Updates: Maintenance rituximab for patients with remission for maximum of 2 years

Introduction

Mantle cell lymphoma (MCL) is the third most common subtype of lymphoma, accounting for 5-10% of all non- Hodgkin’s lymphomas [1]. Median age at presentation is about 63 with three quarter of individuals affected being male and 70% presenting as advanced disease. Over the past decade, while there have been major advances in our understanding of the pathophysiology of this entity, and new therapeutic options have become available, clinical outcomes do not appear to have been significantly improved. As standard therapy yield suboptimal results, these patients should be considered for clinical trials.

Diagnosis

The diagnosis of mantle cell lymphoma is dependent on an adequate biopsy specimen (preferably open surgical biopsy) with immunohistochemistry and flow [2]. In most cases the tumor is composed exclusively of small to medium lymphoid cells. MCL expresses pan B-cell antigen (CD19+, CD20+). Distinguishing characteristics are CD23 -, CD5 +, CD43+ and FMC 7+. About 70% have the t(11:14)(q13;q32) translocation and the vast majority will overexpressed Cyclin D1 [3]. Mantle cell must be distinguished from other CD5+ lymphoproliferative disorders, including CLL. Particular attention must be paid to patients who clinically appear to have CLL, but lack CD23 expression. Such patients appear to have a relatively favorable prognosis and should be managed like other patients with CLL.

Baseline Investigations

The nature of initial staging investigations depends on the treatment intent. Patients who are planned for intensive treatment should have the following investigations:

- CBC, differential
- Blood film
- Serum electrolytes and creatinine
- Liver function tests
- Serum LDH, uric acid
- Chest x-ray
- CT chest, abdomen, pelvis
- Bone marrow biopsy
- Hepatitis B status

Patients who are planned for palliative or conservative treatment such as chlorambucil should be investigated less intensively with basic blood work (CBC, electrolytes, creatinine, uric acid) as well as chest x-ray and abdominal ultrasound.

Cardiac Assessment

Patients planned for anthracycline-based chemotherapy should undergo 2D-echocardiogram or MUGA scan if they have a history of:
Anthracyclines should be used with caution in patients with an EF < 45%, recent MI (< 3 months) or severe arrhythmia.

### Prognosis & Staging

The median survival of mantle cell lymphoma in most series is 3-5 years. A number of publications have evaluated prognostic factors. In general most prognostic factors that predict outcome in large cell lymphoma are also useful in mantle cell lymphoma. The International Prognostic Factor Index (see Diffuse Large B-Cell Lymphoma) has prognostic value in mantle cell, with 5-year survival reported to be 0% for patients with 4 or 5 adverse factors and 57% for patients with 0 or 1 factors [4]. However, in a recent study FLIPI was noted to be superior as a prognostic model compared to the IPI with 5 year overall survival of 65%, 42% and 8% in patients with low-, intermediate-, or high-risk designations, respectively [5]. Other factors that have been reported to be important are leukemic disease, liver and bone marrow involvement [6, 7]. Histology also appears to be prognostic. Nodular and mantle zone subtypes appear to do relatively well, while patients with diffuse or blastic mantle cell lymphoma do poorly [7-11]. A high Ki-67 or mitotic index is also an adverse prognostic [7, 9, 11]. While we are able to identify patients who are at high-risk there is no evidence that such patients benefit from more aggressive therapy.

#### Ann Arbor Stage

The Ann Arbor staging system continues to be in use in mantle cell lymphoma [12]. This system provides limited prognostic information, but is of use in determining patients eligible for treatment with combined modality therapy. All patients should have an Ann Arbor stage assigned.

### Stage Definition

<table>
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<tr>
<th>Stage</th>
<th>Description</th>
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<tr>
<td>Stage I</td>
<td>Involvement of a single lymph node region or a single extranodal site.</td>
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<tr>
<td>Stage II</td>
<td>Involvement of two or more lymph nodes on the same side of the diaphragm or localized involvement of an extra lymphatic organ or site and one or more lymph nodes on the same side of the diaphragm.</td>
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<tr>
<td>Stage III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm that may also be accompanied by involvement of the spleen or by localized involvement of an extra lymphatic organ or site or both.</td>
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<tr>
<td>Stage IV</td>
<td>Diffused or disseminated involvement of one or more extra lymphatic organs or tissues, with or without associated lymph node involvement.</td>
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The absence or presence of fever > 38.5 °C, drenching night sweats, and/or unexplained weight loss of 10 percent or more body weight in the six months preceding admission are to be denoted in all cases by the suffix A or B respectively.
Treatment

Numerous agents have been studied in the treatment of mantle cell lymphoma, but few randomized trials have been published.

1. Radiotherapy

Mantle cell lymphoma is a radiosensitive histology. While localized presentations are rare, favorable long-term outcomes have been reported with involved field irradiation [13]. Radiation also offers palliative benefit in selected patients with advance stage disease.

2. Alkylator-based Chemotherapy Regimens

A number of relatively small phase II trials have examined the efficacy of regimens such as chlorambucil, COP, and CVP in mantle cell lymphoma. Such therapy is well tolerated and appears to be associated with median survivals of 3-5 years.

3. CHOP and other Anthracycline-based Regimens

Anthracycline-based regimens such as CHOP have been compared to alkylating agents in a number of randomized and non-randomized comparative studies. These trials must be interpreted with caution as they antedate modern classification systems and suffer from methodologic flaws. The two randomized comparisons of CVP vs CHOP and CHOP vs MCP [14, 15], do not report superior outcome with anthracycline use. The results of non-randomized comparisons are more inconsistent with one of the four trials reporting superior outcome when CHOP was compared to non-anthracycline based therapy. More recently a randomized trial comparing fludarabine to fludarabine plus idarubicin in 199 patients with follicular or mantle cell lymphoma reported no advantage to the addition of idarubicin [16].

4. Purine Analogos

Limited data is available on fludarabine in mantle cell lymphoma. One small trial of front-line monotherapy reported a response rate of 41% with a median time to progression of 1.1 years [17]. A higher response rate of 65% was observed more recently in a study of fludarabine +/-idarubicin in indolent and mantle cell lymphoma. This study did not report time to progression for the mantle cell subgroup. The addition of idarubicin to fludarabine was not reported to improve response rate or duration [16]. The German low-grade study group reported results of the combination of fludarabine, cyclophosphamide, and mitoxantrone with or without rituximab in 48 patients with relapsed mantle cell lymphoma. The response rate reported in the FCM arm was 46% with a median progression-free survival of 4 months and an overall survival of 11 months [18].

5. Hyper-CVAD

Promising phase II results of the Hyper-CVAD regimen with or without stem cell transplantation have been presented. In small single-centre trials of highly selected patients, response rates of > 85% with two year overall survivals of > 80% have been reported [19]. This regimen is toxic and resource intensive and would be feasible only in a select group of patients. The Southwestern Oncology Group (SWOG) has recently completed a nonrandomized multi-centre phase II study of the Hyper-CVAD regimen. Among 40 evaluable patients, the response rate was an acceptable 88% (58% CR or CRu), but a continuous rate of relapse was observed over time and the therapy was associated with severe hematologic toxicity, suggesting some concern with the application of this regimen outside of the single-centre setting [20].
6. Stem Cell Transplantation

One randomized trial comparing autologous stem cell transplantation to interferon maintenance following conventional chemotherapy in first remission has been published [21, 22]. This study suggests transplantation is associated with improved progression-free survival, but not overall survival. One case control study comparing autologous stem cell transplantation with Rituximab to conventional chemotherapy as first-line therapy reported superior survival with high-dose therapy (3 yr OS 88% vs 65%; p = 0.05) [23]. Outcomes following stem cell transplantation beyond first-line therapy appear less promising [24]. Allogeneic transplantation offers the potential for cure at the cost of significant toxicity. Reports of allogeneic transplantation in mantle cell lymphoma are too scant to draw firm conclusions regarding its role.

7. Rituximab

Rituximab has activity in mantle cell lymphoma but its optimal use remains unclear. As a single agent it has moderate activity with response rates of ~30% [25]. The addition of rituximab to first and second-line chemotherapy has been studied in randomized trials. In a randomized trial of 122 patients with previously untreated mantle cell lymphoma, CHOP-rituximab was associated with a higher response rate (94% vs. 75% p = 0.005) and superior time to treatment failure (21 vs 14 months; p = 0.01), but not improved progression-free survival or overall survival [26]. A randomized trial comparing mitoxantrone, chlorambucil, and prednisone (MCP) to MCP and rituximab in follicular, mantle cell lymphoma, and other indolent lymphomas reported improved response rate and event-free survival in the MCP-rituximab arm [27]. The results for the mantle cell subgroup were not reported separately. A further randomized trial comparing the combination of fludarabine, cyclophosphamide, and mitoxantrone (FCM) to FCM and rituximab in patients with relapsed or refractory follicular and mantle cell lymphoma has been published in full paper form [18]. This paper reports superior response rate, event-free survival, and overall survival in favor of the FCM-rituximab arm. In the subset of patients with mantle cell lymphoma, the response rate was no different between the two arms (58% vs 46%; p = 0.282), but overall survival favored the FCM-rituximab arm (median not reached vs 11 months; p = 0.004). A second randomization of this trial tested the effect of 2 courses of maintenance Rituxan (at 3 and 9 months) with median response duration slightly prolonged at 14 vs 12 months [28].

8. Other Agents

The activity of agents such as flavopiridol [29], thalidomide [30], temsirolimus [31] has been studied in mantle cell lymphoma. Recent trials have shown promising results with Bortezomib in relapsed and refractory MCL with RR ~ 33 - 50% [32-34]. These agents are not routinely available outside of the setting of a clinical trial.

Odette Cancer Centre Policy

**Limited Stage (I/II):**
- Involved field radiation (30-36 cGy in 15-18 fractions). Chemotherapy will not be given.

**Advanced Stage (Asymptomatic):**
Patients who are asymptomatic without pending organ impingement can be observed without treatment.

**Advanced Stage (Symptomatic):**
- CVP-rituximab will be considered first-line therapy for most patients. Responders should receive maintenance Rituximab q 3 months until relapse or 2 years maximum
- Patients with rapidly progressive disease and those eligible for high-dose therapy in first CR will be treated with CHOP-rituximab.
- Younger patients with good performance status will be considered for autologous transplantation in first remission. All patients should receive maintenance rituximab following induction therapy.
Dose Modification & Growth Factor Support

As therapy is not curative, a policy of dose delay and reduction will be used in most patients in the case of neutropenia complications. G-CSF is not routinely indicated (see CCO-PEBC EBS 12-2 at www.cancercare.on.ca).

Assessment of Response

Responses are classified according to the Cheson criteria (Appendix C). As treatment of mantle cell lymphoma is palliative, treatment should be guided by patient’s symptoms more than the extent of radiologic response. Imaging such as abdominal ultrasound or CT’s may be used to follow up with life threatening organ involvement. After completion of therapy, patients will be followed clinically at 3-monthly intervals. Routine CT scans are not warranted and should not be performed.

Second-line Therapy

Patients who fail to respond to or relapse after first-line therapy do poorly. Such patients should be considered for clinical trials. Patients with long remissions after first-line therapy can be retreated with the same regimen if feasible. CHOP (+/-rituximab) is recommended for patients who fail after chlorambucil or CVP and have a good performance status and wish further therapy. Purine analogs such as fludarabine or 2-CDA have been tried, but response rates are low [17, 35]. Patients failing after CHOP therapy may be treated with FCM +/- rituximab. Entry into clinical trials is encouraged. Bortezomib may be an option. Stem cell transplantation may be an option for selected patients in this setting. Intensive cisplatin-based regimens such as DHAP, and ESHAP should be reserved for patients considered eligible for high-dose therapy.

References


