Lancashire and South Cumbria Haematology CRG Guideline for the management of Waldenstrom's macroglobulinaemia

1.0 Initial staging investigations

The following tests should be performed:

- FBC, U&Es, creat, LFTs, calcium, LDH, Igs, serum electrophoresis, paraprotein quantitation, Direct Coomb's test, plus in selected cases cryoglobulins
- Bone marrow aspirate and trephine biopsy
- CT scan neck, thorax and abdomen (PET-CT is not recommended due to the relatively low metabolic activity of this lymphoma but may be helpful if there is a clinical suspicion of high grade transformation)
- Hepatitis B, hepatitis C (HCV), HIV serology
- Ophthalmology review for fundoscopy if there are visual symptoms or high levels of paraprotein.
- Assess for peripheral neuropathy; if present test for anti-MAG/GM antibodies and refer for neurophysiological testing.

2.0 Initial treatment

- Asymptomatic patients with low level paraproteinaemia and mild cytopaenia may be managed with observation alone.
- Consider urgent plasma exchange for patients with severe hyperviscosity symptoms or cryoglobulinaemia.
- Chemotherapy options are dexa-RC, bendamustine-R and bortezomib-combinations e.g BDR, BCR. Note that there appears to be significantly less neurotoxicity when bortezomib is given subcutaneously and weekly. Also when a rapid response is required bendamustine-R or BDR/BCR are preferable options.
- In younger patients and where autologous stem cell transplantation may be a future treatment option avoid exposure to potentially stem cell toxic agents such as cyclophosphamide.
- For less fit or for frail patients options are rituximab alone or chlorambucil.
- Note that rituximab may be associated with a rapid increase in IgM levels leading to hyperviscosity symptoms, usually when given as a single agent. Consideration must be given to initial 'debulking' cytotoxic therapy or pre-emptive plasma exchange in patients with high baseline IgM levels e.g >30-40g/l.

3.0 Management of relapsed and refractory disease

- In apparent slow or non-response to rituximab-based regimens consider bone marrow biopsy since bone marrow responses with selective depletion of B-cells and persistence of plasma cells may occur.
- Treatment choice will depend on age, performance status, comorbidity, previous treatments, access to clinical trials and compassionate use programmes (*note pirtobrutinib appears to be effective where patients have previously been treated with BTK inhibitors and is available via compassionate use programme at the time of writing).*
- Options are zanubrutinib, dexa-RC, bortezomib-based regimens (BCR, BDR), bendamustine-rituximab.

- High dose therapy and autologous stem cell transplant should be considered in younger fit patients, particularly if duration of response to earlier lines of therapy has been short and if they have achieved at least a PR with second or later lines of therapy.
- In selected younger patients e.g <50 years, who have failed chemoimmunotherapy, BTK inhibitors and bortezomib-based regimens, and who are in at least PR referral for allogeneic stem cell transplant should be considered.
- Where further chemotherapy is not an option further management is supportive. Regular plasma exchange may be indicated to control hyperviscosity symptoms.

4.0 Management of high grade transformation

- Histological confirmation of high grade transformation must be obtained where possible. Note that PET-CT scans may be helpful in guiding the site for biopsy.
- Note that transformation in patients with Waldenstrom's macroglobulinaemia has been associated with a high incidence of extranodal disease, particularly involving the CNS.
- Treatment should be as for diffuse large B-cell lymphoma with R-CHOP where feasible. If the patient is unsuitable for R-CHOP second line salvage regimens should be considered e.g R-Gem-Ox, R-ICE, R-GDP. Consolidation with high dose therapy and autologous stem cell transplant should be considered in younger, fit patients who have responded to treatment.

5.0 Waldenstrom's macroglobulinaemia-associated peripheral neuropathy

- Patients must be referred to Neurology for assessment and investigation which should be undertaken according to the recommendations of the IWWM-8 consensus panel[1].
- Note that neuropathy in Waldenstrom's is most often a distal chronic symmetrical predominantly sensory neuropathy, often in association with anti-MAG IgM antibodies however, neuropathy may also be associated with cryoglobulinaemia/vasculitis, amyloidosis, lymphomatous nerve infiltration and CNS infiltration (Bing-Neel syndrome), especially where there is a short history, atypical features and non-demyelinating neuropathy on nerve conduction studies.
- The presence of peripheral neuropathy is an indication for treatment of Waldenstrom's macroglobulinaemia.
- Note that plasma exchange, steroids, IV immunoglobulins are of little value in management.
- Treatment options are rituximab alone, dexa-RC, bendamustine-rituximab, bortezomib combinations (BDR, BCR).
- Note that a worsening of neuropathy, usually transient, is reported in patients treated with rituximab hence consider initial 'debulking' cytotoxic therapy or pre-emptive plasma exchange in patients with high baseline IgM levels e.g >30-40g/l.
- Ibrutinib has been shown to be effective second line therapy in Waldenstrom's associated peripheral neuropathy that has progressed after rituximab.

6.0 Bing-Neel syndrome

- Refer to 'Guideline for the diagnosis, treatment and response criteria for Bing-Neel syndrome'[2].

- Treatment must be with CNS-penetrating agents. Appropriate options are bendamustine-rituximab, Ibrutinib +/- rituximab, intensive CNS-directed therapy as for primary CNS lymphoma.

References

1. D'Sa, S et al. Investigation of IgM and Waldenstrom's-associated peripheral neuropathies: recommendations from the IWWM-8 consensus panel. Br J Haem, 2017, 176; 728-742
2. Minemma, MC et al. Guideline for the diagnosis, treatment and response criteria for Bing-Neel syndrome. Haematologica 2017; 102; 43-51

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