Updates (extensive re-write):

- Major changes to initial therapy of younger and older patients
- Use of thalidomide, bortezomib
- Changes to bisphosphonate and erythropoietin use
- Section on amyloidosis added
- CVP-R now front-line therapy for lymphoplasmacytic lymphoma

Introduction

The WHO classification of plasma cell dyscrasias are a group of clonal disorders of terminally differentiated B-cells. These include multiple myeloma, solitary plasmacytoma, lymphoplasmacytic lymphoma (Waldenström’s macroglobulinemia), plasma cell leukemia as well as monoclonal gammopathy of uncertain significance. Substantial advances have been made in the management of these disorders in the past five years [1]. Despite these improvements, outcome for many patients remains suboptimal. For this reason, patients should be offered enrolment in clinical trials where available.

Plasma Cell Neoplasms:

- Monoclonal Gammopathy of Uncertain Significance (MGUS)
- Solitary Plasmacytoma
- Multiple Myeloma
- Plasma Cell Leukemia
- Monoclonal Immunoglobulin Deposition Disease
- Primary Amyloidosis
- Monoclonal Light & Heavy Chain Disease
- Osteosclerotic Myeloma (POEMS)
- Lymphoplasmacytic Lymphoma

Monoclonal Gammopathy of Uncertain Significance (MGUS)

Monoclonal gammopathy is defined as the presence of excessive amounts of immunoglobulin of identical shape and change in the serum or urine [2]. Identification of a monoclonal protein (paraprotein) in either the serum or urine implies the presence of a clonal disorder.

Diagnosis

A paraprotein may be detected on serum protein electrophoresis, serum protein immunoelectrophoresis, or urine for light chains (Bence Jones protein). MGUS is defined by the presence of a stable paraprotein of < 30 g/L in the absence of symptoms and with little or no Bence Jones proteinuria. Patients also require a normal serum calcium, creatinine, and hemoglobin. While many references require a normal bone marrow examination and skeletal survey, we do not routinely perform these tests in asymptomatic patients.
Baseline Investigations

All patients should have the following tests at baseline:

- Serum protein electrophoresis (SPE)*
- Serum protein immunoelectrophoresis or immunofixation
- Immunoglobulin quantitation
- CBC
- Serum calcium, creatinine, and albumin
- Random urine for total protein
- Serum free light chains [3]

Serum beta-2-microglobulin should not be performed, as it is not prognostic in MGUS

Immunofixation electrophoresis (IFE) will be automatically performed if SPE is positive*

Indications for Bone Marrow Testing

Bone marrow testing is not routinely performed.

Absolute indications include:

- Unexplained anemia, hypercalcemia, or renal failure
- Symptoms suggestive of myeloma, amyloidosis, or lymphoma

Relative Indications include:

- Free light chain ratio < 0.25 or > 4.0 or 100 mg/L
- Paraprotein: ≥ 15 g/L

Skeletal Survey

Skeletal surveys will be performed if bony symptoms are present or if suspicion of myeloma is high.

Prognosis

Kyle, et al. [4, 5] recently published results of a long-term study of prognosis of MGUS. This study of 1384 patients followed for a median of 15 years revealed a rate of progression to myeloma, lymphoma, amyloidosis or CLL of approximately 1% per year (12% after 10 years, 25% after 20 years and 30% after 25 years). This rate represented a seven times relative risk increase compared to a comparative group. No features can reliably predict patients who will progress to myeloma or other B-cell malignancies. However factors that appear to predict increased progression in this and other series are:

- Concentration of M protein ≥ 15 g/L,
- IgM or IgA (rather than IgG) monoclonal protein, and
- Abnormal serum light chain ratio (< 0.26 or > 1.65).

Each of these factors is reported to be associated with a relative risk of progression to myeloma or B-cell malignancy of 2-4 times. The Mayo Clinic report that patients with 3 of these risk factors have a 20-year risk of progression of 58%, 37% with 2 risk factors, 21% with one risk factor, and 5% with no risk factor [5].

Other factors reported to be predictive in some series include polyclonal serum immunoglobulin reduction, elevated ESR and marrow plasmacytosis. These factors will not be routinely used to risk stratify patients in our Centre [6].
**Therapy**

Patients will be managed with observation alone. There is no evidence to support the use of alkylator-based chemotherapy or bisphosphonates to delay progression.

**Monitoring**

Patients with MGUS who are felt to be at low-risk of progression to myeloma (0-1 risk factors) do not require follow-up at the Cancer Centre. Such patients should be followed yearly with their family doctor.

Patients felt to be at higher risk of progression (2-3 risk factors) should be followed at the Centre yearly. Patients will have blood work performed 2-3 weeks prior to clinic visits in order that results are available at the time of the visit. The following tests should be performed with each visit:

- CBC
- Serum creatinine and calcium
- Serum protein electrophoresis
- Immunoglobulin quantitation
- Random urine for protein*

*24-hour urine for protein, light chain quantitation and creatinine clearance if random urine protein abnormal

**Repeat immunoelectrophoresis and free light chain assay should not be performed**

Patients showing a progressive increase in paraprotein level should undergo bone marrow testing and a skeletal survey.

**Solitary Plasmacytoma**

Solitary plasmacytomas are rare, accounting for < 5% of patients with plasma cell neoplasms. Solitary plasmacytomas can be divided into two distinct clinical entities: osseous and extraosseous plasmacytomas.

**Diagnosis**

Solitary plasmacytomas are defined as a collection of clonal plasma cells on tissue biopsy, negative skeletal survey, absence of clonal plasma cells on bone marrow biopsy, and no evidence of anemia, hypercalcemia, or renal involvement suggesting myeloma [7].

A solitary plasmacytoma of bone (SPB) is defined as a single lesion in bone. Older definitions have allowed for up to 2 lesions and up to 10% marrow plasmacytosis. Multifocal bone involvement has traditionally been excluded by skeletal survey (plain x-ray), but more recent series have suggested that MRI of the spine, pelvis and proximal femora and humerus will detect additional lesions in ~30% of patients. Identification of further lesions is highly predictive of progression to myeloma. For this reason, it is suggested that patients with solitary plasmacytomas of bone undergo MRI of the spine and pelvis to exclude disseminated disease.

Solitary extraosseous plasmacytoma is defined as a single clonal plasma cell lesion as above, but arising outside of bone, commonly in the nasopharynx.
Baseline Investigations

The following investigations should be performed at baseline in most patients:

- CBC, differential and blood film
- Electrolytes, urea, creatinine, calcium, albumin
- Serum protein electrophoresis, immunoelectrophoresis, or immunoquantitation
- Random urine for protein, Bence-Jones protein
- Skeletal survey
- Unilateral Bone marrow aspiration and biopsy (with FISH panel)
- MRI spine and pelvis (SPB only)

*24-hour urine for protein, light chain quantitation and creatinine clearance if random urine protein abnormal

Staging & Prognosis

Patients with solitary plasmacytoma have a relatively favourable prognosis. Median survival for patients with SPB ranged from 7.5-12 years +. Prognosis for patients with extraosseous plasmacytomas is likely even better.

Treatment

Patients should be treated with local radiation to the involved area. **4000 cGy in 20 fractions** should be administered with an adequate margin of normal tissue. Where appropriate, CT or MRI planning should be used to assess soft tissue extension and to minimize damage to critical structures. Patients should not receive systemic chemotherapy, as there is no evidence that it delays progression and may interfere with future high-dose therapy. Patients without osteopenia will not routinely be offered bisphosphonate therapy.

Monitoring

Careful follow-up is essential particularly in the first three years. Patients should be seen every three to four months for the first two years and every six months thereafter. The following tests should be performed 2-3 weeks prior to each visit:

- CBC, differential
- Electrolytes, urea, creatinine, calcium, albumin
- Serum protein electrophoresis, immunoglobulin quantitation
- Random urine for protein

*24-hour urine for protein, light chain quantitation and creatinine clearance if random urine protein abnormal

- Serum protein immunoelectrophoresis should not be repeated
- Skeletal survey should be repeated annually
Multiple Myeloma

Myeloma is a rare malignancy of plasma cell origin that accounts for < 1% of all cancers. The management of myeloma has changed substantially over the past 5 years and has become quite complex and resource intensive.

Diagnosis

There are two commonly used sets of diagnostic criteria for myeloma - the WHO criteria and those proposed by the International Myeloma Working Group. While there are commonalities, there are significant differences. Both are summarized below:

WHO Criteria [8]:

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Bone marrow &gt; 30% plasma cells</td>
<td>1. Bone marrow plasmacytosis 10-30%</td>
</tr>
<tr>
<td>B. Plasmacytoma on tissue biopsy</td>
<td>2. Monoclonal protein less than above levels</td>
</tr>
<tr>
<td>C. Paraprotein level: serum IgG &gt; 35 g/L, IgA &gt; 20 g/L or light chain excretion &gt; 1 g/day</td>
<td>3. Lytic bone lesions</td>
</tr>
<tr>
<td></td>
<td>4. Reduced non-clonal immunoglobulin levels</td>
</tr>
</tbody>
</table>

The diagnosis of myeloma can be made in the presence of:

- Any two major criteria, or
- Major criterion A or B plus minor criterion 2, 3, or 4, or
- Major criterion C plus minor criterion 1 or 3

The International Myeloma working group criteria are as follows [9]:

Multiple Myeloma (all 3 criteria must be met)
- Presence of a serum or urinary monoclonal protein
- Presence of clonal plasma cells in the bone marrow or a plasmacytoma
- Presence of end organ damage felt related to the plasma cell dyscrasia, such as:
  - Increased calcium concentration
  - Lytic bone lesions
  - Anemia, or
  - Renal failure

Asymptomatic (smoldering) multiple myeloma (SMM, both criteria must be met)
- Serum monoclonal protein ≥ 30 g/L and/or bone marrow plasma cells ≥ 10 percent
- No end organ damage related to plasma cell dyscrasia (see list above)

Monoclonal gammopathy of undetermined significance (MGUS, all 3 criteria must be met)
- Serum monoclonal protein < 30 g/L
- Bone marrow plasma cells < 10 percent
- No end organ damage related to plasma cell dyscrasia or a related B-cell lymphoproliferative disorder (see list above)
Baseline Investigations

The following investigations should be performed in most patients:

- CBC, differential and blood film
- Serum electrolytes, urea, creatinine, albumin and calcium
- Serum beta-2-microglobulin
- Serum protein electrophoresis
- Immunoglobulin quantitation
- Random urine for protein*
- Serum free light chain assay
- Bone marrow aspiration and biopsy (with FISH panel)
- Skeletal survey (myeloma survey)

*24-hour urine for protein, light chain quantitation and creatinine clearance if random urine protein abnormal

Patients in whom management will be purely supportive may have less extensive investigation.

Staging & Prognosis

The most common staging system in use in myeloma has been the Salmon and Durie system [10]. It remains in use, particularly for clinical trials, but is not utilized commonly in clinical practice. This system divides patients into three stages based on the following criteria:

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the following:</td>
<td>Intermediate (neither stage I or III)</td>
<td>Anyone of the following:</td>
</tr>
<tr>
<td>Hemoglobin &gt; 100 g/L</td>
<td>Hemoglobin &lt; 85 g/L</td>
<td></td>
</tr>
<tr>
<td>IgG &lt; 50 g/L, IgA &lt; 30 g/L</td>
<td>IgG &gt; 70 g/L, IgA &gt; 50 g/L</td>
<td></td>
</tr>
<tr>
<td>Normal serum calcium</td>
<td>Elevated serum calcium</td>
<td></td>
</tr>
<tr>
<td>Urinary monoclonal protein 4 g/24 hrs</td>
<td>Urinary monoclonal protein &gt; 12 g/day</td>
<td></td>
</tr>
<tr>
<td>0 or 1 lytic bone lesion</td>
<td>Advanced lytic bone lesions</td>
<td></td>
</tr>
</tbody>
</table>

A - Creatinine level < 200 g/L B - Creatinine level > 200 g/L

Reported median survivals range from > 5 years for stage IA to 15 months for stage IIIB disease.

An alternate system that is increasingly being used is the ISS system [11]

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I — B2M &lt; 3.5 mg/L and serum albumin &gt;= 35 g/L</td>
<td>62 months</td>
</tr>
<tr>
<td>Stage II — neither stage I nor stage III</td>
<td>44 months</td>
</tr>
<tr>
<td>Stage III — B2M &gt;=5.5 mg/L</td>
<td>29 months</td>
</tr>
</tbody>
</table>

Other factors said to predict poor prognosis include:

- Elevated plasma cell labeling index
- Adverse karyotype (13q deletion)

The presence of the 13q14 deletion is felt to be the most important adverse prognostic factor[12]. In one study detection of the 13q14 abnormality was associated with a lower response rate (41% vs 79%; p=0.009) and shorter survival (24 mo vs > 60 mg; p < 0.005), whereas hyperdiploidy and t(11; 14) are associated with a good prognosis [13]. Patients with 13q deletions appear to do poorly with conventional and high-dose treatment options and should be considered for enrolment in clinical trials, however, insufficient evidence exists to suggest a different sequence of treatment options for such patients.
The prognosis and clinical course of smouldering myeloma from the Mayo Clinic is summarized in a recent publication [14]. Risk of progression at 5 years is 10% with serum protein level, idiootype (IgA – higher risk); urinary light chain and marrow plasmacytosis are reported as risk factors for progression.

Management

Over the past few years, the management of myeloma is increasingly being defined by large, well-conducted randomized trials, however the treatment of myeloma remains palliative with few treatment options being shown to improve long-term outcome.

Watch and Wait: Most patients with myeloma are symptomatic at presentation and require treatment. For asymptomatic patients, however, observation without treatment is an option. Two randomized trials report that patients randomized to deferred treatment have comparable outcomes to those started on treatment at diagnosis [15, 16]. These trials are small and cannot exclude a small clinically important benefit, but given the palliative nature of treatment and the toxicities of treatment, watch and wait, is the recommended option for such patients.

Alkylator-based Therapy: Alkylator-based regimens such as melphalan and prednisone were the first treatment options available for myeloma and remain in widespread use. A meta-analysis of 27 trials comparing alkylator-based regimens to more intensive regimens reported no benefit for the more intensive regimens [17]. Our Center uses the standard NCIC dosing strategy for melphalan and prednisone for primary therapy and cyclophosphamide and prednisone as a palliative later line regimen (see Appendix B). For younger patients with good performance in who high-dose therapy and autologous stem cell transplantation are contemplated, alkylator-based regimens should be deferred given the potential adverse impact on stem cell mobilization.

High-dose Dexamethasone Based Regimens: High-dose dexamethasone based regimens such as VAD or high-dose dexamethasone are used commonly as pre-transplant therapy, as salvage treatment, as well as palliative induction treatment for patients requiring rapid response such as those with rapidly progressive renal failure [18, 19]. No randomized trials comparing VAD to high-dose dexamethasone have been performed, however, expert consensus suggest that VAD may be modestly more effective in producing a response at the cost of toxicity and the need for a central line. Our Center uses High-dose dexamethasone preferentially (see Appendix B). Thalidomide may be added if suboptimal response is observed (see thalidomide discussion below).

High-dose Therapy: The role of high-dose therapy (HDT) in myeloma is addressed in the CCO-PEBC EBS guideline 6-6. There is no evidence that allogeneic transplantation improves outcome in myeloma as the curative potential is offset by toxicity. Ten randomized trials compare high-dose therapy to conventional dose therapy in myeloma. These trials have been performed in younger patients with the maximum age of enrolment ranging from 55 to 65 years of age. The maximum age for transplantation is unclear, however given the limited evidence available in patients over age 65, performance status and comorbidities should be considered prior to recommending transplantation to older patients. These trials demonstrate that transplantation is associated with improved progression free survival in selected patients and a number demonstrate improved 5-year survival rates, but do not demonstrate curative potential. One randomized trial, recently published reports improved survival in patients randomized to melphalan, prednisone and thalidomide compared to reduced-intensity transplantation in older patients [20]. The greatest impact on survival was reported in a trial by Attal, in which 5-year survival was 52% vs for 12% for conventional treatment. Other trials have demonstrated less impressive differences [21]. An individual patient meta-analysis of 9/10 trials published in 2007 did not identify a survival benefit with HDT though a PFS benefit was observed (HR of progression of 0.75) [22]. The PFS benefit was not restricted to patients with chemoresponsive myeloma. Autologous stem cell transplantation is generally done using high-dose melphalan induction without total body irradiation. Some studies suggest a benefit of double (tandem) transplantation over a single transplant, however, this remains controversial and in our Center, tandem transplantation is generally reserved for patients with a suboptimal response to a single transplant. Maintenance therapy post-transplant is considered experimental, and is currently the subject of clinical trials.
**Thalidomide:** The use of thalidomide in myeloma is the subject of a CCO-PEBC EBS guideline 6-21 (see www.cancercare.on.ca). Thalidomide as a single agent has modest activity in relapsed or refractory myeloma [23]. When used in this fashion, thalidomide is associated with ~30% response rate and significant toxicities including sedation and peripheral neuropathy. Recently, new evidence evaluating the roles of thalidomide in combination with conventional chemotherapy is emerging. Thalidomide dosing combination studies is 100-200 mg/day. Seven randomized trials comparing chemotherapy to chemotherapy plus thalidomide have been reported [3, 24-27]. A meta-analysis of these trials is included in the CCO-PEBC EBS guideline 6-21. The addition of thalidomide is associated with improved overall survival (hazard ratio 0.67; 95% CI 0.52 to 0.87), response rate weighted relative risk of 1.49 (95% CI 1.31 to 1.70), but an increased risk of TVE and grade 3-4 peripheral neuropathy (RR 2.80 95% CI 1.85 to 4.24 and 3.11 (95% CI 1.44 to 6.74) respectively with thalidomide. For patients not planned for high-dose therapy and autologous stem cell transplantation, the CCO Hematology DSG recommends that thalidomide be given along with melphalan and prednisone. The evidence that the addition of thalidomide to pre-transplant induction chemotherapy improves outcome is weaker and is not routinely recommended by the CCO Hematology DSG. One commonly used strategy is to initiate pre-transplant treatment with high-dose dexamethasone alone and add in thalidomide (100-200 mg) in non-responding patients. It is clear from the randomized trials that thalidomide is associated with an excess risk of venous thromboembolism (relative risk 2.86 [CCO-PEBC EBS guidelines 6-21]). There is a suggestion that this risk is lower in trials that include thromboprophylaxis. There is no agreement on optimal thromboprophylaxis as both ASA 325 mg PO daily and low molecular weight heparin have been used.

**Obtaining Thalidomide:** At the time of writing, thalidomide is not approved by the Canadian Health Protection Branch (HPB) and is not funded though any Ministry of Health Program. Thalidomide can still be obtained for patients, but requires individual patient HPB approval and may require application to the Celgene Cantap Program for funding. HPB approval can be obtained by submitting the special access approval form, which can be downloaded from the HPB web site at www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/acces/sapf1_pasf1_e.pdf and faxed to 613-941-3194. The cost for thalidomide at a dose of 200 mg/day is ~ $2400/month. There is no Ontario Ministry of Health Program which will contribute to the funding of this agent. In some cases, patients may have all or part of the cost covered by private drug insurance. Celgene offers a means-based patient assistance program. An application form for the program can be downloaded from the BC Cancer Agency web site at http://www.bccancer.bc.ca/NR/rdonlyres/D2AED198-E2C7-4DBB-9490-7B6A332610C4/17188/CANTAPregistrationformEN.pdf.

**Bortezomib:** Bortezomib is a novel proteosome inhibitor with activity in myeloma. The use of bortezomib is the subject of CCO-PEBC EBS guideline 6-18. One randomized control trial comparing bortezomib to high-dose dexamethasone in relapsed myeloma has been published [28]. Time to progression was greater (6.2 versus 3.5 months; p < 0.001) and greater one-year survival (80% versus 66%; p = 0.003) in the bortezomib arm. Grade 3 adverse events were more common in the bortezomib arm (61% versus 44%; p=0.01). The CCO Hematology DSG recommends bortezomib as the preferred option for patients relapsing within one year of initial or subsequent treatment and as a reasonable option for patients relapsing greater than one year following autologous stem cell transplantation.

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**Odette Cancer Centre Policy (Initial Therapy)**

All patients should have dental assessment

**Asymptomatic (Smoldering) Myeloma:**
- Observation without chemotherapy
- No bisphosphonates
- Vaccination for pneumococcus and influenza
- Monitoring every 3 months with testing 2-3 weeks prior to return:
  - CBC
  - Serum electrolytes, creatinine, albumin, calcium,
  - Serum protein electrophoresis
  - Serum protein immunoquantitation
  - Urine protein (random)
Progression to symptomatic myeloma occurs in most patients, often within 9 to 12 months, but a minority may remain progression-free for a number of years.

**Symptomatic Myeloma**

**A. Patients potentially eligible for high-dose therapy**
- Patients up to age 70 are potentially eligible for high-dose therapy
- Patients not eligible or interested in transplantation should be preferentially enrolled in clinical trials and should otherwise be treated similar to patients who are over the age of 70 years
- Patients considering high-dose therapy and autologous stem cell transplantation:
  ♦ High dose dexamethasone for 2-4 cycles
  ♦ Addition of thalidomide 100-200 mg/day in patients not responding to therapy
  ♦ Thromboprophylaxis with LMW heparin for patients at high-risk of VTE and EC-ASA for lower risk patients *(see Appendix B)*
  ♦ Referral to PMH for consideration of transplantation

**B. Patients not eligible for high-dose therapy**
- Melphalan, prednisone, and thalidomide (see above for thalidomide availability)
- Thromboprophylaxis with LMW heparin for patients at high-risk of VTE and EC-ASA for lower risk patients *(see Appendix B)*

**C. Maintenance:** Studies of steroids [29], interferon [30], thalidomide [31] and bortezomib in maintenance [32] have been performed. While a number of these agents show promise, it is unclear whether maintenance improves survival or whether the benefits out risk the disadvantages of ongoing treatment.

**Monitoring**

Patients on chemotherapy will be seen monthly. Therapy typically continues until one of the following occurs:
- One year elapses
- Stable reduction of paraprotein by > 50% for at least two months
- Disease progression

After completion of therapy, patients should be seen at three-monthly intervals with CBC, serum electrolytes, calcium, creatinine, and serum protein electrophoresis and immunoquantitation. Skeletal survey should be repeated annually.

Patients who do not show at least a 50% reduction in paraprotein and are not symptomatically improved after six months should have therapy discontinued *(see refractory myeloma)*.

**Management of Relapsed or Refractory Myeloma**
- As therapy of relapsed/refractory disease is suboptimal, all patients should be considered for randomized trials
- Relapsed following melphalan and prednisone (+/- thalidomide):
  ♦ ≥ 1 year response retreat with melphalan and prednisone (+/- thalidomide)
  ♦ < 1 year response – bortezomib x 6 cycles
- Relapse following high-dose therapy: Bortezomib x 6 cycles
Supportive Care

Pain Management: Bony pain is a common feature of myeloma and has a major impact on quality of life. Clinicians need to ask about pain at each visit. Initial pain management should involve narcotic analgesics (morphine sulfate 5-10 mg q2H prn) with titration until adequate pain control before introducing long-acting narcotic agents such as MS-Contin. Patients should also be started on Tylenol 1-2 q4H. Patients with localized back pain should be considered for vertebroplasty. Such patients should undergo CT scanning of the involved area and if compression fractures are identified, a referral to interventional radiology should be initiated.

Radiotherapy: Radiation is underused in the management of myeloma. Early referral for radiation should be considered in patients with painful bony lesions, patients at risk for pathological fractures, particularly in the femur or lower extremities and patients at risk for spinal cord compression. Brief courses of radiation (800 cGy in 1 fraction to 2000 cGy in 5 fractions) are indicated in the palliation of bone pain. If the patient is a candidate for autologous stem cell transplantation, 2500 cGy in 10 fractions is advised if the spinal cord is in the volume.

Large pelvic fields should be avoided early in the course of the disease so as not to compromise tolerance to subsequent systemic therapy.

Patients with pathologic fractures who undergo surgical stabilization should routinely be given postoperative radiotherapy (2000 cGy in 5 fractions) following adequate healing. Patients with diffuse bone pain in whom no systemic therapy is contemplated should be considered for hemibody irradiation (600 cGy in 1 fraction to upper half-body/800 cGy in 1 fraction to lower half-body). Pre-treatment with steroids and anti-emetics is mandatory.

Bisphosphonates: The evidence for bisphosphonate use is summarized in the CCO-PEBC EBS guideline 6-4 (www.cancercare.on.ca). There is evidence that routine use of bisphosphonates decreases skeletal events in myeloma and improves pain and quality of life [33-35]. The strongest evidence is for the use of pamidronate (90 mg IV over 2-4 hours) monthly, zoledronate 6mg IV monthly or clodronate 800 mg PO BID. Recently, evidence of toxicity of chronic use is emerging, in particular evidence of nephrotoxicity and osteonecrosis of the jaw.

Patients with myeloma and osteolytic bone lesions or osteopenia should be started on pamidronate 90 mg IV q 4 weeks at diagnosis and given for a two-year period. After two years, pamidronate should be discontinued for patients who are in remission, and should be continued at three monthly intervals for patients with evidence of active myeloma. Patients with no bone abnormalities should be counseled on the risks and benefits of bisphosphonate use and may be offered clodronate 800 mg PO BID for a period of two years.

Patients on bisphosphonates should have regular monitoring of renal function and the drug should be held if increasing albuminuria is detected. Patients should be made aware of the signs and symptoms of osteonecrosis of the jaw and should be advised to maintain good dental hygiene and avoid dental extractions while on treatment. More details on the prevention and management of osteonecrosis of the jaw can be found in CCO-PEBC EBS guideline 6-4.

Erythropoietin: The use of erythropoietic agent such as erythropoietin or darbopoietin can decrease transfusion requirements in patients with myeloma and symptomatic anemia [36, 37]. The evidence for the use of erythropoietin in myeloma is summarized in CCO evidence-based guideline 6-12. There is no evidence that these agents improve quality of life, however, and there is emerging evidence that rates of cancer progression may be increased with the use of these agents. Judicious use of these agents in selected patients on chemotherapy in an effort to avoid transfusion is reasonable and should be discussed with patients with hemoglobin < 100 g/L on chemotherapy. Darbopoietin 500 µg sc q 3 weeks or erythropoietin 40,000 U sc weekly are the preferred dosing regimens. These agents should be stopped once Hb reaches 110-120 g/L. Erythropoietin agents are not recommended for patients not receiving chemotherapy (see policy on Management of Anemia in Cancer).
Management of Renal Dysfunction

Patients with significant renal dysfunction should be seen in consultation by nephrology on an urgent basis. Acute management includes correction of dehydration and hypercalcemia. Patients should be started on sodium bicarbonate in order to alkalinize the urine and should have chemotherapy initiated soon after diagnosis. Patients with rapidly progressive renal failure will generally be started on high-dose dexamethasone chemotherapy rather than melphalan and prednisone (see Appendix B).

Plasma Cell Leukemia

Plasma cell leukemia is defined as a condition in which > 20% of peripheral blood cells are plasma cells and the absolute plasma cell count in the peripheral blood is at least $2 \times 10^9/L$ [38].

Baseline Investigations

Patients should be investigated in the same way as those with myeloma.

Management

Patients with plasma cell leukemia have an extremely poor prognosis when treated with melphalan and prednisone. Although no randomized trials exist, data from small single arm studies suggest response rates are higher to high-dose dexamethasone. Patients under age 65-70 years of age should be considered for ABMT.

Monoclonal Immunoglobulin Deposition Disease

The monoclonal immunoglobulin deposition diseases are a group of related disorders characterized by Immunoglobulin deposition in organs and soft tissues [39]. These conditions are plasma cell neoplasms, but symptoms may develop prior to development of overt myeloma. These include primary amyloidosis, and monoclonal light and heavy chain deposition diseases.

Primary Amyloidosis

Primary amyloidosis involves the deposition of abnormal immunoglobulin in the form of Beta-pleated sheets that bind Congo red dye. Accumulation in the heart, liver, kidneys, gut and nerves can result in organ failure.

Diagnosis

The diagnosis of amyloidosis is generally made through biopsy of affected organs or abdominal fat pad using Congo red staining.
Staging & Prognosis

Patients should be staged according to the myeloma staging systems (Salmon-Dury or ISS). Patients with amyloidosis typically have worse prognosis than comparable patients with myeloma without amyloidosis. In a large retrospective series of 810 patients with Amyloidosis reported by Kyle from the Mayo clinic, survival was reported to be 51% at one year, 16% at 5 years and 5% at 10 years with most patients receiving alkylator-based therapy [40].

Treatment

Patients are typically treated comparably to patients with myeloma, though response to treatment may be harder to evaluate in the absence of a significant paraprotein. High-dose therapy and autologous transplantation may be an option for younger patients, but treatment-related mortality tends to be higher than for patients with myeloma. Our policy would be for consideration of high-dose therapy in patients of appropriate age, performance status and organ function, and the use of melphalan, prednisone, and thalidomide in remaining patients.

Monoclonal Light & Heavy Chain Deposition Disease

These rare disorders present similarly to primary amyloidosis, but the immunoglobulin deposits do not bind Congo red [39]. The diagnosis is generally suspected in cases where a paraprotein is detected in peripheral blood and deposition of protein is identified on routine staining, but Congo red staining is negative. These patients are managed similarly to patients with primary amyloidosis, but have a very poor prognosis.

Osteosclerotic Myeloma (POEMS)

Osteosclerotic myeloma is a rare variant of myeloma typically characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes [41]. The pathophysiology of this disorder remains unknown, though the frequently observed high levels of Interleukin 1-B, tumour-necrosis factor alpha and interleukin-6 are thought to potentially play a role. Prognosis is generally better than other patients with myeloma [42]. Patients should be treated comparably to other patients with myeloma, though thalidomide should be used with caution given the incidence of neuropathy. Radiation can be highly effective for sclerotic lesions and skin changes and has been reported to improve neuropathy in some cases.

Lymphoplasmacytic Lymphoma

Waldenström’s macroglobulinemia

Waldenström’s macroglobulinemia (WM) is a rare cancer that accounts for < 2% of hematologic malignancies. It affects ~150 Canadians each year [43]. Because of its rarity, little randomized trial evidence is available to guide therapy.
Diagnosis

The original description of WM was of a lymphoplasmacytic infiltration of the bone marrow accompanied by a high level of circulating IgM. According to the REAL and WHO classifications, patients with WM would be classified as having a lymphoplasmacytic lymphoma [39]. Morphologically patients have a distinct disorder of small lymphoid cells that show maturation to plasma cells. They usually lack CD5 and lack features of follicular lymphoma, mantle cell, marginal zone lymphoma or CLL. The cells have surface and cytoplasmic IgM.

Baseline Investigations

All patients should have the following investigations:

- CBC, differential and blood film
- Serum electrolytes, urea, creatinine, calcium profile, LDH
- Serum protein electrophoresis
- Serum protein immunoelectrophoresis or immunofixation
- Immunoglobulin quantitation
- Serum viscosity
- Bone marrow biopsy
- CT scans of chest, abdomen and pelvis

Prognosis & Staging

Patients with WM are staged using the Ann Arbor staging system [44], though most patients present with stage IV disease due to bone marrow involvement.

Most series found that the following factors predict for shorter survival: Age > 60, male gender, and hemoglobin < 110 g/L. Other investigators report that high Beta-2-microglobulinemia levels, Serum IgM > 40 g/L and hemoglobin < 120 g/L could be used to define four distinct prognostic groups with five-year survivals ranging from 22-87% [27].

Prognostic Factors in Waldenström’s (1 point for each)

- Age > 65 years
- Albumen < 40 g/L
- At least 1 cytopenia
- At least 2 cytopenias

<table>
<thead>
<tr>
<th>Index</th>
<th>No risk factors</th>
<th>% of patients</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0 or 1</td>
<td>27</td>
<td>83</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>27</td>
<td>62</td>
</tr>
<tr>
<td>High</td>
<td>3 or 4</td>
<td>46</td>
<td>25</td>
</tr>
</tbody>
</table>

Treatment

Patients who are asymptomatic without end-organ damage can be followed carefully without treatment.

IgM-induced complications: When high levels of circulating IgM result in hyperviscosity, cryoglobulinemia, or peripheral neuropathy, immediate treatment is warranted. Such patients should be referred for plasma exchange and should be started on systemic chemotherapy (alkylator or purine analog-based). Patients should not generally be treated for asymptomatic elevations in serum viscosity alone.
**Lymphoma:** Patients with progressive adenopathy or cytopenias should be started on systemic chemotherapy. Standard therapy for WM has been alkylator-based chemotherapy such as chlorambucil (with or without prednisone) or CVP [43]. Daily chlorambucil (0.1 mg/kg/day) has been found to be equivalent to intermittent therapy (0.3 mg/kg x 7 days every six weeks) [45].

More recently purine analogs such as fludarabine or 2-CDA are being increasingly used. No randomized trials comparing alkylating agents to purine analogs as primary therapy have been published. In a non-randomized comparative study published in 1994, chlorambucil was as effective as CVP or CHOP. The responses to fludarabine or 2-CDA was not significantly better than chlorambucil, although responses to chlorambucil are often slow, often taking six months or more. A number of small single arm studies of fludarabine and 2-CDA report higher response rates, but little long-term outcome data are available. The data from these studies are summarized below:

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Treatment</th>
<th>RR%</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>[45]</td>
<td>46</td>
<td>Chlorambucil</td>
<td>70%</td>
<td>5.4 years</td>
</tr>
<tr>
<td>[46]</td>
<td>22</td>
<td>2-CDA</td>
<td>41%</td>
<td>Not reported</td>
</tr>
<tr>
<td>[47]</td>
<td>71</td>
<td>Fludarabine</td>
<td>62%</td>
<td>Not reached</td>
</tr>
<tr>
<td>[48]</td>
<td>231</td>
<td>Fludarabine</td>
<td>36%</td>
<td>6.0 years</td>
</tr>
<tr>
<td>[49]</td>
<td>26</td>
<td>2-CDA</td>
<td>85%</td>
<td>Not reported</td>
</tr>
<tr>
<td>[50]</td>
<td>33</td>
<td>M2 protocol</td>
<td>82%</td>
<td>4.2 Years</td>
</tr>
</tbody>
</table>

M2 Protocol: Melphalan, cyclophosphamide, carmustine, vincristine and prednisone

A multicenter randomized trial comparing chemotherapy with cyclophosphamide, adriamycin, and prednisone to fludarabine in patients who relapsed or were refractory to alkylator therapy has recently been published [51]. Response rates and progression-free survival rates were superior for fludarabine, but survival was similar in the two arms.

Rituximab has been used in a small number of patients with results similar to those seen in other indolent CD20-pos lymphomas [52, 53]. One randomized trial comparing CHOP to CHOP+ rituximab has been reported in 72 patients including patients with lymphoplasmacytic lymphoma [54]. Time to treatment failure was improved in the CHOP-R arm (not reached vs. 22 mo; \( p=0.0057 \)). There is little direct data on maintenance rituximab in lymphoplasmacytic lymphoma, but funding is available through CCO based on generalization from other indolent histologies (see CCO-PEBC EBS guideline 6-8) [55]. Case reports of Allogeneic and autologous transplantation have been published suggesting that high-dose therapy is feasible in WM, but larger studies are required before this approach is routinely offered to patients [56-58]. Bortezomib, a novel proteosome inhibitor is being studied in WM.

**Odette Cancer Centre Policy (Initial Therapy)**

- Asymptomatic patients should be observed without treatment. Patients with hyperviscosity, cryoglobulinemia, or peripheral neuropathy should be referred for plasma exchange.
- First-line therapy for most symptomatic patients should be CVP-R for 6-8 cycles followed by maintenance rituximab for 2 years
- Patients under age 55 years with poor prognostic factors should undergo HLA-testing and should be considered for allogeneic transplantation if a donor is identified.
- Patients who progress after primary therapy should be considered for experimental treatment. If no trials are available a sequence of treatment appropriate for many patients is: CVP-R → CHOP (+/-R) → FC (+/-R)
References


