Optimal care pathway for people with Waldenstrom's macroglobulinaemia

Quick reference guide

The optimal care pathways describe the standard of care that should be available to all cancer patients treated in Australia. The pathways support patients and carers, health systems, health professionals and services, and encourage consistent optimal treatment and supportive care at each stage of a patient's journey. Seven key principles underpin the guidance provided in the pathways: patient-centred care; safe and quality care; multidisciplinary care; supportive care; care coordination; communication; and research and clinical trials. This quick reference guide provides a summary for clinicians of the *Optimal care pathway for people with Waldenstrom's macroglobulinaemia (WM)*.

Please note that not all patients will follow every step of the pathway.

Support: Assess supportive care needs at every step of the pathway and refer to appropriate health professionals or organisations.

Step 1: Prevention and early detection

Prevention

The cause of WM is not fully understood, and there are currently no effective prevention strategies. At present, there is no evidence linking lifestyle, environmental or behavioural factors to prevention of WM.

Risk factors

The risk factors for developing WM include:

- age (occurs mainly in people over 60)
- family or personal history of WM, multiple myeloma and Non-Hodgkins lymphoma and autoimmune disease
- Caucasian males are more likely to get WM
- autoimmune diseases both organ specific and systemic
- infective disorders such as Hepatitis C.

Early detection

There is no established benefit regarding early detection of asymptomatic WM.

Screening recommendations

Routine screening for WM is not currently recommended in either the general population or in asymptomatic relatives of people with WM. Patients with WM are also at increased risk (almost 2-fold) of other second malignancies.

General health checklist

- ❑ Recent weight changes discussed and the patient's weight recorded
- ❑ Alcohol intake and smoking status discussed and support offered if appropriate
- ❑ Physical activity recorded
- ❑ Referral to a dietitian considered

Step 2: Presentation, initial investigations and referral

WM is an indolent lymphoma; therefore, it often develops slowly. Patients with WM may present with subtle signs and symptoms, however approximately half of all newly diagnosed WM patients are asymptomatic and 30% are identified through abnormal blood tests.

Symptoms, when present can include:

- fatigue due to anaemia and/or hyperviscosity. Hyperviscosity syndrome is a medical emergency (see treatment section).
- B symptoms such as night sweats, fevers, unexplained weight loss >10% of body weight within the past 6 months
- headache, blurred vision, confusion, epistaxis, shortness of breath, other bleeding symptoms.
- neuropathy such as numbness, weakness, balance difficulties, falls and pain
- easy bruising or bleeding
- dyspnoea
- muscle cramps.

Initial investigations by the GP should include:

- history and physical examination of the skin, all lymph node groups, abdomen, neurological and cardiorespiratory examination
- full blood count and imaging (ultrasound, chest x-ray, CT)
- urea, electrolytes, creatinine, lactate dehydrogenase (LDH)
- liver function tests iron studies
- beta-2 microglobulin
- serum EPG and immunofixation to confirm underlying monoclonal protein.

Checklist

- ❑ Symptoms indicative of hyperviscosity require urgent clinical investigation
- ❑ Signs and symptoms recorded
- ❑ Patient notified of support services such as Cancer Council 13 11 20, Leukaemia Foundation 1800 620 420 or Lymphoma Australia 1800 953 081
- ❑ Referral options discussed with the patient and/or carer including cost implications

Timeframe

All investigations should be completed, and a path of action decided, **within 4 weeks**.
For patients with symptoms suggestive of hyperviscosity, the blood tests should be performed **within 1 day** of presentation.

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Support: Assess supportive care needs at every step of the pathway and refer to appropriate health professionals or organisations.

Step 2: Presentation, initial investigations and referral continued

Referral options

At the referral stage, the patient's GP or other referring doctor should advise the patient about their options for referral, waiting periods, expertise, potential out-of-pocket costs and the range of services available. This will enable patients to make an informed choice of specialist and health service.

Communication

The GP's responsibilities include:

- explaining to the patient and/or carer who they are being referred to and why
- supporting the patient and/or carer while waiting for specialist appointments
- informing the patient and/or carer that they can contact Cancer Council 13 11 20, Leukaemia Foundation 1800 620 420 and Lymphoma Australia 1800 359 081.

Timeframe continued

In most cases referral to a specialist **within 2 weeks** is appropriate. Urgent referral should occur **within 72 hours** if the patient presents with severe B symptoms, anaemia (Hb <80g/L), or **within 24 hours** if symptoms of hyperviscosity are observed.

Step 3: Diagnosis, staging and treatment planning

WM is diagnosed by blood tests demonstrating an IgM paraprotein in the peripheral blood. Additionally, either a bone marrow biopsy to detect infiltration of clonal B cells, plasmacytoid lymphocytes and plasma cells in the bone marrow or lymph node biopsy to demonstrate involvement with clonal plasmacytoid lymphocytes is required to differentiate WM from other low-grade lymphomas or from IgM MGUS.

Other routine investigations include:

- evaluation of relevant organ function (creatinine, uric acid, bilirubin, lactate dehydrogenase, haptoglobin, transaminases, alkaline phosphatase, ß2-microglobulin)
- iron studies
- chest radiograph (unless computed tomography [CT] has been performed for other reasons)
- viral serology (hepatitis B, hepatitis C, HIV, Epstein-Barr virus and cytomegalovirus)
- if there are clinical suspicions, or laboratory notification, of cryoglobulinemia, the serum sample should be collected and transported to the laboratory at 37 degrees.

Under certain circumstances the following investigations may be undertaken:

- CT scan and other imaging
- nerve conduction studies and laboratory evaluations (and a referral to a neurologist considered)
- when Bing Neel syndrome is suspected neurologist review and MRI brain, and spine should be undertaken and lumbar puncture considered.
- molecular tests.

Genetic testing

Currently there are no genetic tests applicable to predict family risk of WM.

Treatment planning

The multidisciplinary team should discuss patients with WM before starting any disease-directed therapy.

Research and clinical trials

Consider enrolment where available and appropriate. See the OCP resources appendix and relevant steps for clinical trial resources relevant to WM.

Checklist

- ❑ Diagnosis has been confirmed
- ❑ Performance status and comorbidities measured and recorded
- ❑ Patient discussed at multidisciplinary meetings and decisions provided to the patient and/or carer
- ❑ Clinical trial considered
- ❑ Supportive care needs assessed and referrals to allied health services actioned as required
- ❑ Referral to support services (such as Cancer Council, Leukaemia Foundation, Lymphoma Australia)
- ❑ Treatment costs discussed with the patient and/or carer.

Timeframe

Patients presenting with WM and symptoms of hyperviscosity should be assessed urgently **within 1-2 days** for potential plasmapheresis.

The timing of diagnostic work-up should be guided by the severity of anaemia, level of paraprotein and symptoms and in general should be completed **within four weeks** following assessment by a haematologist.

Support: Assess supportive care needs at every step of the pathway and refer to appropriate health professionals or organisations.

Step 3: Diagnosis, staging and treatment planning continued

Communication

The lead clinician's[1] responsibilities include:

- discussing a timeframe for diagnosis and treatment options with the patient and/or carer
- explaining the role of the multidisciplinary team in treatment planning and ongoing care
- encouraging discussion about the diagnosis, prognosis, advance care planning and palliative care while clarifying the patient's wishes, needs, beliefs and expectations, and their ability to comprehend the communication
- providing appropriate information and referral to support services as required
- communicating with the patient's GP about the diagnosis, treatment plan and recommendations from multidisciplinary meetings.

Timeframe continued

Patients suspected to have only IgM MGUS can be reasonably reviewed, with their results **in 6 months**. If their IgM remains stable, it is appropriate they return to their GP for **6 monthly review** of symptoms and IgM levels thereafter **annually** if stable, and re-referral to the haematologist in accordance with the criteria above.

Step 4: Treatment

Establish intent of treatment

WM is a highly treatable low grade lymphoma. While incurable with current therapies, many patients with WM have such a prolonged survival that they may have a 'functional cure' of their WM.

The stages of WM are as follows:

- smouldering WM – asymptomatic phase, IgM paraprotein, no cytopenias, hyperviscosity or organomegaly. Regular surveillance, 'watch and wait' is indicated and may last for years
- symptomatic WM – treatment is indicated, most commonly due to symptoms of bone marrow failure or autoimmune manifestations.

Accurate classification is important as treatment is only indicated for symptomatic WM.

Watchful waiting

Many patients with newly diagnosed WM have asymptomatic smouldering disease which does not warrant treatment. Many people diagnosed with WM will not start treatment immediately, but instead have regular check-ups for symptoms. This is known as 'active surveillance', or 'watch and wait'. As WM is often a slow growing disease, it is a safe strategy which means people diagnosed with asymptomatic WM can avoid the side-effects that treatment can bring.

The most adopted, currently available approach for systemic treatment of WM in Australia is rituximab-based chemotherapy, either in combination with dexamethasone and cyclophosphamide (DRC), or bendamustine (BR). For patients considered ineligible for rituximab-chemotherapy, single agent zanubrutinib BTK inhibitor is PBS-funded for patients with a CIRS score ≥6.

Palliative care

Early referral to palliative care can improve quality of life and in some cases survival. Referral should be based on need, not prognosis. For more information, visit the Palliative Care Australia website <www.palliativecare.org.au>.

Communication

The lead clinician and team's responsibilities include:

- discussing treatment options with the patient and/or carer including the intent of treatment as well as risks and benefits
- discussing advance care planning with the patient and/or carer where appropriate
- communicating the treatment plan to the patient's GP
- helping patients to find appropriate support for exercise and nutritional programs where appropriate to improve treatment outcomes.

Checklist

- ❑ Intent, risk and benefits of treatment discussed with the patient and/or carer
- ❑ Treatment plan discussed with the patient and/or carer and provided to GP
- ❑ Supportive care needs assessed and referrals to allied health services actioned as required
- ❑ Early referral to palliative care considered and advance care planning discussed with the patient and/or carer

Timeframe

Watchful waiting is usually recommended for newly diagnosed WM with asymptomatic smouldering disease which does not warrant treatment. Watchful waiting may also be recommended for mildly symptomatic patients if symptoms are not severe enough to warrant urgent treatment. Determining the tempo of disease progression during the period of watchful waiting is of value for prognostication.

When systemic therapy is indicated, timing should align with patient preferences but not be delayed to the point where the condition worsens.

1 Lead clinician – the clinician who is responsible for managing patient care.
The lead clinician may change over time depending on the stage of the care pathway and where care is being provided.

Support: Assess supportive care needs at every step of the pathway and refer to appropriate health professionals or organisations.

Step 5: Care after initial treatment and recovery

Provide a treatment and follow-up summary to the patient, carer and GP outlining:

- the diagnosis, including tests performed and results
- treatment received (types and date)
- current toxicities (severity, management and expected outcomes)
- interventions and treatment plans from other health professionals
- potential long-term and late effects of treatment and care of these
- supportive care services provided
- a follow-up schedule, including tests required and timing
- contact information for key healthcare providers who can offer support for lifestyle modification
- a process for rapid re-entry to medical services for any issues arising.

Communication

The lead clinician's responsibilities include:

- explaining the treatment summary and immediate and long term follow-up care plan to the patient and/or carer
- informing the patient and/or carer about secondary prevention and healthy living
- discussing the follow-up care plan with the patient's GP.

Checklist

- ❑ Treatment and follow-up summary provided to the patient and/or carer and the patient's GP
- ❑ Supportive care needs assessed and referrals to allied health services actioned as required
- ❑ Patient-reported outcome measures recorded

Step 6: Managing relapsed or progressive disease

Detection

Most relapsed or progressive disease will be detected via routine follow-up or by the patient presenting with symptoms.

Treatment

Treatment will depend on the features of disease, previous management, duration of response and the patient's preferences. Initial relapses/progression of WM in need of treatment is usually very responsive to treatment (for years).

Advance care planning

Advance care planning is important for all patients but especially those with multiply relapsed and refractory disease. It allows them to plan for their future health and personal care by thinking about their values and preferences. This can guide future treatment if the patient is unable to speak for themselves.

Survivorship and palliative care

Survivorship and palliative care should be addressed and offered early. Early referral to palliative care can improve quality of life. Referral should be based on need, not prognosis.

Communication

The lead clinician and team's responsibilities include:

- explaining the treatment intent, likely outcomes and side effects to the patient and/or carer and the patient's GP.

Checklist

- ❑ Treatment intent, likely outcomes and side effects explained to the patient and/or carer and the patient's GP
- ❑ Supportive care needs assessed and referrals to allied health services actioned as required
- ❑ Advance care planning discussed with the patient and/or carer
- ❑ Patient referred to palliative care if appropriate
- ❑ Routine follow-up visits scheduled

Step 7: End-of-life care

Palliative care

Consider a referral to palliative care. Ensure an advance care directive is in place.

Communication

The lead clinician's responsibilities include:

- being open about the prognosis and discussing palliative care options with the patient
- establishing transition plans to ensure the patient's needs and goals are considered in the appropriate environment.

Checklist

- ❑ Supportive care needs assessed and referrals to allied health services actioned as required
- ❑ Patient referred to palliative care
- ❑ Advance care directive in place

Visit our guides to best cancer care webpage <www.cancercareguides.org.au> for consumer guides. Visit our OCP webpage <www.cancer.org.au/OCP> for the optimal care pathway and instructions on how to import these guides into your GP software.

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