Lancashire and South Cumbria Haematology NSSG Guidelines for Mantle Cell Lymphoma (MCL)

1.1 Pre-treatment evaluation

The following tests should be performed followed by MDT discussion:

- FBC, U&Es, creat, LFTs, calcium, LDH, immunoglobulins/serum electrophoresis
- CT scan neck, thorax and abdomen
- Where there is clinical evidence of CNS disease, or in cases with blastoid cytology – CT and/or MRI scan of brain and CSF cytospin examination.
- PET-CT scan to confirm stage I/II disease where single agent radiotherapy is being considered
- GI endoscopy should be performed if there is a clinical suspicion of GI involvement
- Bone marrow aspiration and trephine biopsy where the findings are will influence management - see 2.1. Whether a TP53 mutation/deletion is present should be determined in selected cases – see 2.2.
- HIV, hepatitis B, C serology
- Assessment of cardiac function where anthracycline-based treatment is an option if >60 years, or with a history of or risk factors for cardiac disease, or when mediastinal irradiation may be indicated
- Determination of stage and MIPI score or if Ki67% available MIPI-c score (online calculator available via European MCL Network homepage: www.european-mcl.net/de/clinical_mipi.php, go to 'Scores')

1.1 Post-treatment evaluation

- On completion of treatment the patient must be reassessed clinically and where treatment is given with curative intent all abnormal tests at baseline repeated. This must be followed by MDT discussion with review of an end of treatment CT scan and other tests where this is required to assess response.

2.1 Stage I/IIA, non-bulky disease

- This must be confirmed with bone marrow aspiration and trephine biopsy and PET-CT scan if single agent radiotherapy is a treatment option
- Offer radiotherapy although it should be stressed to the patient that the evidence base in early stage MCL is limited.
- In asymptomatic patients with low volume disease observation is appropriate.
- Patients with symptomatic large volume stage I-II disease should be treated as for advanced stage.

2.2 Advanced stage disease IA bulky, IIB-IVB

- A small subgroup of patients with advanced stage, low volume disease are asymptomatic and have more indolent disease. Most commonly they have a leukaemic presentation +/- splenomegaly. They may remain well for several years. Hence observation should be offered.
- In patients up to the age of 65-70 years and who are fit, the option of an intensive treatment approach must be considered. This will be the Nordic regimen followed by autologous stem cell transplantation in patients who achieve PR/CR. A decision to

offer this approach must be take after considering baseline prognostic factors - it must be noted that outcomes with Nordic regimen and autologous transplant are poor in patients with TP53 abnormalities, especially mutations.

- For patients <50-60 years with poor prognostic factors i.e high risk MIPI-c score, blastoid cytology, Ki67 >30%, TP53 abnormalities, consider referral to discuss the option of allogeneic transplantation rather than autologous transplant following Nordic induction.
- Alternatives to intensive therapy are CHOP-R, VR-CAP, bendamustine-R or R-BAC.
- For patients unable to tolerate CHOP-R, bendamustine-R, options are CVP-R, chlorambucil +/- R, cladribine, gemcitabine, etoposide, palliative RT for local disease control
- Maintenance R should be offered to patients in CR/PR following Nordic regimen and autologous transplant. Maintenance should be every 2 months for 3 years.
- Maintenance rituximab should be offered to patients in PR/CR following induction therapy. Maintenance should be every 2 months for 3 years. Note that no benefit of maintenance has yet to be demonstrated following bendamustine-R.

2.3 Relapsed/refractory disease

- Management will depend on age, performance status, comorbidity, previous treatments especially rituximab exposure, baseline prognostic factors e.g MIPI/MIPI-c score, presence of TP53 abnormalities, Ki67%, eligibility for autologous or allogeneic stem cell transplant, suitability and eligibility for funding for Ibrutinib or CAR-T cell therapy, availability of drugs on compassionate use programmes. It is also now recognised that relapse within 24 months of starting first line therapy (POD24) is associated with poor survival from second line therapy. It must be noted that the responses to ibrutinib appear significantly better when used as second line therapy compared to later use, and the results in TP53 mutated cases remain poor.
- Nordic regimen followed by autologous stem cell transplant for those in CR/PR should be considered if not performed as first line therapy.
- Offer referral for consideration of allogeneic transplantation to younger patients <50-60 years who respond to second or greater line treatment and have poor risk features e.g TP53 abnormalities, POD24.
- CAR-T cell therapy is an option for patients relapsing after two lines of therapy which included ibrutinib and may be considered in fit patients up to 75-80years.
- If intensive therapy is not appropriate options are ibrutinib, or R-chemo unless relapsing within 6 months of rituximab e.g CHOP-R, bendamustine-R, R-BAC, CVP-R, R-Gem-Ox, chlorambucil +/-R. Other options are gemcitabine, RT for local disease control, drugs available via compassionate use programmes e.g lenalidomide, pirtobrutinib.

Author	Dr MP Macheta
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