Mantle Cell Lymphoma

Diagnosis

Staging
Consider PET if possible candidate for radiotherapy with localised disease

Prognosis
- K67
- Blast variant
- MIPI
  - Age > 60 years
  - ECOG PS ≥ 2
  - LDH > ULN
  - Extranodal ≥ 2
  - Stages III or IV

Watch and Wait
- Consider K67 < 10%
- Low disease burden
- Asymptomatic

Present at Lymphoma Conference

Advanced Stage Disease
Requiring systemic therapy K67 > 10%

Transplant Eligible
≤ 65 years + PS ≤ 1
Nordic Protocol
R-hyperCVAD+/- PBSCT

Transplant Ineligible
> 65 years + PS ≥ 2
RFM or RCHOP or RCVP

Localised Disease
- Consider Radiotherapy
- +/- chemotherapy

Less common scenarios

Transplant Eligible
≤ 65 years + PS ≤ 1

Nordic Protocol
R-hyperCVAD+/- PBSCT
1. Introduction

MCL accounts for approximately 6% of all cases of NHL. The median age of patients in most series is in the mid-60s with a male predominance. Most patients present with advanced stage disease at diagnosis.

MCL has a variable course. A small number of patients can have an indolent disease course. However, the majority of MCL present with advanced stage and have an aggressive disease course. Median OS with conventional chemotherapy is 3-5 years.

More aggressive treatment strategies including consolidation with autologous transplants are aimed at improving outcome in this disease. There is no currently available evidence that these more aggressive programs are curative although some appear promising.

2. Pathology and Cytogenetics

MCL is thought to originate from the marginal zone or from a peripheral blood memory B-cell. The immunophenotype of the malignant cells in MCL is typically CD20+, CD5+, CD10-, CD23-, with either kappa or lambda light chain cell surface expression. The cytogenetic hallmark of MCL is the expression of cyclin-D1 protein in the tumor cells as a result of a translocation of the cyclin-D1 gene (CCND1) on 11q13 to the promoter of the heavy chain locus on 14q32. A subgroup of MCL have immature morphology – so called Blastoid variant.

3. Staging Investigations

- Full blood count, Na, K, Ca, PO₄, renal function, urate, liver function tests, LDH, immunoglobulins, HIV, hepatitis B and C testing.
- Bone marrow biopsy obtaining 20 mm of haematopoietic tissue for assessment.
- CT scan chest, abdomen and pelvis +/- neck if lymph node palpable in the neck.
- PET CT scan is more accurate than CT alone. A PET scan should be undertaken in early stage disease where a PET scan could lead to upstaging of disease and thereby alter eligibility for radiotherapy.
- Asymptomatic GI involvement is fairly common and consideration could be given to upper and lower GI endoscopy if clinically appropriate.
- Cardiac echocardiogram or gated heart scan should be considered for those to be treated with an anthracycline
- The Ann Arbor staging system is used.
4. Prognosis

Both the IPI and MIPI scores provide prognostic information. The MIPI is the preferred score.

4.1 Mantle Cell International Prognostic Index (MIPI)

The MIPI is designed specifically for advanced stage mantle cell lymphoma.

<table>
<thead>
<tr>
<th>Points</th>
<th>Age (Years)</th>
<th>ECOG</th>
<th>LDH ratio to ULN</th>
<th>WBC</th>
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<tbody>
<tr>
<td>0</td>
<td>&lt;50</td>
<td>0-1</td>
<td>&lt;0.67</td>
<td>&lt;6.7</td>
</tr>
<tr>
<td>1</td>
<td>50-59</td>
<td>0-1</td>
<td>0.67-0.99</td>
<td>6.7-9.99</td>
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<tr>
<td>2</td>
<td>60-69</td>
<td>2-4</td>
<td>1-1.49</td>
<td>10-14.99</td>
</tr>
<tr>
<td>3</td>
<td>&gt;70</td>
<td>&gt;1.49</td>
<td>&gt;14.99</td>
<td></td>
</tr>
</tbody>
</table>

- Low risk 0-3
- Intermediate 4-5
- High 6-11

Figure 3. Overall survival according to the new prognostic index (MIPI). LR indicates low risk, prognostic score less than 5.7; IR, intermediate risk, score 5.7 or more but less than 6.2; and HR, high risk, score 6.2 or more. The prognostic score is calculated as \[0.03535 \times \text{age (years)} + 0.6978 \times \text{(ECOG > 1)} + [1.387 \times \log_{10}(\text{LDH/ULN}) + [0.9393 \times \log_{10}(\text{WBC})].\]
4.2 International Prognostic Index (IPI)

One point is given for each of the following risk factors:

- Age >60 years
- ECOG PS ≥ 2
- LDH>ULN
- Extranodal sites ≥ 2
- Stage III or IV

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Number of Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1</td>
</tr>
<tr>
<td>Low Intermediate</td>
<td>2</td>
</tr>
<tr>
<td>Higher Intermediate</td>
<td>3</td>
</tr>
<tr>
<td>High</td>
<td>4-5</td>
</tr>
</tbody>
</table>

4.2 Ki67

Ki67 has independent strong prognostic relevance.
4.3 Blastoid Variant

This also predicts for poorer survival.

5. Rationale for Therapy

Where possible, cases should be enrolled in clinical trials.
5.1 Localised Disease

Diagnosis of localized disease requires full staging investigations including a PET-CT scan. Consideration can be given to an UGI and lower GI endoscopy. Only a minority of patients present with localized disease and have better OS than for advanced stage disease. Patients with stage IA or IIA (non bulk < 10 cm) have an OS of 6.8 years. Radiotherapy has been shown to provide effective disease control in this group with superior outcomes to chemotherapy. Chemotherapy in addition to radiotherapy may provide additional benefit but numbers from studies are too small to draw firm conclusions. Cases should be considered on a case by case basis taking into account high risk features such as blastoid variant and Ki67 >30% who potentially may benefit more from chemotherapy in addition to radiotherapy.

5.2 Role for Watch and Wait Strategy

A Ki67 of <10% may predict a more indolent disease. A watch and wait approach in asymptomatic low volume disease with Ki67 < 10% may be appropriate. Each case should be considered on a case by case basis.

5.3 Management of Patients < 66 Years of Age with Performance Status 0-1 or Transplant Eligible patients

The optimal therapy is uncertain in the absence of randomised trials comparing different therapy approaches. Recent evidence has confirmed the efficacy of different modalities in the treatment of MCL including conventional chemotherapy (eg CHOP/CVP), added high dose cytarabine, added rituximab and consolidation with autologous transplant, especially if performed in CR1, and regimens have incorporated these different modalities in varying combinations. More aggressive combination treatment options should be considered in younger patients with good PS with the hope of prolonging PFS and OS. The aggressive treatments investigated for this group have included:

a. **CHOP-based chemotherapy, + rituximab with autologous transplantation in CR1** (Canada and Nordic group)

b. **HyperCVAD, +rituximab +/- autologous transplant in CR1** (MDACC)

The use of autologous transplantation after intensive front-line immunochemotherapy with in vivo-purged stem cells by the Nordic Lymphoma Group in a phase 2 multicentre non-randomised trial has shown encouraging results. The Nordic study protocol MCL-2 was reported on 159 newly diagnosed MCL patients stages II-IV age <66 years and shows five year EFS and OS of 63% and 74% respectively. There appears to be an emerging PFS plateau after five years. Longer term follow up is required but the appearance of a plateau suggests long-term freedom from lymphoma and perhaps cure may be possible. Treatment-related mortality is 3.8%.

R-hyperCVAD has reported CR rates of 87-58%. Seven year PFS and OS of 68% and 52% have been reported. However, treatment toxicity is high with rates of inability to complete planned treatment 29-63%. Treatment-related deaths 8%. Increased rates of AML and MDS were reported in those in CR. R-hyperCVAD followed by autologous transplant has been studied in only small numbers of patients.

There is emerging data for 3 cycles of RCHOP with 3 cycles of R-DHAP followed by high dose AraC and cyclophosphamide/TBI autologous stem cell transplant (ASH 2010 Abstract 110 – full paper awaited).
Strong recommendations over which is the optimal regimen cannot be made and the decision must be based on consideration of toxicities.

5.4 Management for Patients >65 Years or Performance Status ≥2 or Transplant Ineligible

- Most chemotherapy regimens have not been compared directly and it is not possible to provide strong recommendations as to which is best nor to provide the optimal sequence of use of these regimens as initial therapy and at disease progression.
- Treatment options include rituximab containing combination chemotherapy regimens including:
  - RCVP
  - RCHOP
  - RFM

5.5 Role of Radiotherapy in Advanced and Relapsed Disease

The benefit of RT in addition to chemotherapy in advanced disease in patients obtaining a CR is not proven.

Radiation should be considered as part of a palliative treatment package as low doses of radiotherapy (4Gy) even to extended fields has been shown to be safe and efficacious.

5.6 Role of Allogeneic Transplant

Reduced intensity allogeneic transplantation has been reported with failure free survival and OS of 55% at 3 years. Complete remissions have been achieved in patients with relapsed disease. This area requires further study but should be considered in younger patients with chemosensitive disease. With a suitable donor who have relapsed following initial intensive therapy strategies (such as post autologus stem cell transplant or R-hyperCVAD).

5.7 Novel Agents for MCL

Patients who fail SCT, or relapse after other treatment modalities, are eligible for experimental therapy. Recent studies have identified new treatment approaches for relapsed MCL.

5.8 Maintenance Rituximab

Maintenance rituximab may prolong response duration. Not currently funded.
7. References


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