 2008, the topic was 'Cancer: Prevention is Better than Cure.' The essays are judged by members of Cancer Council Australia's Oncology Education Committee.

This article is the winning essay by Sonakshi Sharma. As the winner, Sonakshi attended the World Health Organisation's Collaborating Centre for Cancer Education's International Summer School, 'Oncology for Medical Students,' in The Netherlands in July 2008.

CANCER: PREVENTION IS BETTER THAN CURE

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"When meditating over a disease, I never think of finding a remedy for it, but, instead, a means of preventing it."

Louis Pasteur (1822–1895)

Cancer treatment breakthroughs have generated significant media coverage for several decades. Fuelling the fervent community desire for a 'magical' cure for cancer, media articles have incessantly spoken of numerous impending discoveries in cancer treatment. Yet sadly, no significant cure has materialised. Meanwhile, the incidence of cancer in Australia has steadily increased by 36% between 1990 and 2000.[1] Considering the aging population, the total number of new cases of cancer is projected to rise by yet another staggering 31% between 2001 and 2011.[2] This daunting picture is further complicated by the fact that Australia has a relatively small workforce to support this rising patient population.[3]

Dealing with this unprecedented challenge in cancer control therefore requires a new approach. Owing to the tremendous impact of modifiable factors on cancer risk, it has been estimated that at least one-third of all cancers are preventable.[4] Cancer prevention is defined as the reduction of cancer mortality through a reduction in the incidence of cancer.[5] This involves reducing exposure to modifiable risk factors, along with population-based screening to allow early detection of pre-cancerous lesions. The success of prevention campaigns is evident from the prevention of more than 17,000 premature deaths in 1998 due to a range of successful tobacco control measures initiated in the 1970s.[6] The decline in the incidence and mortality of cervical cancer due to early detection of pre-cancerous abnormalities by Pap smears is an additional example of an effective intervention at the population level.[1] Furthermore, according to the World Health Organisation, prevention offers the most cost effective long-term strategy for the control of cancer.[4] Therefore, the future of cancer control in Australia lies not in the discovery of an elusive cure, but in a national commitment to prevention, with a rebalancing of the focus, as well as the funding of research.

"The broad goal, of course, is to end the disease. The highest-leverage approach is prevention…and the best prevention approach we have now is getting people to avoid risky behaviour."
Bill Gates 2007[7]

This essay will analyse the common modifiable risk factors for cancer and the existing and emerging preventative strategies in Australia, and the associated population-based screening programs.

Modifiable risk factors and cancer screening

Tobacco

With regards to modifiable risk factors, the most consistent finding over decades of research is the strong association between tobacco use and cancer.[5] Smoking contributes to 12% of all cancers in Australia, causing over 90% of lung cancers in addition to a large range of other malignancies.[3] The cancer risk is dose-related: longer duration and heavier consumption

patterns increase the likelihood of developing cancer. This has specific implications for the Australian youth. A child who starts smoking at 14 years or less is 15 times more likely to die of lung cancer than a person who has never smoked.[8] Given that eight out of 10 people take up smoking before the age of 18 and may remain addicted for life,[3,9] reducing the prevalence of tobacco use in the young population has been one of the major targets of cancer prevention policies in Australia. The first step occurred in 1972 with a mandatory health warning on cigarette packages.[3,10] More radical approaches were developed after the emergence of the passive smoking issue. Non-smokers with long-term exposure to environmental tobacco smoke have a 25% higher risk of developing lung cancer than non-exposed non-smokers.[11] This resulted in the announcements of smoke-free policies in all enclosed licensed premises including pubs and clubs.[12]

In addition, there have been graphic public education campaigns such as the National Tobacco Campaign and support services and Quit lines have been made available to assist after the decision to quit has been made.[3] Other major developments have included bans on most forms of tobacco advertising (under the Tobacco Act 1987) with a rise in the price of cigarettes, restrictions on sales to minors and the use of graphic health warnings on all tobacco products.[3,9-10] As a result, the smoking prevalence of adult Australians has consistently declined to a daily smoking rate of 17.4% in 2004 for smokers aged over 14 years of age.[13] The incidence rate for men of cancers attributable to smoking fell by an average of 1.4% per year, while the rate for women rose by 0.7% per year between 1991 and 2001. The increase is predominantly in females aged 65 years and over, while rates in younger women have generally remained stable or fallen.[4] Furthermore, in terms of cost-effectiveness, the returns have been enormous, with the $176 million spent on anti-smoking campaigns over 30 years delivering $8.6 billion in benefits.[13]

Although there has been an incremental reduction in smoking prevalence in Australia, 17.4% of Australians still continue to smoke and hence face a significant yet avoidable cancer risk.[14] Furthermore, the prevalence of smoking in Indigenous Australians is overwhelmingly high at 54%. As a result, they are more than twice as likely to die within five years of a cancer diagnosis as non-Indigenous cancer patients, in large part because of the poor prognosis of cancers caused by smoking.[3] Thus, there is still room for improvement. In fact, estimates based on recent trends indicate that if adequate resources are committed to tobacco control in Australia, the smoking prevalence can be lowered by a further 1% per annum.[6] Steps are already being taken in this direction. The Victorian Government has announced an additional $5.6 million of funding for anti-smoking marketing campaigns to further reduce adult smoking rates in Victoria to 14% by 2013.[15] The Rudd Government has introduced a $14.5 million plan to cut smoking rates in Indigenous communities.[16] Some other strategies that can be implemented include a national production of health warning labels on cigarette packs in the Aboriginal language, as was done in Nhulunbuy Miwatj Health service in 1998.[17] There are clearly new opportunities being developed to target smoking and reducing smoking prevalence now that would lead to significantly fewer overall cancer diagnoses in the longer-term future.

Human Papillomavirus (HPV) and cervical cancer

Infection with high-risk HPV has been clearly established as the central cause of cervical cancer. Currently, early identification and treatment of pre-cancerous abnormalities associated with persistent HPV infection is the best protection against the disease.[3-5] Routine screening with Pap smears has been the main focus of the National Cervical Cancer Screening Program in Australia. As a result of this screening, between 1991 and 2001 the incidence rates of cervical cancer have almost halved among women aged 20 to 69 and the mortality rates are among the lowest in the world, demoting cervical cancer to the 13th most common cancer in women in Australia.[3,18-19]

Nevertheless, there is tremendous potential for improvement given that the aged standardised participation rate in 2003-04 for women aged 20 to 69 years was only 60.7%. Recruiting unscreened women to the program still remains a priority.[20] This is especially true for the Indigenous populations with numbers never screened, ranging from 20–64%. Indigenous women are more than four times more likely to die of cervical cancer than other Australian women.[20] Participation may be enhanced by using strategies such as Aboriginal community involvement in planning and delivery of screening programs and gender-sensitive provision of culturally appropriate services by GPs. Given that approximately 80% of Pap tests are taken by GPs, the Australian Government introduced a cervical screening practice incentive payment in 2001 to support general practices to enhance cervical cancer screening, with 91.7% of practices in Australia signed on to participate by 2006.[3] Other initiatives should address issues such as reduced access to services. For example, in Queensland a network of 13 specially trained mobile women's health nurses has been established to provide preventive health services such as cervical cancer screening to women in rural/remote areas.[21]

A major development in the prevention of cervical cancer has been the introduction of a vaccine designed to prevent two of the most common types of high-risk HPV (HPV 16 and 18), which are responsible for 70% of cervical cancers. This vaccine has been shown to be 100% effective against these HPV strains. However, as the vaccine does not protect against all types that cause cervical cancer, vaccinated women should still have regular Pap tests. Furthermore, vaccinating Aboriginal women will help lower the incidence and mortality from cervical cancer in these populations. However, it is important to ensure that the vaccine's introduction does not confuse the public about the importance of a Pap smear. Successful implementation of the vaccination program requires education of the general public about HPV and the need for Pap smears, de-stigmatising HPV infection and gaining acceptance for vaccinating adolescents for a sexually transmitted infection before their sexual début.[3,22-24] While the National Cervical

Screening Program has been effective at reducing cervical cancer incidence and mortality, the vaccine offers the potential to further decrease the incidence of and mortality from this disease in a cost-effective manner.

Diet, physical activity and obesity

In Australia, more than 6000 deaths from cancer each year are attributable to three major risk factors: inadequate intake of fruit and vegetables; inadequate physical activity; and overweight or obesity. In fact, it is estimated that 11% of colon cancer and 9-11% of post-menopausal breast cancer can be attributed to overweight and obesity.[3,9] Between 1985 and 1995 the level of combined overweight/obesity in the Australian people more than doubled.[25] This rate is even higher in the Indigenous population.[3] To achieve and maintain a healthy weight, the Cancer Council recommends adults undertake 30 minutes of physical activity on most days of the week. Individuals who are physically active can reduce their risk of developing breast cancer by 20 to 30% and colorectal cancer by 30 to 40%. Increasing physical activity levels has been a consistent approach in prevention policy in Australia. *Be active Australia: a framework for health sector action for physical activity,* is the current strategic framework for population-based physical activity promotion in Australia.[3]

In addition to obesity, diet also influences cancer risk.[26] Inadequate vegetable and fruit intake has been estimated to cause 11% of the total cancer burden, including colorectal and breast cancer.[3] It has been estimated that combined changes in diet and physical activity could reduce the incidence of colorectal cancer by 66% to 75%[27] and randomised trials have shown that breast cancer rates are lower in women who are on low fat diets.[28] In Australia, there have been several state-wide campaigns aimed at promoting increased consumption of vegetables and fruit.[3] These campaigns have been successful in improving public attitudes towards fruit and vegetables and some programs, such as the 'Go for 2&5' campaign in Western Australia, have also increased consumption.[3] Furthermore, Cancer Council Australia has recently developed a public health campaign called 'Avoid the Cure' which links these three elements with colorectal cancer prevention.[29]

Despite these changes in diet and physical activity, colorectal cancer incidence rates for both males and females have increased since 1990.[30] Because of its high prevalence, its long asymptomatic phase and the presence of a treatable pre-cancerous lesion, colorectal cancer ideally meets the criteria for screening.[31] Faecal occult-blood testing (FOBT) has been assessed for population screening in the Bowel Cancer Screening Pilot Program. Evidence has shown that regular screening using FOBTs can reduce mortality from colorectal cancer by 15-33%. FOBTs are also cheap, safe and acceptable to the population.[32] The Australian Government has allocated $13.4 million over three years from 2006-08 to phase in a nationally coordinated, population-based, bowel cancer screening program using FOBTs.[33] Combination of prevention measures, such as diet and physical activity with the National Bowel Cancer Screening Program, may help reduce the impact of bowel cancer in Australia.

Ultraviolet radiation

Skin cancer (non-melanoma and melanoma) is the most common and the most expensive cancer in Australia. Unprotected exposure to ultraviolet radiation is the single most important modifiable risk factor for skin cancer. Australia is recognised as having the most extensive, comprehensive and longest-lasting skin cancer prevention programs in the world, including the Slip! Slop! Slap! program in the early 80s and the SunSmart program since 1988.[3,34-35] These programs have resulted in changes in the attitudes, knowledge as well as behavior of the Australian people. Over 90% of Australian people recognise that skin cancer is dangerous and that they themselves are at risk of skin cancer.[34-35] Since SunSmart was launched, the proportion of Victorians who like to get a suntan has decreased from 61% in 1988 to 35% in 1998. There has been a 50% reduction in people getting sunburnt in the decade from 1988. Finally, clear evidence is now emerging that skin cancer incidence rates are beginning to plateau after decades of increase.[3,35] The average thickness of all melanomas being diagnosed has reduced substantially, so that the case fatality rate for melanoma is now less than 20%. Since 1990 the rate of death from melanoma in Australia has been relatively stable, but remains twice as high for men compared to women (generally older men). Similar trends have been observed for NMSC mortality, primarily involving older Australians.[34-35] This indicates that it is the younger population who have been influenced by the primary prevention programs in Australia. To improve these rates to include the entire population, continuing public and professional education is required with specific focus on the elderly. Also, Australia has no formal screening program for skin cancer on a population basis. Pilot programs for regular screening and research are needed to determine the cost-effectiveness of such a screening program.

Strategies to optimise cancer prevention in Australia

Evaluation of the literature above indicates that Australia has pioneered in the development of effective cancer prevention programs. In addition to the emerging strategies mentioned above, some recommended strategies include:

1. Preventing the uptake of smoking in teenage years by introducing a compulsory long-term educational unit on smoking and its effects in primary school, and continuing this unit until the end of high school. This may help induce an anti-smoking behaviour in children from a young age.
2. Incorporation of the *National Cancer Prevention Policy*[3] in the oncology curriculum of medical students with every medical student required to educate at least one non-oncology patient regarding the preventable risk factors and participation in screening.
3. Medical curriculum change whereby medical students who complete the 5th year in rural clinical school should communicate with a certain number of Indigenous women and other rural women regarding participation in screening.

Future of cancer prevention in Australia

The greatest potential gains for reducing cancer incidence and mortality are in primary prevention and early detection. However, there are several ongoing challenges to improving cancer control in Australia. These include the rising incidence of smoking-related cancers in older women and skin cancers in older men, along with poor cancer control in the Indigenous population. Despite these challenges, Australia has been very successful so far in reducing the incidence and mortality rates for several preventable cancers such as cervical cancer. With the introduction of population-based screening for bowel cancer, as well as the new HPV vaccine, Australia has the potential to further optimise the cancer prevention potential and hopefully lead to a future free of preventable cancers.

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AUSTRALIAN BEHAVIOURAL RESEARCH IN CANCER

Centre for Health Research and Psycho-oncology (CheRP), New South Wales

Sun protection and vitamin D deficiency: Are the messages getting mixed?

Vitamin D is produced endogenously following UV irradiation of precursors in the skin. Vitamin D deficiency and insufficiency have been implicated in a range of conditions including bone and skeletal diseases and the development of breast, prostate and colon cancers. If such links are confirmed, achieving vitamin D adequacy at a population-level could be an important disease prevention measure. However, it is important that the right balance is struck between recommending the public gets enough sun for vitamin D, but not too much as to cause skin cancers. CHeRP is embarking on two studies which will examine behavioural aspects of vitamin D deficiency.

Together with the Australian Sun and Health Research Laboratory in Queensland and the University of Sydney, School of Public Health, CHeRP is conducting a large cross-sectional survey of the community's understanding of vitamin D deficiency and the effect on protective behaviours. At four study sites in Australia (Townsville, Brisbane, Canberra, Hobart), a cohort of 1000 adults will be asked about their knowledge, attitudes and behaviours in relation to sun protection and vitamin D deficiency.

In the second study, over 500 GPs in New South Wales (NSW) will be asked to complete an online survey of their knowledge, attitudes and self-reported practices with regards to vitamin D deficiency diagnosis and management and sun protection advice.

It is intended this research will inform the development of suitable strategies for the general public and GPs for communicating balance for safe sun exposure.

Cancer survivors' preferences for lifestyle interventions

There are approximately 300,000 cancer survivors in Australia. These survivors are at increased risk for secondary cancers and for developing other chronic diseases. Reasons for this increased risk may be genetic, treatment-related, or related to behavioural risk factors (smoking, physical inactivity, poor diet, being overweight). However, little is known about Australian cancer survivors' interest in pursuing healthier lifestyle behaviours, nor their preferences for the delivery of related intervention programs.

We conducted telephone interviews with 114 survivors of breast, colorectal and prostate cancers selected via the *Cancer Survival Study*, a longitudinal study of cancer survivors recruited through the NSW and Victorian cancer registries. The interviews assessed: survivors' current lifestyle-related behaviours (diet, physical activity, smoking); receipt of provider advice regarding lifestyle changes since their diagnosis; and preferences for the content, timing and delivery mode (face-to-face, telephone, mailed, computer, DVD) of lifestyle interventions.

In general, survivors were not meeting lifestyle recommendations. Only a third of survivors recalled being advised to make lifestyle changes in relation to their cancer diagnosis. There was a high level of interest in lifestyle programs. Participants suggested programs be offered at diagnosis and upon completion of treatment. The most popular delivery mode was written materials and the least popular was telephone delivered. Males tended to prefer programs delivered by DVD and the internet, whilst females indicated a preference for individual face-to-face counselling.

These results will help inform future health promotion efforts to deliver health behaviour interventions to the growing number of Australian cancer survivors.

Behavioural Research and Evaluation Unit (BREU), South Australia

In addition to other ongoing evaluations and research run by the Behavioural Research and Evaluation Unit (BREU) in South Australia, results were recently reported for several key studies.

Pack and advertising displays at point-of-sale

BREU recently published a study of 2026 South Australian adults highlighting that 63% of the community approved of a hypothetical total ban on cigarette displays at the point of purchase, with over three-quarters believing this should happen in the next 12 months. Results also showed that a further 24% believed that cigarette displays should be restricted and 82% would approve of a ban on displays in stores that sell confectionary. Only 7% of adult smokers reported making their decision about the brand of cigarettes to buy at the point of purchase and 90% made their decision before they even entered the shop.

The results strengthen arguments that cigarette displays are not necessary to maintain brand loyalty or to encourage brand switching of established smokers. Instead, the results make arguments more credible that

cigarette displays normalise and promote smoking among young people and may also promote unplanned purchase or increased consumption among less frequent or former smokers.

Smoke-free cars legislation

On 31 May 2007, South Australia (SA) was the first jurisdiction in Australia to implement legislation banning smoking in cars when children under the age of 16 years are present. Two random representative telephone surveys were conducted with the SA community including a pre-legislation survey of 1975 adults and a post-legislation survey of 1877 adults. Community support was high pre-legislation and further increased post-legislation. The majority of smokers reported it would make no difference to their consumption. An added benefit was that a small but significant minority indicated that it may encourage them to smoke fewer cigarettes overall or to quit altogether. Overall, the law appeared popular with the SA community and hopefully these findings will encourage other jurisdictions to adopt similar legislation.

Progress against the SA Tobacco Control Strategy

In June 2008, BREU released the annual report *Progress against the South Australian Tobacco Control Strategy 2005-2010,* including data reported from a statewide, face-to-face survey of 2398 South Australians. This report shows tracking of key indicators in tobacco control in SA over time. Smoking prevalence among adults aged 15+ years was found to be 21% in 2007 and was not significantly different than 2006. There were some increases in the community's awareness that active smoking causes illness and/or damage to one's health with 96% believing in negative effects. However, there was no significant change in the community's belief about the negative effects of passive smoking. Support for smoke-free bars and gaming venues increased and there was a decrease in the amount of people exposed to passive smoke in the two weeks preceding the survey. The report also details exposure in indoor workplaces, homes and cars, smoking prevalence of young people, people with a mental illness and Aboriginal people. These key indicators will be reported again by BREU in 2009.

Centre for Behavioural Research in Cancer (CBRC) Victoria

UICC global survey of cancer-related beliefs and behaviours

In 2007, the International Union Against Cancer (UICC) developed a population survey about cancer-related beliefs and behaviours, using a standard set of survey methods and comparable questions that could be administered in all member countries. The overall aims of the project are to enhance the collection and comparability of population survey data on knowledge, attitudes and behaviours relevant to cancer risk across UICC member countries, and to develop the capacity in cancer control organisations to understand and use such survey data in order to develop population-based cancer control programs and policies, and to evaluate their impact. To date, the survey has been conducted in 29 countries, with a further 12 countries presently in the field. The survey is generously supported by the Roy Morgan Research company and their Gallup International affiliates, and guided by a Technical Advisory Group.

The survey includes questions on risk factor behaviours (tobacco use, sun protection, alcohol use, physical activity, body mass index), participation in cancer screening, and perceptions about risk factors for cancer, cancer curability and treatment issues. Survey administration has been either face-to-face or via telephone, depending upon each country's communication infrastructure and the practices of each Gallup research affiliate. Details and data from the survey can be found on www.cancervic.org.au/uicc.

The PROSPECT Program (Patient Responses: An Ongoing Survey of People Experiencing Cancer Treatment)

The PROSPECT Program aims to develop a statewide system for monitoring the experiences of Victorian cancer patients. This will be done through regular cross-sectional surveys of cancer patients recruited through the Victorian Cancer Registry. Development work undertaken for the program has comprised two phases. The first involved the development of a new survey to assess continuity of care and patient experiences at key phases of the disease trajectory, such as diagnosis and treatment planning. Item generation was informed by recommendations for psychosocial care from the *Psychosocial Guidelines for the Care of Adults with Cancer* and other practice guidelines. Critical feedback on the relevance and comprehensiveness of the items was obtained from two consumer discussion groups, 11 consumer reviewers, nine experts in cancer care and the Cancer Voices Executive Committee. Minor changes were made to items following qualitative feedback.

The second phase, currently underway, involves pilot testing the new survey and comparing the acceptability and feasibility of two data collection methods. Four hundred people who are within six months of diagnosis, English speaking and aged 18 or older will participate. Participants are recruited from the Victorian Cancer Registry and randomly assigned to complete the survey by postal questionnaire or telephone interview. In addition to the newly developed measure of patient experience, measures of quality of life and distress are included.

Centre for Behavioural Research in Cancer Control (CBRCC), Western Australia

National Bowel Cancer Screening Program

CBRCC in conjunction with Cancer Council WA conducted two cross-sectional, computer-assisted telephone surveys of Western Australian adults aged 55–74 years in April 2007 (n=505) and June 2008 (n=500) to assess awareness of and participation in the Federal Government's National Bowel Cancer Screening Program (NBCSP), which was launched in January 2007. In the first phase of the program, the eligible population comprised individuals turning either 55 or 65 years-old

during the period May 2006 to June 2008. These individuals were mailed an invitation to participate and a faecal occult blood test was enclosed. Mail-outs were conducted from 29 January 2007 to 30 June 2008. The second phase of the program commenced on 1 July 2008 and extends the program to include individuals aged 50 years. The intent is to expand the program over time to more ages within the 55–74 year target group. Little is known about this target group's level of knowledge of the risk factors, signs and symptoms, and screening tests for bowel cancer, nor their beliefs about bowel cancer in terms of its prevalence relative to other cancers, its preventability and the impact of early detection on life expectancy. Such information is essential for informing and improving the potential efficacy of education programs and screening campaigns such as the NBCSP, and this is what has been gathered in the Western Australian surveys. Analysis is currently underway and being prepared for publication.

Ecological momentary assessment of point-of-sale cigarette displays and unplanned purchases

CBRCC is currently undertaking exit interviews with smokers in Western Australia who have just purchased cigarettes from retail outlets that comply with the state's point-of-sale (POS) tobacco display restrictions (no advertising, only one example of each tobacco product and maximum $1m^2$ total display area). Preliminary analyses with the first hundred smokers suggests unplanned cigarette purchases were made by 22% of participants. POS displays influenced nearly four times as many unplanned purchases as planned purchases (52% v 14%, $p<.01$) and accounted for 11% of total purchases (95% CI: 5–17%). Brand switching was reported among 10% of participants, of whom none had made an unplanned purchase. Half of brand switchers looked at the POS display to aid purchase decisions, but the other half based decisions solely upon friends' recommendations. Of those who could recall the first time they purchased cigarettes, 62% claimed to have made an unplanned purchase. Twice as many smokers were supportive of a total ban on POS cigarette displays compared to unsupportive (37% v 14%) and 23% agreed that such a ban would make it easier to quit. It appears that POS displays account for around half of spontaneous decisions to purchase cigarettes and banning POS tobacco displays is therefore quite likely to reduce overall cigarette purchases. POS displays also play important roles in tempting trialist and ex-smokers, but play only a minimal role in brand switching – their main purpose according to the tobacco industry.

Viertel Centre for Research in Cancer Control (VCRCC), Queensland

CanChange – a psychosocial and lifestyle supportive care program for colorectal cancer survivors

CanChange is an evidence-based novel telephone-delivered psychosocial and lifestyle intervention for colorectal cancer survivors that aims to: improve psychological, physical, social and vocational functioning; reduce demands on the health system; and potentially reduce cancer recurrence and extend survival. A large scale randomised control trial is currently underway funded by Cancer Australia (2008-2010). We will recruit n=300 recently diagnosed colorectal cancer survivors from the Queensland Cancer Registry during 2008-2009. If successful, the program will be immediately translatable into cancer care practice utilising existing telehealth lines in Australia (Cancer Council Helpline) and internationally, or using trained nurses in acute clinical settings.

ProsCan – Prostate Cancer Supportive Care and Patient Outcomes Project

ProsCan is a large scale longitudinal study investigating the pathways to care and psychosocial and physical outcomes of men diagnosed with prostate cancer in Queensland. In addition, men with localised prostate cancer are invited to participate in a randomised control trial of a decision support and psycho-education intervention, designed to support men from the time of diagnosis through the early phase of rehabilitation. Recruitment was completed in August 2007, with over 1000 men participating in the longitudinal study and over 700 men participating in the RCT. The project is now in the early stages of data analysis. Information gained from this study will assist clinicians and patients when making decisions about treatment options and will provide information to guide the future planning of service delivery for men with prostate cancer.

HELP Study – Psychological distress screening by a Cancer Helpline

Consecutive cancer patients and carers who contacted the Cancer Council Helpline from September-December 2006 (n=341) were invited to participate in a study investigating psychological distress screening. Up to one-third of people affected by cancer experience psychological distress, however screening rarely occurs in routine clinical practice. This study investigated the feasibility of cancer helpline operators screening callers for their level of distress using a brief screening tool (Distress Thermometer, DT). Most callers were moderately-severely distressed (63%). The DT (11-point scale 0-10) had good overall accuracy (area under the curve=0.72) with a cut-off of 4 yielding optimal sensitivity and specificity in detecting general psychosocial morbidity. Our data suggest it is feasible for a community-based cancer helpline to screen callers for distress using the DT.

Melanoma Survivor Study

Queensland has the highest rates of melanoma in the world, yet little is known about the psychosocial outcomes patients and their families experience following a melanoma diagnosis, particularly for long-term survivors. The *Melanoma Survivor Study* aims to contact approximately 3000 melanoma survivors whose original diagnosis was between 2000-2003. The project aims to investigate clinical surveillance issues, as well as psychosocial and clinical supportive care needs of long-term melanoma survivors. Information gained from this study will guide the development of educational materials for clinicians, along with supportive care programs to address the longer term supportive care needs of melanoma patients and their families.

IMPROVING MULTIDISCIPLINARY CARE FOR PATIENTS WITH ADVANCED DISEASE: NATIONAL BREAST AND OVARIAN CANCER CENTRE PILOT REPORT

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Abstract

In 2007, National Breast and Ovarian Cancer Centre developed and piloted the *Multidisciplinary principles for advanced disease.*[1] The principles are based on the *Principles of Multidisciplinary Care*[2] developed by National Breast Cancer Centre* and adapted to reflect the role of multidisciplinary care teams in the advanced disease setting. The primary goal of the principles for advanced disease is to improve care and quality of life of patients with advanced disease, while maximising comfort and functioning. The multidisciplinary care approach provides opportunities for multidisciplinary discussion, enabling teams to facilitate effective treatment and care planning for patients with advanced disease. Four multidisciplinary care cancer teams (two breast and two ovarian) implemented the *Principles for advanced disease* from August to December 2007. There were a number of common themes and issues identified across pilot sites. These included the importance of patient-defined goals of care, complexity of cases and communication issues. The *Principles for advanced disease* provided sites with opportunities to reflect and improve on their practice, and to identify areas of improvement and work towards change.

Multidisciplinary care in the advanced disease context

Multidisciplinary care is an integrated team approach to health care in which medical, nursing and allied health care professionals consider all relevant treatment options and collaboratively develop an individual treatment and care plan for each patient.[3] Evidence shows that this approach improves patient survival and quality of life. There is also evidence that it increases patient satisfaction with care and increases access to information and support.

Multidisciplinary care is recognised as best practice in treatment planning and care for patients with cancer. The focus to date has been around early disease. In 2007, National Breast Cancer Centre (NBCC)* reviewed the existing principles of multidisciplinary care with the aim of adapting them to reflect the role of multidisciplinary care teams in the advanced disease setting.

Improvements in cancer treatment mean that there are now more patients surviving longer and many receiving treatment and care for advanced disease. Patients with advanced disease have specific needs and issues and a different approach to multidisciplinary care is required.

The needs and issues of patients with advanced disease include:

- specific psychosocial issues including impact of diagnosis at an advanced stage, poorer prognosis and recurrence[4,5]
- the management of physical symptoms and side-effects related to the spread of cancer and side-effects of cancer treatments[6]
- quality of life issues associated with disease progression[3]
- practical issues and support for patients living with advanced disease.[7]

As a result of the review, NBOCC developed and piloted *Multidisciplinary principles for advanced disease.* Please refer to table 1 for details. For this purpose, advanced disease is defined as cancer where the goal of treatment and care may not be cure, or where cure is not an option. The principles stress the importance of continuity of care, coordination, and the involvement of the patient and their nominated caregivers, where appropriate, in the treatment and care planning process. They also highlight the shift from primarily hospital-focused interventions to a more community-based approach to care. The principles provide a flexible definition of multidisciplinary care, allowing services to implement multidisciplinary care in a way that is relevant to the cancer type and service.

Table 1: *Multidisciplinary Care Principles for Advanced Disease*

Patient-defined goals of care – patients and their nominated caregivers, where appropriate, are involved in decisions about their care.

Team – a team approach, involves disciplines integral to the provision of good care, with input from others as required.

Communication and Information – ongoing, timely information and communication is facilitated among all team members, including patients and their nominated caregivers throughout the cancer journey.

Standards of care – provision of medical and supportive care is in accord with nationally agreed standards.

Pilot process

NBOCC invited multidisciplinary teams of various cancer streams nationally to participate in the pilot. They were asked to implement the principles by either incorporating them into their existing multidisciplinary treatment planning meetings, or by setting up a new treatment planning meeting for at least six patients with advanced disease, over a three-month period.

The purpose of the pilot was to evaluate the usefulness and relevance of the principles within a multidisciplinary care team setting. NBOCC was intentionally non-prescriptive about how each service should implement the principles, acknowledging differences between teams and their approaches.

Patient confidentiality and routine clinical care were not compromised as NBOCC did not request nor have access to any personal patient information as part of the pilot.

Each member of the site team received information about the pilot, the draft principles and *Multidisciplinary meetings for cancer care: a guide for health service providers.*

A nominated team member liaised with NBOCC and completed pre and post-evaluation forms. NBOCC provided a one-off payment of $1500 to assist sites with administrative costs.

Four sites nationally participated in the pilot from August to December 07:

- Maroondah and Box Hill hospitals, VIC, breast cancer
- Royal Adelaide hospital, SA, breast cancer
- King Edward hospital, WA, ovarian cancer
- Westmead hospital, NSW, ovarian cancer.

All four sites completed pre and post-evaluation forms. Some sites provided NBOCC with case study summaries and examples of strategies implemented during the pilot. Common themes and issues across sites are discussed below and summarised in table 2.

Multidisciplinary care teams

All sites participating had established multidisciplinary treatment planning meetings. The Maroondah and Box Hill breast cancer site was the only site with a dedicated, established advanced disease treatment planning meeting. Sites met weekly or fortnightly. Team members included clinical, allied health and community health representation. All sites included representatives from palliative care as core members of their treatment planning meetings. Sites found that routine participation of palliative and psychosocial team members enabled end-of-life care planning to be addressed when required. One site noted "...information provided by the psychosocial team members directly influenced treatment decisions".

In addition to the core team members, processes were in place to invite other disciplines to attend meetings, depending on the needs of the particular patients discussed. For example, one site noted that a specialist colorectal surgeon might participate in the discussion about treatment planning for women with ovarian cancer whose advanced disease involves the bowel. Another site invited a family support worker to attend the treatment planning meetings. This site established a protocol for obtaining access to women at hospital who had previously been seen by a family support worker at home. The breast care nurse who facilitated this process stated that participation from the family support worker resulted in good networking with community palliative care.

Table 2: *Key themes identified in the pilot*

Multidisciplinary care teams
Members of the multidisciplinary care team should reflect both clinical and psychosocial aspects of care. The inclusion of supportive and palliative care in the team and a focus on optimising function and comfort for patients with advanced disease is essential.

Patient-defined goals of care
Patients should be offered appropriate information to assist in decision making about treatment and care options. Opportunities should be made available for patients to review treatment planning recommendations and provide input into their treatment plan.

Complexity of cases
Decision making in the advanced disease setting is challenging. Multidisciplinary care principles need to be flexible and tailored to the needs of the patient.

Communication
A communications framework should be established which supports and ensures interactive participation from all relevant team members. Timely communication between all members of the multidisciplinary care team will facilitate continuity of care.

Access to GPs and communication with GPs
Systems should be implemented to ensure links with GPs. This will enable GPs to have an opportunity to provide input and be informed about treatment planning recommendations.

Resourcing
Adequate staffing and time will allow effective implementation of the *Multidisciplinary care principles for advanced disease.*

One site had two different teams that both met weekly, a tumour conference meeting and a multidisciplinary team meeting. Mainly clinical staff attended the tumour conferences. The purpose of the tumour conference meetings was to discuss the previous week's surgical cases and treatment planning. The purpose of the multidisciplinary team meetings (attended mainly by allied health workers) was to discuss current patients and outpatients who needed team review. The site reported that this two-team approach worked well and there was generally effective communication between teams.

Patient-defined goals of care

A common theme across sites was the importance of patient-defined goals of care. All sites acknowledged the patient as the primary focus of care. Sites noted that at the advanced stage of the disease, the need for individualised treatment options was essential. One site stated that they "... relied less on practice guideline recommendations and more on patient circumstances, preferences and morbidity".

Sites reported that direct involvement of patients in the multidisciplinary discussion through attendance at the hospital-based meeting was not common practice. This approach to patient involvement was not feasible or practical for the site or the patients. In preference to patients attending meetings, various other strategies were implemented to involve patients and their caregivers in decision-making about their care, including:

- providing patients and their caregivers with a 'plain English' copy of the written summary of the meeting recommendations
- convening family conferences to discuss meeting recommendations
- providing information resources in a range of languages which patients and their caregivers could use to further their understanding and initiate ongoing discussion.

One site developed a 'my care diary' for women. This resource allowed women to record all aspects of their care including clinicians' contact details, appointments, care planning, clinical notes and current medications.

The complexity of treating women with advanced disease was a common theme across sites. Sites reported that the implementation of the principles needed to be flexible and discretionary to the individual. Sites also reported that decision making at recurrence was more variable and challenging than at initial diagnosis for women with advanced disease.

Communication

All sites stressed the importance of communication among team members. To increase effective communication between clinicians and encourage participation in the team, one site developed an 'information pack', which included an information sheet about the team, what happens at the meeting and process for discussing recommendations with patients. The package also included resources specific to women with advanced disease and information about local support groups and programs for women and their caregivers.

Communicating effectively and in a timely manner with GPs was challenging for all sites. Each developed processes in order to ensure that the GPs had an opportunity to provide input and were informed of treatment recommendations. One site nominated a key contact person, the breast care nurse, to be the liaison between the patient's nominated GP and the multidisciplinary care team. The breast care nurse contacted the GPs at specific times to gain their input prior to meetings and provide them with feedback after the team had met (if the GP was unable to attend). The breast care nurse has had a good response to this process, with relevant information received by the GP shared at the treatment planning meetings.

Resourcing issues

Resourcing was a significant issue for most sites, with members finding it difficult to attend treatment planning meetings because of overlapping commitments and time restraints. One site noted that the loss of breast care nurse hours was a major issue, which affected the ability of the team to implement the principles. The extent to which sites could participate in the pilot was also limited due to staffing issues. One nurse commented: "The ability to co-ordinate and comment on our team and the initiatives that have been implemented has been limited without the support of a full-time breast care nurse."

Conclusions

The *Principles for advanced disease* provided sites with opportunities to reflect and improve on their practice, and identify areas of improvement and work towards change. Sites found the principles improved care beyond the point of initial diagnosis. Sites also found that by implementing the principles, accountability and patient care could be improved. Evaluation found no areas of the principles that needed significant changes. Site feedback was positive and highlighted the usefulness and applicability of the principles within a multidisciplinary care approach to cancer care. *Multidisciplinary care principles for advanced disease: a guide for cancer health professionals* has been disseminated nationally to cancer health professionals and can be accessed on line at www.nbocc.org.au.

*In February 2008, National Breast Cancer Centre incorporating the Ovarian Cancer Program (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC).

'Multidisciplinary care principles for advanced disease: a guide for cancer health professionals' is available as an online PDF on the National Breast and Ovarian Cancer website www.nbocc.org.au and can be ordered free of charge by calling 1800 624 973.

Acknowledgements

NBOCC gratefully acknowledges the support of all the individuals and groups who contributed to the development of the *Multidisciplinary care principles for*

advanced disease and the multidisciplinary care teams who piloted the principles.

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KEEPING ABREAST OF MEDIA COVERAGE OF CANCER ISSUES: AN EVALUATION OF THE 'CANCER IN THE NEWS' SERVICE

Franca Marine ■ Cancer Council Australia, Surry Hills, New South Wales
Email: franca.marine@cancer.org.au

In order to work effectively, Cancer Council staff and committee members need to keep abreast of media coverage relating to cancer, so they can identify any organisational responses required and respond effectively to inquiries from the media and public.

To address this need, Cancer Council Australia has for a number of years provided a *Cancer in the News* (CITN) service to Cancer Council staff, committee members and key stakeholders, in the form of a brief, daily email summary of print media articles.

An evaluation of the CITN service was conducted in 2007 to ensure the service remains relevant and useful to recipients and to identify any possible improvements.

Key features of *Cancer in the News*

CITN is a daily email summary of print media articles relating to cancer, compiled and distributed by staff of Cancer Council Australia with the aim of keeping staff, committee members and key stakeholders up-to-date on media coverage relating to cancer.

The email summary is delivered as early in the morning as possible, usually around 9am, so that recipients are aware of major news stories as they start work.

Only major news stories covered in the print media are included in the service. Television and radio broadcasts and magazine feature articles are not included, as media monitoring reports covering broadcast media are delivered later in the day and their inclusion would delay the distribution of the email summary, compromising the timeliness of the service.

A media monitoring service provides complete articles to Cancer Council Australia on the basis of a brief specifying cancer related topics to be monitored. These articles are then summarised under the following headings:

- Clinical trials
- Detection
- Nutrition
- Obesity
- Physical activity
- Prevention
- Public health
- Risk
- Research
- Screening
- Skin
- Support
- Tobacco
- Treatment

Daily summaries are emailed to those on the mailing list, which includes:

- Cancer Council staff and committee members
- Health professionals working in cancer
- Affiliate organisations and key contacts.

Evaluation method

A questionnaire was developed and distributed in May 2007 to all recipients on the CITN mailing list and responses were compiled and analysed.

Survey results

Response Rate

Of the 401 recipients emailed, 152 responses (38%) were received.

Usage

CITN was read every day by 97% of respondents, with the remaining 3% indicating they read CITN weekly or irregularly.

Half indicated that they read only the items of interest to them, while 49% read it in full.

Just over 70% indicated that they found the headings in CITN very useful, with a further 25% finding them somewhat useful.

Less than 19% suggested changes to the headings and the way they are used. Suggestions for additional topics included complementary and alternative therapies and tumour streams.

CITN was sometimes or always forwarded to other people by 70% respondents. Responses indicate that CITN is forwarded to more than 1300 other people in addition to direct recipients. Of those who forwarded CITN, 52% forwarded it to work colleagues, 11% to an organisational network, 15% to a special interest group and 6% to others, mostly family and friends (some respondents indicated more than one category).

CITN or extracts from it were kept by 64% for future reference.

Reasons for subscribing

When asked the reasons for subscribing to CITN, the most common included:

- for general information (78%)

- for information on cancer issues in media, in preparation for inquiries (67%)
- to know what had been reported about a particular cancer type or issue (57%)
- to identify issues requiring an organisational response (55%).

Value

The vast majority of respondents (88%) found the CITN service very or quite valuable (very valuable, (62%); quite valuable, (26%)). Only 8% found it somewhat valuable and only one respondent found it not valuable. (Four respondents did not indicate the value to them of the service.)

Most respondents (58%) indicated that CITN mostly covered articles of interest to them, while 38% indicated it always covered articles of interest to them,

Most and least liked features

Recipients were asked what they liked most and what they liked least about the CITN service.

The most popular aspects of CITN were its brevity and conciseness, its promptness and regularity and its convenient and easy to read format.

The most common complaints were that some articles were missed, that too many irrelevant articles were included and that CITN was too long.

Suggested improvements

When asked to suggest improvements, the most frequent comment was that no changes were required and that the service was fine as it was.

The next most frequent category of comments was that CITN should provide links to the full article, or the full article itself. This category includes suggestions for journal references relevant to the article to be included. The next most frequent category of comments related to extending the coverage of CITN to include (mainly) TV and radio and in a few cases, magazine and feature articles.

Conclusions

CITN is a popular and well received service provided by Cancer Council Australia which delivers prompt and concise daily email summaries of major cancer stories in the printed news media to Cancer Council staff, committee members, health professionals and key stakeholders.

CITN is considered very or quite valuable by 88% of recipients on the direct mailing list, who use it to keep up-to-date with developments in cancer and with media coverage of cancer issues, and to alert them to issues that may be raised by the public or that may require an organisational response.

The most popular aspects of CITN are its brevity and conciseness, its promptness and regularity and its convenient and easy to read format.

Based on results of the review, the Cancer in the News service will continue to be provided in its current format, with opportunities to enhance the service considered as they arise.

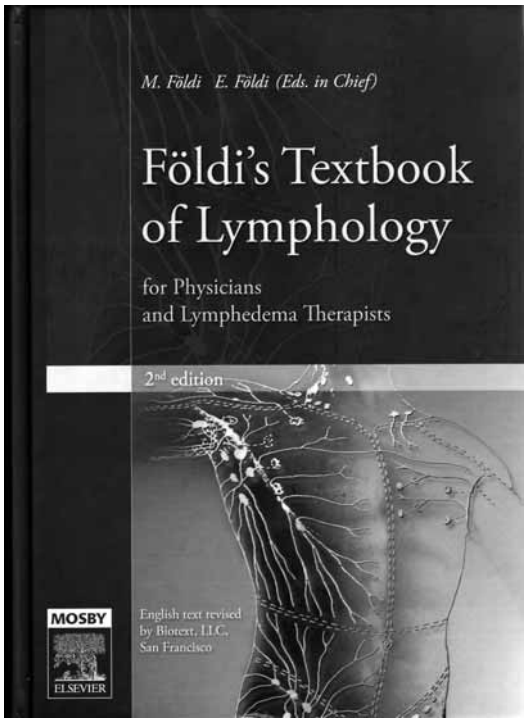
BOOK REVIEWS

Földi's Textbook of Lymphology: for Physicians and Lymphedema Therapists 2nd Edition

M. Földi & E. Földi (Eds. In Chief)
Mosby Elsevier (2006)
ISBN: 9780723434467
735 pages
RRP: $315.00

Földi's Textbook of Lymphology: For Physicians and Lymphedema Therapists is a large and comprehensive text, which has been compiled by the internationally renowned pioneers in the field of lymphology, Michael and Ethel Földi from Germany. Contributions have also been made by a large number of leading experts from around the world. This present 2nd English edition is based on the 6th German edition updated with literature published through to May 2006.

This textbook explores all aspects of lymphological science, including the causes, diagnoses, prognoses and treatments for primary and secondary lymphoedema. The text is divided into two main sections, scientific and practical. The scientific section includes 16 in-depth chapters on the anatomy, physiology and patho-physiology of the lymphatic system, with discussions on defining, assessing and classifying lymphoedema. Throughout the text, there are excellent photos, diagrams and tables to enhance the explanation of content presented.



The practical section of the text describes in great detail the techniques used by therapists in managing lymphoedema through Complete Decongestive Therapy. The components include manual lymphatic drainage (massage), compression therapy, exercise and skin care. The basic principles of each technique are described in depth. Again, the photos, diagrams and practical tips assist therapists to learn and understand the lymphatic pathways and the management of this long-term chronic condition.

This text was originally written for those working within the German health system, so there is a large focus on the management of moderate to severe lymphoedema rather than the latent (sub-clinical) and early stages of lymphoedema often seen in Australia. There is increasing evidence for using bioimpedance spectroscopy to detect early lymphoedema and monitor long-term lymphoedema, which is not mentioned in the book.

The extensive section on compression therapy describes and recommends the compression garments and bandages of one company which is the predominant supplier in Germany. In the Australian healthcare system, therapists have access to over 10 garment suppliers offering greater choice in ready-to-wear or custom-made garments to meet individual patients' specific needs.

One of the book's shortcomings is its lack of information and focus on the functional and psychosocial effects of living with lymphoedema, which may have a profound impact on an individual's daily activity and quality of life. Although this is mentioned briefly, the balance among the physical, functional and psychosocial aspects of management is skewed towards the physical manual treatment for the condition and not how the condition impacts on an individual's life.

Overall this text provides a comprehensive description of the lymphatic system and an in-depth knowledge of the techniques used for managing lymphoedema. The text is easy to read and understand, and is recommended for therapists and health professionals interested in learning about or already managing people living with lymphoedema. It is an excellent resource book for therapists faced with challenging or more complex issues in lymphoedema management.

Louise Koelmeyer, Occupational Therapist, NSW Breast Cancer Institute, Westmead Hospital, Sydney, New South Wales.

Mosby's Oncology Drug Reference

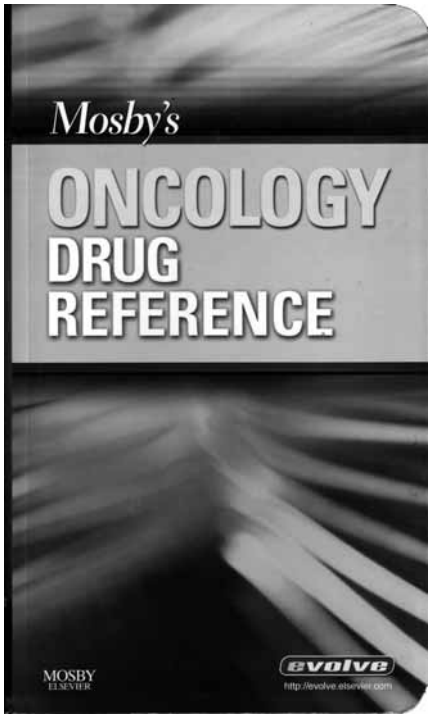
RJ Ignoffo, CS Viele and Z Ngo (Eds)
Mosby Elsevier (2007)
ISBN: 978-0-323-02818-9
558 Pages
RRP: $80.00

With the ever increasing pace of health and the evolving workforce, it is important to have a resource readily available for the provision of quick, concise, accurate and clinically applicable information. *Mosby's Oncology Drug Reference* fulfils this and is small enough to be on hand throughout a department. While it is not specifically directed at nursing staff, it is particularly relevant for the oncology nurse.

The book is divided into six units:

- cancer drugs
- paediatric oncology
- supportive care
- drug interactions
- considerations in preventing medication errors
- occupational exposure to hazardous drugs.

The cancer drugs unit is the most comprehensive with excellent, easy to understand information covering 107 cancer medications, including the newer agents and targeted therapies. The information provided is excellent for nurses administering or caring for patients receiving these mediations. Each medication is alphabetically listed according to its generic name and includes information about the class of agent, clinical pharmacology, indications, doses, unlabelled uses, precautions, contraindications, drug handling, administration, y-site compatibilities, interactions, lab effects, side-effects and special considerations. For some agents they also provide specific information such as dose modification, toxicity grading and monitoring. The information is easy to understand, concise and relevant to clinical practice. Of particular note is the information regarding clinical pharmacology, which provides an excellent overview of the mechanism of action and metabolism of the agent.



The other five units provide a variety of information, though this is more generalised. The paediatric oncology unit provides general information about the different tumour types seen in the paediatric population. While it is difficult to accurately appraise due to working in the adult population, this section appears very basic and may not provide a substantial amount of information for those working in paediatric oncology.

The supportive care unit provides a solid overview of the pathophysiology, grading and management of haematologic toxicities, nausea/vomiting, mucositis, bowel symptoms, bone disease and cancer pain. The information is once again concise and easy to understand and provides the clinician with a solid foundation to build their knowledge, although it would have been beneficial if the medications described in this unit were either discussed in the same manner as unit one, or had been included in the unit with the other cancer therapies. While there is information about the different classes of anti-emetics, it would have been useful to have information about the interactions, administration and side-effects. The one outstanding feature of this section is the bone disease information. The descriptions and pictures about the development of bone metastasis are exceptional and well worth a read by any oncology clinician.

The drug interaction unit includes a comprehensive table containing the interactions of 74 anti-cancer agents with other medications. It is well-referenced, concise, easy to read and provides information about effect, possible mechanism of action and management options. A table describing the dosing guideline for patients with hepatic or renal dysfunction is also included.

The unit regarding prevention of medication errors would provide most clinicians with no new information, however is worth the read just as a reminder about the care that must be taken in the prescribing and administration of these agents.

The hazardous exposure unit is very basic and seems almost to have been included as an afterthought. It is haphazard and very much based on practices overseas.

Finally the various formulas, such as body weight and creatinine clearance that are provided in the appendices are worthwhile to have available for clinical practice.

While this book is by no means the definitive oncology drug reference text, it is a wonderful resource to have on hand in the clinical area for clinicians to readily access information or as a foundation on which to develop further knowledge. It would be a worthwhile addition to any oncology unit.

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Oncology Nursing

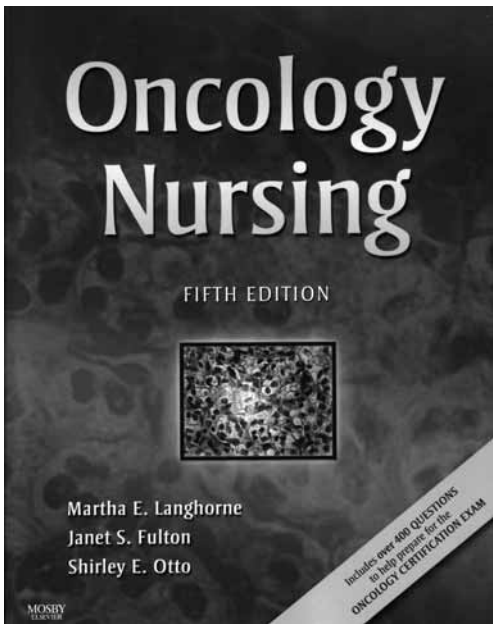
ME Langhorne, JS Fulton, SE Otto
Mosby Elsevier, 2007
ISBN: 978-0-323-04185-0
Pages: 756 (including Appendices)
RRP: $130.00

Oncology Nursing has been known by many in the oncology nursing field, simply as 'Otto'. This textbook has been a mainstay for oncology nurses since its first publication in 1991. The most recent edition, being the fifth, has seen Otto pass the editing reigns over to two new editors in Langhorne and Fulton. The two new editors heading up the revision have complimentary backgrounds of clinical expertise in the oncology nursing field and academic expertise. The revised edition makes for easy reading and has an extended inclusion of tables that summarise key points within each chapter.

The book is comprised of 33 chapters, divided into five units, covering: Clinical Aspects of The Cancer Diagnosis; Clinical Management of Major Cancer Diseases; Cancer Treatment Modalities; Cancer Care Supportive Therapies; and the new unit of Symptom Management.

This text book provides a good general source of information for nurses new to the oncology setting. It also serves as a good reference guide for nurses wishing to review and refresh their knowledge in regard to particular cancers. It is an excellent reference to have available for nurses working on general oncology wards, as it provides information on most cancers and treatment modalities, including paediatric cancers. Nurses seeking detailed information on specific cancers would benefit more from accessing books and information beyond this text.

As with many cancer nursing textbooks, this book is developed and printed for the North American cancer nursing market. It includes questions for nurses in preparation for the Oncology Certificate, and although there is no such certificate in Australia, it serves as a good review, as well as a measurement tool for individuals to ascertain their comprehension of the content. This text also includes many areas of discussion throughout the book that relate to treatment and care options for patients within the US dependant on their insurance status. This same consideration is not nearly as significant in Australia, however it does help to highlight the excellence in health care that we as Australians are able to access.



New to this edition is the inclusion in each chapter of a section entitled 'Consideration of Older Adults'. Given the advances in detection, prevention, screening and management of many cancers, it is not surprising the see the inclusion of this section, which is considered by many as the new niche cancer group. I would say however, that the inclusion of this area in this book is limited and provides only general comment. I believe that a chapter dealing with treatment and management issues in geriatric oncology would have been more beneficial to the reader.

As previously mentioned, a new section on symptom management has been included in this edition. This section provides a reasonable reference source, however, it is fairly generalised. Nurses wanting more concise information on specific symptom management would benefit from sourcing texts written specifically on symptom management in cancer care.

An additional appendix has been added to this edition. Appendix C provides a resource guide for cancer internet resources, and although most of the resources are US based, the list is extensive and includes many disciplines across the cancer spectrum.

This is a text that I would recommend as a resource guide on any general cancer ward or hospital library. It is easy to read and well set out, and frequently updated to include changes to statistics (although US driven) and treatment options.

Samantha Gibson, St. John of God Hospital, Subiaco, Western Australia.

"NOW WHAT..?" Dealing with your parent's cancer

CanTeen
Free ordered via phone – 1800 669 942, SMS – 0429838151 or online at www.nowwhat.org.au
92 pages

This book is aimed at 12-25 year-olds who have a parent diagnosed with cancer. It provides information, support, advice and additional resources. It is published by CanTeen, an Australian organisation supporting young people living with cancer.

A dedicated research team spent the last two years investigating the needs of their members. Questionnaire, telephone interviews and focus groups were utilised to gain an understanding of the impact a parent's cancer diagnosis had on adolescents and young adults.

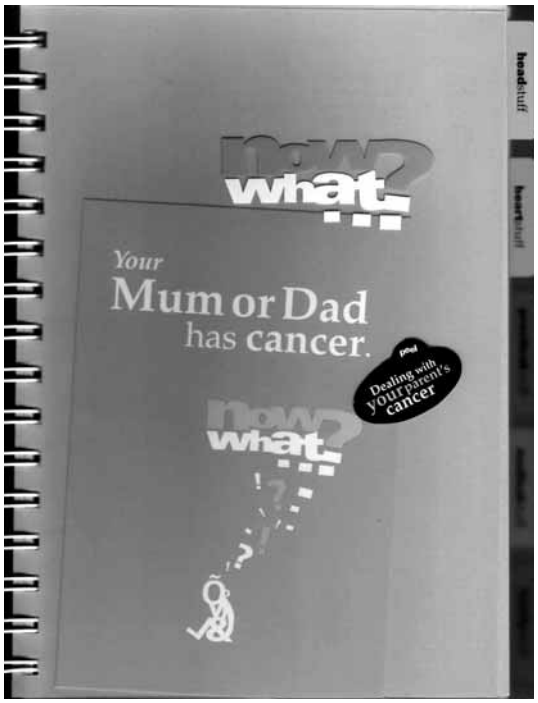
The presentation and tone of the book feel like it has been written by teens for teens. This is continually reflected throughout the book, which has a focus on the impact on the individual, friends, school, workplace, relationships, peer support, and dealing with normal and difficult feelings and emotions. Interesting strategies are provided to empower young people when seeking accurate information, questioning the treating team about their parents' symptomology, or simply trying to understand the language used by health care professionals.

Aesthetically, the A3 publication is graphically designed and user friendly with pages to keep your own notes. It is written in everyday language with clear, easy to understand explanations of cancer, including outlines of common adult cancer diagnosis, investigations, treatments and glossary. Early on myths of how and why people get cancer are demystified and while it is generally a positive publication, it also briefly considers 'if treatment doesn't work'. It can be read in any order and carries handy hints. The sections are colour coded and grouped under the headings: 'head stuff' (when to worry, getting advice), 'heart stuff' (relationships, changing roles, family), 'practical stuff' (how to look after yourself, finances and a few easy recipes), 'medical stuff' and 'handy stuff'. Finally, 'talking cards' are included for young people to use as a way of sharing information. Although I have reservations about the frequency with which they would be used, they may appeal in a non-threatening way to the target audience.

This comprehensive book helps fill a dearth of readily accessible information of this nature and effectively begins to normalise a young person's lived experience of their parents' cancer. Irrespective of the young persons affiliation with CanTeen this is a tremendous resource. I would suggest as health care professionals we are unprepared and frequently underestimate the need for information and the questions many young people have when suddenly and unwillingly thrust into this situation.

I recommend each individual is offered a copy or given the web address – after all it's free!

Sharon Bowering, Adolescent Young Adult Cancer Care Coordinator South Australia and Flinders University, South Australia.



OncoLink Patient Guide: Prostate Cancer

JM Metz and MK Hampshire
Saunders (2007)
ISBN-13: 9780702028649
227 pages
RRP: $50.00

OncoLink is one of the largest cancer information resources on the internet, developed by cancer specialists to provide patients and healthcare providers with current information on cancer related issues. *OncoLink Patient Guide: Prostate Cancer* is the third book published from OncoLink based on a specific disease. As indicated by the title, it is specifically aimed at patients, their carers and families.

The first section offers general information on the different health professionals that make up an oncology team, their role and the function of cancer treatment centres. OncoLink is based at the Abramson Cancer Centre of the University of Pennsylvania, therefore, some of the contact information and healthcare recommendations put forward are aimed at an American audience.

OncoLink receives many email requests for information on prostate cancer. The majority of this book is a compilation of some of those questions and answers.

The question and answer component of the book is divided into six sections. Each section commences with a short introduction related to the topic and then relevant questions for the section. Section headings include: Risk and Prevention; Screening and Diagnosis; Treatment; Complementary and Alternative Medicine; Nutrition and Prostate Cancer; and Living with Prostate Cancer. The treatment section was the largest and covered surgery, hormonal therapy, radiation therapy and chemotherapy. The question and answer format was logically presented in the appropriate sections with clear explanations for the reader. There is also an index in the back of the book for quick reference.

Overall, I think the book is a good reference for those who have been affected by prostate cancer, their carers and families. I also feel it is a good reference for health professionals caring for prostate cancer patients, particularly those with limited experience in this field.

Carmel Raymond, Tamworth Oncology Clinic, Hunter New England Health, New South Wales.

Oxford Handbook of Cancer Nursing

M Tadman and D Roberts
Oxford University Press (2007)
ISBN: 9780198569244
693 pages
RRP: $69.95

Not quite small enough to fit in your pocket, but not far off it, this book delivers instant information in a very easy format. Each cancer related topic is covered in a concise one or two page format. A useful bonus is the two attached page markers in different colors. Although the writing is small, it is set out with clear headings and doesn't give the impression of too much information for each page.

This first edition, written by experienced nurses, aims to fill a void in the market of a concise instant reference book for nurses in the UK. Although written for UK nurses and with some references specific to UK programs and the health system, it is still very relevant for Australian nurses.

The editors acknowledge that getting a balance between concise, yet detailed information would not please everyone. However, there are many sections that refer to further readings and internet sites and to avoid repetition, some sections have a link indicating further relevant reading in other sections of the book.

There are eight sections, starting with an introduction and finishing with oncological emergencies. Those in between are:

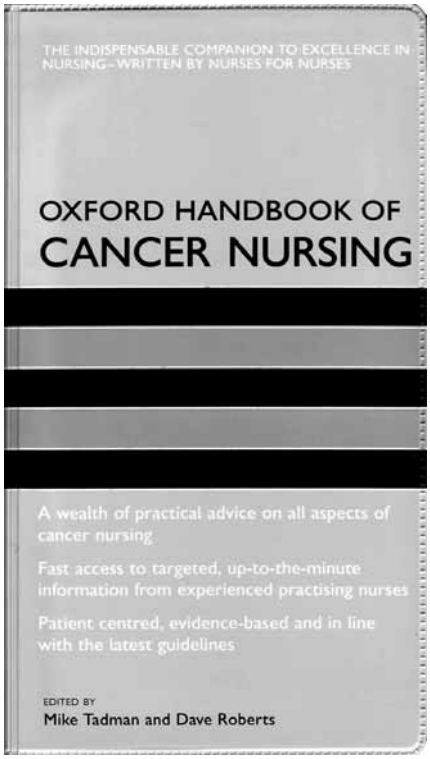
- The cancer problem
- The experience of cancer
- Supportive and palliative care
- Clinical management of cancer
- Management of major cancers
- Symptom management.

Sections are further broken down into detailed contents, which allow the reader to see at a glance the topic they are looking for, along with the usual index at the back of the book. The two sections on 'management of major cancers' and 'symptom management' account for around half of the 693 pages.

It was great to see a focus on psychosocial factors and consideration given to social context, as well as reference to non-pharmacological approaches. There is a definite focus on the patient, their family and specific information for nurses on managing everything from relationships with people with cancer to managing nausea, pain, stomas etc. There are also reflection points scattered in various sections of the book.

This book would definitely be an asset in any oncology setting, particularly because of its size and the ease with which information can be found, yet it would also be very useful for those nurses who work in general areas. Because it is written in a way that is easy to understand, a reader without an oncology background would still find useful information to benefit them. For this reason, I will be recommending it be purchased by my hospital to be easily accessible in the medical/surgical units, as well as our chemotherapy unit.

Anne Johnson, Latrobe Regional Hospital, Victoria.



Recent Results in Cancer Research Vol 178: Cancer and Pregnancy

A Surbone, F Peccatori, N Pavlidis
Springer (2008)
ISBN: 978-3-540-71272-5
252 pages
RRP: $US159.00

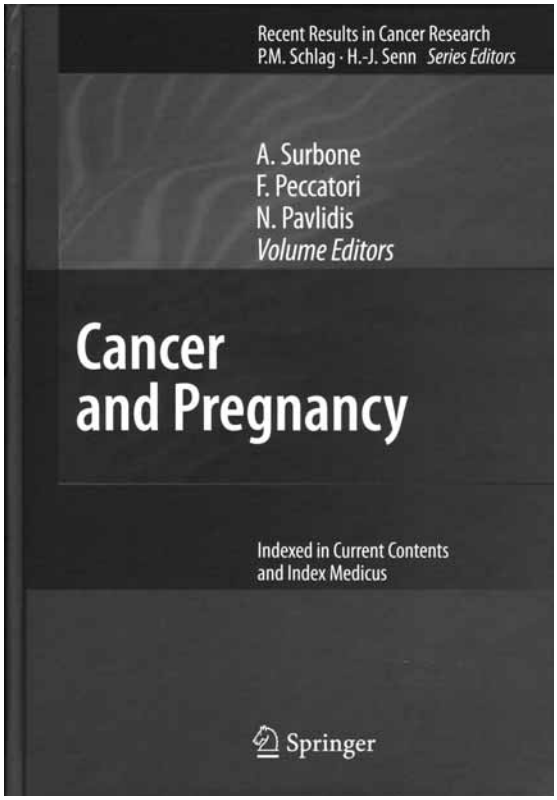
A diagnosis of cancer occurs in approximately one in 1000 pregnancies. At a time usually characterised by eager expectation, it can be a devastating event for the woman, her partner and family, while presenting therapeutic and ethical challenges for her health care providers. Management of the woman requires true multidisciplinary care, including not only the oncology/haematology team, but also obstetric and neonatal teams.

This book is the product of an advanced course on Cancer and Pregnancy hosted by the European School of Oncology. The 21 chapters from 36 contributing European, UK and US authors represent the latest information from experts in their fields about what are essentially uncommon cancer presentations. There are individual chapters on the presentation and management of the more familiar cancers in pregnancy such as breast, cervical, melanoma, lymphoma and leukaemia and also on rarer presentations such as thyroid, lung, gastrointestinal, ovarian, endometrial and urological malignancies.

The chapters 'Prenatal Irradiation and Pregnancy' and 'Effects of Systemic Therapy' provide very practical information and advice with the inclusion of safety parameters for both cytotoxic chemotherapy and diagnostic and therapeutic radiation procedures. The chapter 'Obstetric Care' highlights the normal physiological changes in pregnancy, discusses altered drug metabolism, provides guidelines for pharmacotherapy to minimise the effects on the fetus while maximising symptom control in the mother and outlines the special considerations with regard to the delivery of the baby. Chapters on fertility, reproductive issues and psychosocial care nicely round off the book.

While this book is a welcome addition to my personal library, it probably has a niche market. The book's take home message is one of these women being optimally managed in large tertiary centres with high level cancer, obstetric and neonatal expertise. It is these services that would benefit most from such a text, however it would also not be out of place in many hospital libraries.

Letitia Lancaster, Department of Gynaecological Oncology, Westmead Hospital, Sydney, NSW.



Targeted Therapies in Oncology

G Giaccone and JC Soria (Eds)
Informa Healthcare (2007)
ISBN: 9789849393716
412 pages

Targeted Therapies in Oncology provides a timely overview of this important and rapidly evolving area in cancer therapeutics. This 412 page book, edited by Jean-Charles Soria and Giuseppe Giaccone, is a compilation of short articles from contributors in the United States and Europe (with French and Dutch authors featuring prominently).

After an initial overview of the spectrum of currently available targeted therapies, the book is organised into 22 chapters which discuss different classes of targeted therapies. These chapters cover established therapeutics such as epidermal growth factor receptor inhibitors, Her-2 inhibitors and vascular endothelial growth factor antagonists, as well as emerging therapeutics such as insulin-like growth factor receptor inhibitors, aurora kinase inhibitors and telomerase interacting agents.

The chapters, although not entirely consistent in format, provide an introduction describing the biology of the target and its role in cancer, available therapeutics and discussion of preclinical studies and clinical studies conducted with these agents. While this book is commendable for its broad coverage of current targeted therapies, some notable omissions include BH3 mimetics and poly (ADP-Ribose) polymerase inhibitors.

A further challenge for a volume like this is keeping up-to-date in this rapidly developing area. For example, the recently recognised impact of *KRAS* mutations in the response of colorectal cancers to cetuximab is not discussed.

Nonetheless, *Targeted Therapies in Oncology* provides a good recent and concise overview of the current status of this dynamic field suitable for oncology trainees, practising oncologists and basic and translational scientists.

Benjamin Solomon, Peter MacCallum Cancer Centre, Victoria.