Evaluation and Management of Newly Diagnosed Multiple Myeloma

Case Study and Commentary, Brendan M. Weiss, MD

ABSTRACT
• Objective: To discuss the diagnosis and management of newly diagnosed multiple myeloma (MM).
• Methods: Review of the literature and case presentation.
• Results: Treatment of MM has evolved over the past 20 years, with the development of immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide) and proteosome inhibitors (bortezomib and carfilzomib) resulting in improved outcomes. Epidemiologic studies from the Mayo Clinic and Sweden have shown dramatic survival gains in recent years due to these novel agents. The current treatment paradigm is divided into 3 phases: induction, consolidation, and maintenance. The approach to each phase of therapy is individualized based on the features of the myeloma, age, comorbidities, and personal preferences.
• Conclusion: Outcomes for patients with MM have improved significantly over the past 20 years due to several therapeutic advances. A major challenge remains to develop effective therapies for high-risk MM subsets that have not been substantially impacted by novel agents.

Multiple myeloma (MM) is an incurable plasma cell malignancy that is diagnosed in about 20,000 patients per year in the United States [1]. Myeloma is the second most common hematologic malignancy, with a median age of presentation of 72 years. It is manifested by the accumulation of malignant plasma cells in the bone marrow, leading to anemia, osteolytic bone lesions, and renal failure [2]. The outcomes for patients with MM have improved substantially over the past 20 years due to several therapeutic advances (Table 1). In the mid 1990s, high-dose melphalan and autologous stem cell transplantation (HDM/AutoSCT) was shown to improve survival compared with conventional chemotherapy. This represented the first major advance in MM since the development of melphalan and prednisone in the 1960s. Subsequently, the development of immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide) and proteosome inhibitors (bortezomib and carfilzomib) have resulted in improved outcomes. Epidemiologic studies from the Mayo Clinic and Sweden have shown dramatic survival gains in these recent years due to novel agents [3,4]. This case-based review will focus on the diagnosis and management of newly diagnosed multiple myeloma.

CASE STUDY
Initial Presentation
A 55-year-old man presents with worsening low back pain. He has had chronic low back pain for years due to degenerative disease, but it has worsened over the past few months. Laboratory studies show a hemoglobin of 12.5 gm/dL, a serum IgG kappa monoclonal immunoglobulin of 1.5 gm/dL and normal creatinine and calcium. Serum free light chain analysis showed a kappa free light chain (FLC) 235.0 mg/L, lambda FLC of 18.0 and a kappa:lambda ratio 13.1. A skeletal survey is negative for osteolytic lesions. A bone marrow biopsy shows 30% kappa-restricted plasma cells.

Does the patient have multiple myeloma?

It is important to establish a diagnosis of symptomatic MM requiring therapy. It is now known that MM always arises from an asymptomatic precursor condition, either monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM) [5,6]. MGUS is present in about 4% of whites over the age of 50 and progresses to MM at an average rate of 1% per year [7,8]. The prevalence of SMM in the general population...
is not known. The average rate of progression in SMM to MM is about 10% per year for the first 5 years but is reduced thereafter [9]. Patients with MGUS and SMM should be followed carefully for the development of myeloma-related organ or tissue impairment (ROTI) or amyloidosis. The most common manifestations of ROTI are hyperCalcemia, Renal failure, Anemia, and Bone disease (“CRAB”). The International Myeloma Working Group (IMWG) criteria for the diagnosis of MM requires the presence of ROTI, otherwise the patient is classified as either MGUS or SMM (Table 2) [10]. The distinction between MGUS and SMM is made on the basis of the monoclonal immunoglobulin concentration and degree of bone marrow plasmacytosis, but the diagnosis of symptomatic MM can be made at any level of M-protein or bone marrow plasma cell infiltration. It is critically important to establish that the clinical manifestations are related to the myeloma. There are numerous examples in the literature and in practice of falsely attributing these manifestations to MM when in fact other conditions are present, such as primary hyperparathyroidism accounting for hypercalcemia or anemia secondary to iron-deficiency. The IMWG has developed guidelines for SMM and MGUS which recommends observation based on the risk of progression (Table 3 and Table 4) [11]. In this case, the patient satisfies the diagnosis of SMM and should be observed at intervals of 3 to 6 months. Patients with SMM should be referred for clinical trials to investigate novel biomarkers for progression of therapeutic interventions to prevent or delay the development of MM.

**Case Continued**

The patient continues with follow-up every 3 months. His back pain resolves with analgesics and physical therapy in 6 weeks. Eighteen months after initial consultation the patient reports generalized fatigue and dyspnea climbing stairs. He also develops acute pain in his upper back. Laboratory studies show hemoglobin 9.2 gm/dL, creatinine 2.2 mg/dL, IgG Kappa 3.2 gm/dL, serum kappa FLC 652.2 mg/L, lambda FLC 8.3, kappa:lambda 78.5, beta-2 microglobulin 6.3 microgm/mL, and albumin 3.7 gm/dL. A bone marrow biopsy demonstrates 40% kappa-restricted plasma cells with normal cytogenetics and fluorescence in situ hybridization (FISH) testing showed t(14;16).
A skeletal survey revealed a vertebral compression fracture at T7.

• What is the recommended approach to initial therapy?

The patient now satisfies a diagnosis of symptomatic MM based on anemia, renal failure, and osteolytic bone disease that requires therapy. The current paradigm for treatment of newly-diagnosed MM is divided into 3 phases: induction, consolidation, and maintenance (Figure). The approach to each phase of therapy is individualized based on the features of the myeloma, age, comorbidities, and personal preferences. Patients with renal failure from myeloma should start induction chemotherapy in an expeditious manner. In addition, MM patients with renal failure should avoid nephrotoxic drugs and maintain euvolemia. The role of plasmapheresis in the management of myeloma-related renal failure remains unclear and is employed on a case-by-case basis in conjunction with chemotherapy. Analgesia and bisphosphonates for painful bone lesions should be started. Consultation with an orthopedic oncologist for bone lesions at high-risk of fracture may be needed for placement of a prophylactic intramedullary nails. Hypercalcemia should be managed with aggressive intravenous fluids and bisphosphonates. Another critically important decision to be made early in the course of therapy is the patient’s candidacy for HDM/AutoSCT. In practical terms, for patients whose age, general medical condition, and interest in the procedure make them suitable candidates, avoidance of melphalan-containing induction regimens is necessary to preserve the option of hematopoietic stem cell collection.

Induction chemotherapy regimens contain drugs from 4 classes: corticosteroids, immunomodulatory drugs, proteasome inhibitors, and alkylating agents. The most common regimens employed and their response rates are in Table 5. The choice of regimen is individualized based on the factors described above. The goal of induction therapy is to reduce the myeloma burden, improve symptoms, and allow for successful stem cell collection. Patients who are transplant candidates should not receive melphalan-based regimens or prolonged (> 4–6 cycles) induction therapy with lenalidomide-based regimens in order to facilitate stem cell collection. Induction therapy can be broadly considered as either 2-drug or 3-drug induction regimens. Although the 3-drug induction regimens result in higher response rates, they are also associated with increased toxicity. Importantly, a randomized controlled trial compared lenalidomide with traditional high-dose dexamethasone (480 mg per month) and low-dose dexamethasone (160 mg per month) and demonstrated that the low-dose dexamethasone resulted in better overall survival and lower toxicity [12]. Therefore, low-dose dexamethasone has become the standard of care for induction regimens. In patients who present with renal failure, high-dose dexamethasone regimens are still commonly used in order to achieve a rapid hematologic response and reversal of renal failure [13]. For patients who are ineligible for transplant, randomized controlled trials have demonstrated that the addition of a novel agent to melphalan and prednisone results in improved outcomes. Palumbo et al compared melphalan, prednisone, and thalidomide (MPT) with classic melphalan and prednisone (MP) [14]. Patients received 6 cycles of MPT followed by maintenance thalidomide until progression versus MP for 6 cycles. They demonstrated an improved event-free survival at 2 years of 54% for MPT versus 27% for MP (P < 0.001). San Miguel reported on the combination of melphalan, prednisone, and bortezomib (VMP) compared with MP, both given for 9 cycles without maintenance therapy [15]. The VMP combination resulted in a partial response or better in 71% of patients compared with 35% in the MP arm. The hazard ratio for overall survival favored bortezomib (0.61, P = 0.008).

Table 4. Mayo Clinic Risk Stratification for SMM

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Rate of Progression at 2 Yr</th>
<th>Rate of Progression at 5 Yr</th>
<th>Rate of Progression at 10 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>26</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>51</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>76</td>
<td>84</td>
</tr>
</tbody>
</table>

Risk factors: bone marrow plasma cells > 10%, sFLC ratio < 0.125 or > 8.0 or serum M-protein > 3.0 gm/dL.
What is this patient’s prognosis?

Prognosis in MM is based on both the International Staging System (ISS) and chromosomal abnormalities (Table 6). The ISS is a simplified staging system incorporating beta-2 microglobulin and serum albumin [16]. These 2 biomarkers reflect tumor mass, renal function and host fitness. In addition, bone marrow karyotype, translocations, chromosome content and gene expression profiling all have prognostic value [17]. At present, there are no specific therapies for specific molecular subgroups of myeloma. Based on the ISS, this patient is stage III (beta-2 microglobulin ≥ 5.5 mg/L) and has an unfavorable translocation.

What is the optimal management of myeloma-related bone disease?

Osteolysis is a fundamental aspect of the biology of MM and is present in the myeloma precursor states. Bone pain and fractures comprise a significant proportion of the morbidity of myeloma in nearly all patients. High-potency intravenous bisphosphonates are a critical component of supportive care and have been shown to reduce skeletal-related events (SRE). Both pamidronate and zoledronic acid are effective at reducing SRE in MM patients [18,19]. Zoledronic acid has an increased risk of adverse renal toxicity. In an important recent trial reported by the UK MRC IX, which randomized patients to zoledronic acid or clodronate (an oral bisphosphonate available in the UK) regardless of the presence of radiographically detected bone disease, zoledronic acid was associated with a 5.5-month increase in median survival [20]. This survival improvement was independent of SRE, suggesting that bisphosphonates have anti-myeloma properties. At present, intravenous bisphosphonates (pamidronate and zoledronic acid) are recommended for all MM patients requiring therapy. These agents need to be used carefully in patients with renal insufficiency. In patients with creatinine clearance (CrCl) less than 30 mL/minute, pamidronate should be given at 90 mg over 4 to 6 hours or at a dose of 60 mg over 2 hours [21]. A lower dose of pamidronate (30 mg) was compared with 90 mg in a randomized controlled trial and was shown to
be equivalent in multiple endpoints: improvement in quality of life, time to SRE, overall survival, and progression-free survival. There was a nonsignificant trend toward lower renal toxicity and osteonecrosis of the jaw with the lower dose regimen. Zoledronic acid also needs to be reduced for renal impairment, with reductions at CrCl 50 to 60 mL/min to 3.5 mg, 40 to 49 mL/min 3.3 mg, and 30 to 39 mL/min 3 mg. Zoledronic acid is not recommended for those with CrCl less than 30 mL/min. It is important to note that denosumab, a monoclonal antibody to RANK-ligand approved for use in breast and prostate cancer metastatic to bone, is contraindicated in MM until further studies in MM patients are completed. In a randomized trial of denosumab compared with zoledronic acid, the subset of MM patients treated with denosumab had inferior survival compared with the zoledronic acid patients [22].

Patients with MM are at increased risk of infection as a consequence of disease-related immunodeficiency as well as our therapies. Traditional high-dose dexamethasone-based regimens resulted in a high risk of infection compared with low-dose dexamethasone [12]. Therefore, antibacterial prophylaxis is less commonly used since the switch to lower-dose dexamethasone regimens. Bortezomib-based regimens are associated with varicella zoster reactivation rates that are nearly eliminated with acyclovir prophylaxis [25]. For patients with recurrent, severe bacterial infections, intravenous immune globulin can be effective [26]. Peripheral neuropathy is an important toxicity of both thalidomide and bortezomib, occurring in about 50% of patients [27]. Peripheral neuropathy from thalidomide is cumulative and dose dependent and is usually permanent. Bortezomib neuropathy is related to dose, schedule, and mode of administration and is mostly reversible. Careful attention to the development of peripheral neuropathy while patients are on therapy is essential. Prompt dose reductions are required with development of neuropathy of any grade with thalidomide. A randomized trial of subcutaneous administration compared with intravenous administration of bortezomib showed a dramatic decrease in peripheral neuropathy of all grades (38% vs. 53%) and grade 3 (6% vs. 16%) peripheral neuropathy [28]. The GIMEMA performed a phase III study of bortezomib, melphalan, prednisone, and thalidomide compared with bortezomib, melphalan and prednisone during which bortezomib dosing was changed from twice weekly IV to once weekly IV. The rate of grade 3 and 4 peripheral neuropathy was 28% in the twice weekly group and 8% in

### How are the toxicities of therapy managed?

Both of classes of novel agents are associated with unique toxicities that require specific management. The immunomodulatory drugs when combined with steroids or anthracyclines result in a marked increase in venous thromboembolic events [23]. The rate of VTE in these regimens ranges from 20% to 40% without prophylaxis. A randomized trial of aspirin (100 mg/day), minidose warfarin (1.25 mg/day) and enoxaparin (40 mg sc daily) in patients receiving thalidomide-based regimens demonstrated equivalence between aspirin and mini-dose warfarin [24].

### Table 5. Induction Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Complete Response Rate, %</th>
<th>Common Toxicities, &gt; 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transplant Eligible</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib-dexamethasone (Vd)</td>
<td>21</td>
<td>Infection, peripheral neuropathy</td>
</tr>
<tr>
<td>Cyclophosphamide, bortezomib dexamethasone (CyBorD)</td>
<td>46</td>
<td>Thrombocytopenia, neutropenia, anemia</td>
</tr>
<tr>
<td>Lenalidomide, bortezomib, dexamethasone (RVD)</td>
<td>29</td>
<td>Lymphopenia</td>
</tr>
<tr>
<td>Lenalidomide, dexamethasone (Rd)</td>
<td>24</td>
<td>Neutropenia, venous thrombosis</td>
</tr>
<tr>
<td><strong>Transplant Ineligible</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melphalan, prednisone, thalidomide (MPT)</td>
<td>13</td>
<td>Neutropenia, venous thrombosis, peripheral neuropathy, infection</td>
</tr>
<tr>
<td>Melphalan, prednisone, bortezomib (VMP)</td>
<td>24</td>
<td>Neutropenia, thrombocytopenia, anemia, peripheral neuropathy</td>
</tr>
<tr>
<td>Melphalan, prednisone, lenalidomide (MPR)</td>
<td>16</td>
<td>Neutropenia, anemia, thrombocytopenia, infection</td>
</tr>
</tbody>
</table>
the once weekly group \((P < 0.001)\), without any difference in efficacy [29]. Therefore, it appears that a strategy of either twice weekly dosing via a subcutaneous route or once weekly by the intravenous route are both effective strategies to reduce the risk of peripheral neuropathy.

**Case Continued**

The patient started therapy with cyclophosphamide 300 mg/m\(^2\) by mouth on days 1, 8, and 15, bortezomib 1.3 mg/m\(^2\) subcutaneously on days 1, 4, 8, and 11 and dexamethasone 40 mg per week. After 1 cycle of therapy the IgG kappa was 2.0 gm/dL and the creatinine was 1.4 mg/dL. Therapy was continued for a total of 4 cycles at which point the hemoglobin was 11.8 gm/dL, IgG kappa was 0.2 gm/dL and the creatinine was 1.0 mg/dL. He reported mild, non-painful paresthesias in his feet. The patient returns for consideration of HDM/AutoSCT.

**What is the role of maintenance therapy following induction therapy or transplant?**

There have been a series of studies exploring the role of maintenance therapy both following conventional chemotherapy and following HDM/AutoSCT. Early attempts with interferon and corticosteroids were of minimal benefit and were not tolerable over the long term [36]. Thalidomide has been shown to increase progression-free survival after conventional therapy and HDM/AutoSCT, however it results in high rates of discontinuation due to toxicity and is not suitable for maintenance therapy [37]. Recently, randomized controlled trials of maintenance lenalidomide following conventional therapy and HDM/AutoSCT have been reported. Palumbo reported a randomized trial of melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance (MPR-R), MPR, and MP [38]. In this study, MPR-R demonstrated improved progression-free survival of 31 months compared with 14 months and 13 months with MPR and MP, respectively. The IFM and Cancer and

**Table 6. Staging and Prognosis in MM**

<table>
<thead>
<tr>
<th>International Staging System</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-2 microglobulin &lt; 3.5 mg/L and albumin ≥ 3.5 gm/dL</td>
<td>Neither stage I or III</td>
<td>Beta-2 microglobulin ≥ 5.5 mg/L</td>
<td></td>
</tr>
</tbody>
</table>

**Chromosomal features**

- High risk: Deletion 17p, t(14:16), t(14:20), chromosome 1 gain, high risk gene expression signature (UAMS-70)
- Intermediate risk: t(4:14), cytogenetic deletion 13, hypodiploid
- Standard risk: t(11;14), t(6;14), hyperdiploid

Since that time numerous clinical trials have been performed comparing HDM/AutoSCT to conventional therapy as well as a single course of HDM/AutoSCT to tandem HDM/AutoSCT (2 planned courses within 3 to 6 months). It is clear that HDM/AutoSCT improves progression-free survival compared with conventional therapy [32]. Tandem HDM/AutoSCT does not appear to be superior to a single course of HDM/AutoSCT, but this is the subject of ongoing studies [33,34]. The timing of transplantation remains controversial, but overall survival is equivalent whether this is performed early or at the time of relapse [35]. Early transplantation is associated with improved time without symptoms, treatment and treatment related adverse events and thus may be preferred in some patients [35]. Several randomized trials are ongoing to answer questions regarding the role of transplant in myeloma (see clinicaltrials.gov).

**What is the role of high-dose therapy and autologous stem cell transplantation?**

The role of HDT/AutoSCT in the management of MM has become less clear with the advent of novel drugs [30]. High-dose melphalan and autologous stem cell transplantation was first reported to improve overall survival compared with conventional chemotherapy by the Intergroupe Francophone du Myeloma (IFM) in 1996 [31].
Leukemia Group B (CALGB) performed trials of lenalidomide maintenance compared with placebo following HDM/AutoSCT [39,40]. Both trials demonstrated a doubling of progression-free survival from about 2 years to 4 years. The CALGB trial also demonstrated an overall-survival benefit. In both studies of lenalidomide maintenance following HDM/AutoSCT there was about a twofold increased risk of second malignancies in the lenalidomide maintenance arm, although absolute event rates were small (about 8%). The inclusion of second malignancies as events still resulted in improved event-free survival, suggesting that maintenance therapy with lenalidomide provides meaningful benefits for patients.

**CONCLUSION**

The treatment paradigm for MM has evolved over the past 20 years, resulting in dramatic survival improvements. This trend is expected to continue with agents approved for relapsed disease (carfilzomib) moving earlier into the disease course. In addition, new classes of drugs to combine with existing regimens are in development, notably monoclonal antibodies (elotuzumab, daratumumab). The majority of MM patients diagnosed today can expect to have disease control over long periods of time with access to all available therapies. A major challenge remains to develop effective therapies for high-risk MM subsets that have not been substantially impacted by novel agents.

**REFERENCES**

nate 30 mg versus 90 mg on physical function in patients
with newly diagnosed multiple myeloma (Nordic Myeloma
Study Group): a double-blind, randomised controlled trial.
Lancet Oncol 2010;11:973–82.
22. Henry DH, Costa L, Goldwasser F, et al. Randomized,
double-blind study of denosumab versus zoledronic acid
in the treatment of bone metastases in patients with advanced
cancer (excluding breast and prostate cancer) or multiple
23. Kristinsson SY, Pleiiffer RM, Bjorkholm M, et al. Arte-
rial and venous thrombosis in monoclonal gammopathy
of undetermined significance and multiple myeloma: a
or enoxaparin thromboprophylaxis in patients with multiple
myeloma treated with thalidomide: a phase III, open-label,
study of bortezomib in relapsed, refractory myeloma. N
27. Sonneveld P, Jongen JL. Dealing with neuropathy in
plasma-cell dyscrasias. Hematology Am Soc Hematol Educ
versus intravenous administration of bortezomib in patients
with relapsed multiple myeloma: a randomised, phase 3,
of once-weekly bortezomib in multiple myeloma patients.
Blood 2010;116:4745–53.
30. Moreau P, Rajkumar SV. Should all eligible patients with
multiple myeloma receive autologous stem-cell transplant
randomized trial of autologous bone marrow transplantation
and chemotherapy in multiple myeloma. Intergroupe
cell transplantation for multiple myeloma beyond 2010.
double autologous stem-cell transplantation for multiple
34. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized
study of single compared with double autologous stem-cell
transplantation for multiple myeloma: Bologna 96 clinical
therapy and autologous blood stem-cell transplantation
compared with conventional treatment in myeloma patients
aged 55 to 65 years: long-term results of a randomized
control trial from the Group Myélome-Autogreffe. J Clin
Oncol 2005;23:9227–33.
36. Ludwig H, Durie BGM, McCarthy P, et al. IMWG con-
sensus on maintenance therapy in multiple myeloma. Blood
therapy with thalidomide improves survival in patients with
lenalidomide treatment for newly diagnosed multiple my-
maintenance after stem-cell transplantation for multiple
40. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalido-
mide after stem-cell transplantation for multiple myeloma.