Multiple Myeloma:
Therapeutic Advances and Comprehensive Care in 2012

CME Learning Objectives

After reviewing the material, the participant should be able to:

• Examine optimal frontline treatment strategies for patients with multiple myeloma using cytogenetics and molecular biomarkers.

• Assess the efficacy, safety, and long-term outcomes associated with the use of various induction regimens for multiple myeloma patients who are eligible/ ineligible to receive autologous stem cell transplantation.

• Recognize the most appropriate treatment options, including novel combinations and investigational novel drugs, for patients with relapsed and refractory multiple myeloma based on recent research data.
Introduction

The advances in the field of multiple myeloma (MM) over the last several years have led to improved patient outcomes. For the community practitioner, the expanding array of treatment options and longer-term survival rates have also brought increasing complexity to therapeutic decision-making in both the induction and relapsed/refractory multiple myeloma (RRMM) setting. Further, as medical therapies and transplant strategies are used in combination and sequence, the clinician must also address the resulting resistance and supportive care issues associated with multiple lines of therapy across the disease state. For example, a population of patients with RRMM that is refractory to both immunomodulatory agents (IMiDs) and bortezomib has been recently characterized. Kumar and colleagues have shown that this double-refractory population—with a median 9-month overall survival (OS) rate—represents a substantial clinical challenge in the era of modern MM therapies.

During the 53rd American Society of Hematology Annual Meeting and Exposition (ASH), December 10-13, 2011, Vindico Medical Education gathered leading clinicians to provide their analysis of the state-of-the-art myeloma care. These experts focused on three clinically-relevant themes that are particularly important for the community practitioner: (1) What is the profile of the new drugs that are coming soon for the management of RRMM? (2) What are the optimal induction regimens for transplant-eligible and ineligible patients? and (3) What are the considerations for long-term therapy in terms of maintenance strategies, as well as, concern over second primary malignancies (SPMs)?

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New Agents Coming Soon for Relapsed/Refractory Multiple Myeloma

Sergio A. Giralt, MD; Heather J. Landau, MD; and Antonio Palumbo, MD

The challenges posed by relapsed/refractory multiple myeloma (RRMM) have led to the development of a number of new agents. The activity of the agents as monotherapy and in combination with their optimal dose and schedule, as well as, safety, efficacy and supportive cases were discussed at the 53rd American Society of Hematology in 2011. In this monograph, we summarize the available data and discuss the role these agents are likely to play when they become commercially available in the United States, as well as, tips on administration based on our experience with these agents in clinical trials.

Carfilzomib

Carfilzomib is one of several next-generation proteasome inhibitors being developed for the treatment of RRMM. These next-generation agents are designed to improve the therapeutic efficacy and reduce side effects compared with the first-generation proteasome inhibitor, bortezomib. The US Food and Drug Administration (FDA) is currently reviewing the carfilzomib new drug application, and the agent is currently available in an expanded access program. Carfilzomib is an irreversible proteasome inhibitor, delivered intravenously, distinct from bortezomib which results in reversible proteasome inhibition.

Carfilzomib has single-agent activity in the RRMM setting (phase 2 study PX-171-004) (Table 1). The efficacy differs based on the patient’s prior exposure and response to bortezomib. For patients failing bortezomib therapy, carfilzomib provides a 21% overall response rate (ORR), and a median duration of response (DOR) of 11.5 months.1 At this year’s ASH symposium, Vij and colleagues presented the final analysis from this study for bortezomib-naïve patients.2 As illustrated in Table 1, the ORR was significantly higher for bortezomib-naïve patients, approximately 40% to 60%, and the median DOR was also higher at 13 months. Carfilzomib was generally well tolerated with impressive response rates and a relatively low peripheral neuropathy (PN) rate.

The optimal dosing of carfilzomib is still being evaluated. There is evidence of a dose-response relationship; 27 mg/m² produced superior outcomes compared to 20 mg/m².2 Based on preclinical data, a slower infusion may allow for a better therapeutic index. Indeed, as presented at this year’s ASH symposium, the PX-171-007 study has evaluated a 30-minute regimen in 33 patients...
at dosages ranging from 36 mg/m² up to 70 mg/m². The 56 mg/m² cohort experienced an ORR of 60% with an acceptable safety profile, suggesting that a slower infusion of carfilzomib may allow escalated doses, and

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<tr>
<th>Table 1. Carfilzomib in Relapsed/Refractory Multiple Myeloma</th>
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<td><strong>Agent/Combination</strong></td>
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<tr>
<td>Single Agent Carfilzomib (Vij, Abs 813) (Siegel, Abs 114)</td>
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<tr>
<td>Carfilzomib, lenalidomide, dexamethasone (CRd) (Wang, Abs 8025)</td>
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<th>Table 2. Carfilzomib as Initial Therapy</th>
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<td><strong>Agent/Combination</strong></td>
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<tr>
<td>Carfilzomib, lenalidomide, dexamethasone (CRd) N=53 (Jakubowiak, Abs 631)</td>
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<td>Carthadex (carfilzomib/thalidomide/dexamethasone) (Sonneveld, Abs 633)</td>
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Key: AE=adverse event; DOR=duration of response; ORR=overall response rate; PN=peripheral neuropathy; po=by mouth; VGPR=very good partial remission

potentially greater efficacy, to be administered with acceptable toxicity. Potentially greater efficacy, to be administered with acceptable toxicity.4

Carfilzomib has also been studied in several combinations. Carfilzomib, lenalidomide, and dexamethasone (CRd), were quite active in the RRMM setting (Table 1).4 More recently, CRd has been studied as initial therapy in both transplant eligible and ineligible patients (Table 2). In this study, the ORR was 100% and the PN rate was low.5 In newly diagnosed transplant-eligible patients, the Carthadex regimen, comprising carfilzomib, thalidomide, and dexamethasone provided a high response rate with similarly low PN frequency (Table 2).6

Data on the first oral proteasome inhibitor to enter clinical testing, MLN 9708, were also presented at ASH. Like bortezomib and carfilzomib, MLN9708 has single-agent activity.7 In the upfront setting in combination with lenalidomide and dexamethasone, it provided an impressive 100% ORR with less PN than bortezomib.8 In the future, this agent may allow a completely oral three-drug induction regimen.

**Table 3. Pomalidomide in Relapsed/Refractory Multiple Myeloma**

<table>
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<tr>
<th>Agent/Combination</th>
<th>Dosage/Schedule</th>
<th>Efficacy</th>
<th>Side Effects</th>
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| Pomalidomide + dexamethasone (Richardson, Abs 634) | Pomalidomide: 4 mg for 21 days of the 28-day cycle  
Dexamethasone: 40 mg per week | Overall population:  
Pomalidomide alone: ORR 13%;  
Pomalidomide + dexamethasone: 34%  
Lenalidomide refractory: 29%  
Double refractory: 30%  
Pomalidomide + dexamethasone: OS: 16.9 mo  
Median PFS: 4.7 mo | Hematologic, fatigue, and rash | Works in previously treated patients; 2 mg better than 4 mg |
| Pomalidomide + dexamethasone (21 vs. 28-day cycle) (LeLeu, Abs 812) | Pomalidomide: 4 mg  
plus dexamethasone 40 mg per week: 21/28 vs. 28/28 cycle | ORR: 65%  
DOR: >21 months | Hematologic, fatigue, pneumonia | Myelosuppression, neutropenia  
21/28 is better; Need growth factors |
| Pomalidomide + cyclophosphamide+ prednisone (Palumbo, Abs 632) | Pomalidomide: up to 2.5 mg/day, days 1-28  
Cyclophosphamide: 50 mg qd,  
Prednisone: 50 mg qd, days 1-28 | ORR: 65.5% | Neutropenia  
17% (Grade 4),  
thrombocytopenia  
37% (Grade 4),  
Rash 10%, DVT prophylaxis required | Works in previous lines,  
70% double refractory |
| Pomalidomide + clarithromycin + dexamethasone (CLaPD) (Mark, Abs 635) | Pomalidomide: 4 mg  
Clarithromycin: 500 mg, bid  
Dexamethasone: 40 mg day 1, 8, 15, and 22 | ORR: 60 (similar in double refractory);  
VGPR 27%;  
Median PFS: 8.13 months | Hematologic, fatigue, rash;  
DVT prophylaxis required | Multiple prior lines,  
70% double refractory |

Key: bid=two times a day; CLaPD=clarithromycin-pomalidomide-dexamethasone; DOR=duration of response; DVT=deep vein thrombosis;  
ORR=overall response rate; OS=overall survival; PFS=progression-free survival; qod=every other day; VGPR=very good partial remission  

**Pomalidomide is an anti-angiogenic, immune modulating agent (IMiD) that was developed as a more potent IMiD than either thalidomide or lenalidomide.**

**Pomalidomide**  
Pomalidomide is an anti-angiogenic, immune modulating agent (IMiD) that was developed as a more potent IMiD than either thalidomide or lenalidomide. Pomalidomide
is currently in phase 3 clinical development. Table 3 outlines various studies of pomalidomide in RRMM at ASH. Pomalidomide has demonstrated single-agent activity—with an ORR of 13%, which goes up to 34% when combined with low-dose dexamethasone.9 In the double refractory population, 4-mg pomalidomide plus low-dose dexamethasone has substantial activity. As was the case with carfilzomib, investigators are examining the optimal dose and schedule of pomalidomide. At the Mayo Clinic, 2 mg/day or 4 mg/day of pomalidomide given 28/28 days has been combined with dexamethasone 40 mg, resulting in an ORR of 65% and DOR of 21.3 months that suggest that the 2-mg dose may be better than the 4-mg dose.10 The French Group examined the effect of schedule—21-day vs. 28-day—on outcomes. The 21/28 cycle provided a better ORR than the 28/28 cycle.11 Triple combination approaches are also promising. Palumbo and colleagues evaluated the combination of pomalidomide plus cyclophosphamide and prednisone (PCP) and showed a high ORR (65.5%).12 Finally, Mark and colleagues evaluated the combination of pomalidomide, clarithromycin, and dexamethasone and showed an impressive ORR of 60% in a population that included a substantial proportion of patients with double-refractory disease.13

Elotuzumab

Elotuzumab is a monoclonal antibody directed against the myeloma cell-surface antigen, CS1. Elotuzumab is the first monoclonal antibody being evaluated in late-stage clinical trials in MM and is currently in phase 3 clinical development. This agent does not have appreciable single-agent activity.14 At this year’s ASH, Lonial and colleagues presented the results of a phase 2 study evaluating 2 doses of elotuzumab plus lenalidomide and dexamethasone, which showed an ORR of 92% in the 10-mg elotuzumab arm (Table 4), which is the dose moving forward in phase 3 trials.15 While these results appear promising, the study was conducted in lenalidomide-naïve patients, so it is difficult to separate out the benefit of elotuzumab over that of lenalidomide alone. Ongoing phase 3 studies of elotuzumab are being conducted in both the relapsed/refractory and upfront settings.

Bendamustine

Bendamustine is an alkylator that has been available in the former East Germany for years and currently in the United States for NHL and CLL.
in the US for the treatment of non-Hodgkin’s lymphoma (NHL) and chronic lymphocytic leukemia (CLL). In terms of single-agent activity, intravenous bendamustine plus prednisone has been studied vs. melphalan prednisone in the upfront setting.\(^1\) Several combination studies involving bendamustine in the RRMM setting were presented at ASH. One, presented by Lentzsch and colleagues, was a dose-escalation study of intravenous bendamustine on D 1 and 2, oral lenalidomide on D 1-21, and oral dexamethasone on days 1, 8, 15, and 22 of a 28-day cycle.\(^1\) The maximal tolerated dose (MTD) was 75 mg/m\(^2\) for bendamustine, 10 mg for lenalidomide, and 40 mg/wk for dexamethasone. The ORR was 52%, and the clinical benefit rate (≥SD) was 92%. Median time to response was 1.6 months; and there was a 24% VGPR rate. The grade 4 toxicities included 24% neutropenia and 7% thrombosis. The authors concluded that bendamustine-based therapy was effective and generally well tolerated in patients up to 80 years of age.

Vorinostat in RRMM

Vorinostat is an oral histone deacetylase (HDAC) inhibitor approved by the FDA for the management of cutaneous T-cell lymphoma. Vorinostat is currently in phase 3 clinical development in MM. Similar to a related HDAC inhibitor under development for MM, panobinostat, vorinostat blocks the activity of several proteins, including HDAC1, HDAC2, HDAC3, and HDAC6, that may result in epigenetic changes of gene expression affecting cell proliferation and survival. As shown in the Figure, another way that vorinostat is thought to work in MM is by inhibiting aggresome formation by affecting the ubiquitin pathway blocking the disposal of cellular waste, leading to the buildup of toxins and cellular death. Ubiquitin is a 76 amino acid polypeptide abundant in all eukaryotic cells. The initial step in the ubiquitin pathway is ATP-dependent and involves the linkage of ubiquitin to a ubiquitin-activating enzyme, or E1, in a high energy thioester bond. Ubiquitin is subsequently transferred in a second thioester linkage to a ubiquitin conjugating enzyme (Ubc), or E2, which in turn catalyzes the transfer of ubiquitin to the substrate protein in a covalent bond.\(^1\) The aggresome pathway may be a means of generating resistance to proteasome inhibitors, such as bortezomib, thus, they may synergize with proteasome activity.\(^1\)

Early work shows that vorinostat has very modest single-agent activity, around 10%.\(^2\) At ASH, David Siegel and colleagues presented the VANTAGE095 study, which investigated vorinostat plus bortezomib in heavily pretreated patients with double-refractory RRMM (Table 5).\(^3\) This study showed a clinical benefit rate (CBR) over 30% in this heavily pretreated population. In the larger, phase 3 trial (VANTAGE 088), bortezomib plus vorinostat was compared with bortezomib alone. A 56% ORR was seen with the combination of bortezomib and vorinostat.\(^4\) The most common side effects associated with the drug were gastrointestinal.

Table 5. Vorinostat Activity in Relapsed/Refractory Multiple Myeloma

<table>
<thead>
<tr>
<th>Agent/Combination</th>
<th>Dosage/Schedule</th>
<th>Efficacy</th>
<th>Side Effects</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Bortezomib + vorinostat (VANTAGE 95) (Siegel, Abs 480)</td>
<td>Bortezomib: 1.3 mg/m(^2) day 1, 4, 8, 11 Vorinostat: 400 mg qd for days 1-14 of 21-day cycle</td>
<td>ORR: 17% CBR (≥SD): 31% DOR: 6.3 months 100% bortezomib failure or failure/ineligible for IMiDS</td>
<td>Nausea, vomiting, diarrhea</td>
<td>Combo that is effective for double-refractory patients</td>
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<td>Bortezomib vs. bortezomib + vorinostat (VANTAGE 088) (Dimopoulos, Abs 811)</td>
<td>Bortezomib: 1.3 mg/m(^2), day 1, 4, 8, 11 + Placebo or Vorinostat: 400 mg qd for days 1-14 of 21-day cycle</td>
<td>Bortezomib: ORR 41%, PFS 6.8 mo Bortezomib + vorinostat: ORR 56% (P&lt;.0001) PFS 7.6 mo (34% reduction)</td>
<td>50% required dose reduction; GI, hematologic AEs</td>
<td>Steroid-free regimen</td>
</tr>
</tbody>
</table>

Key: AE=adverse event; CBR=clinical benefit rate; DOR=duration of response; GI=gastrointestinal; IMiD=immunomodulatory agent; mo=month; ORR=overall response rate; PFS=progression-free survival; qd=once daily; SD=standard deviation

**Discussion of the New Agents**

**Where do you see these new agents fitting into therapy? Any suggestions on administering them?**

**Dr. Palumbo:** Carfilzomib might represent a novel opportunity for patients resistant to bortezomib, since in these patients the peripheral neuropathy rate is approximately 20%. The drug also provides a slight increase in the response for the bortezomib-naive patient in comparison to what has been seen before with bortezomib.

**Dr. Giralt:** Importantly, for the community oncologist, carfilzomib was not associated with peripheral neuropathy.

**Dr. Palumbo:** Hematologic toxicity was also minimal. In terms of the upfront CRD data, at present, this is the best response achieved with a novel agent.

**Dr. Landau:** There are some considerations in administering carfilzomib. Poor renal function is an issue because of the hydration that is required on days one and two as well as eight and nine, when the dose is escalated. This is because of the tumor lysis issue and the increase in creatinine that was seen in the initial studies. There is this incidence of dyspnea that is not well characterized and is seen more at the higher doses, but has been self-limiting. Fatigue is the most significant side effect.

**Dr. Palumbo:** The other issue is that it takes two to three hours for the infusion. The schedule is not very convenient.

**Dr. Giralt:** Carfilzomib is effective in bortezomib refractory patients, and may be appropriate when there is a concern about peripheral neuropathy. Now, in the context of subcutaneous bortezomib, how important is the lack of peripheral neuropathy?

**Dr. Landau:** I think there is not enough data on subcutaneous bortezomib to say that this is not important.

**Dr. Palumbo:** Carfilzomib is the drug that I would use in a patient who has preexisting peripheral neuropathy, before subcutaneous bortezomib is indicated, because they seem to be equally effective. Maybe carfilzomib is more effective, although bortezomib is easier to administer. Carfilzomib is less likely to result in worsening neuropathy.

**Dr. Landau:** Subcutaneous bortezomib, grade I of II peripheral neuropathy, has a rate of approximately 25%, which is not insignificant. For pomalidomide, I would say that we have substantial experience with pomalidomide/dexamethasone, which has shown approximately 30% ORR in patients refractory to lenalidomide and approximately six months extended progression-free survival. This is a major achievement because it allows the clinician to prolong the remission duration in patients resistant to lenalidomide. Further, when added to a three-drug combination, one with cyclophosphamide, the other one with clarithromycin, both increase the response from 30% to 60%. However, the data are too preliminary to make a comment on remission duration.

**Dr. Giralt:** From an administration perspective, pomalidomide will require prophylaxis for deep venous thrombosis. In patients with renal dysfunction, the same precautions that are being taken with lenalidomide are necessary. Patients with worsening renal function should probably have lower doses initially to assess for hematologic toxicities.

**Dr. Landau:** Regarding elotuzumab, I have difficulty interpreting the phase 2 data because the trial was conducted in lenalidomide-naive patients. So it is difficult to say whether the benefit is from lenalidomide vs. elotuzumab.

**Dr. Palumbo:** The major side effect issue with elotuzumab is the infusion reaction. When I think about bendamustine, I see it as an alternative to alkylating agents, such as melphalan. Bendamustine has a better safety profile and less hematologic toxicity. The drug is under evaluation for synergistic activity with novel agents.

**Dr. Giralt:** Although bendamustine is commercially available in the US, it does not have an indication for use, although it is frequently used in Europe.

**Dr. Landau:** I have never been able to get it because of insurance issues and cost. Regarding vorinostat, I was impressed with Siegel’s data showing efficacy in a difficult-to-treat population.

**Dr. Giralt:** With bortezomib/vorinostat, we now have a combination that is effective for truly double refractory patients. When a patient is put on bortezomib, if after the second cycle there is no response, the clinician will add vorinostat. This data supports that approach.

**Dr. Palumbo:** The major benefit from HDAC inhibitors is overcoming resistance.

**Dr. Giralt:** Both vorinostat and panobinostat seem to be able to overcome resistance to bortezomib and, therefore, may provide an added benefit. The phase 3 trial confirms those results and the phase 2 trial of panobinostat supports that these agents can overcome bortezomib resistance.

**Dr. Landau:** Gastrointestinal issues are the main issue with the HDAC inhibitors. Investigators have shared that diarrhea and dehydration can be difficult to manage.
here were updates from 2 important studies in the transplant ineligible population: the phase 3 VISTA trial and the UPFRONT trial in the community setting.

At this year’s ASH meeting, San Miguel and colleagues presented the 5-year update of the VISTA trial comparing bortezomib/melphalan/prednisone (VMP) vs. melphalan/prednisone (MP) in elderly patients ineligible for transplant. Several important findings were made at the 5-year endpoint:

The survival benefit in favor of VMP was maintained at 5 years. The overall survival (OS) was 56.4 months for VMP-treated patients vs. 43.1 months for MP-treated patients (HR=0.695, \( P=0.0004 \)). This is a 13.3 month difference.

VMP shows more benefit as the initial therapy than starting with MP and giving bortezomib at progression. The OS was significantly longer in patients who received VMP upfront vs. those who received bortezomib only at relapse (HR 0.714, \( P=0.0029 \)).

The risk of second primary malignancies (SPMs) was not increased with VMP vs. expected background rates (1.66 for VMP and 1.30 for MP per 100 patient years vs. 1.92 for the age-adjusted general population based on the SEER database).

Unfortunately, the benefits of VMP vs. MP in patients with high-risk cytogenetics did not hold up at the 5-year endpoint.

While these data illustrate the benefit of triple therapy for the elderly nontransplant setting, the UPFRONT trial provided a contrast of actual use and outcomes in the community setting. In this phase 3b study, patients were randomized to receive induction with bortezomib/dexamethasone (VD), bortezomib/thalidomide/dexamethasone (VTD), or VMP followed by weekly bortezomib maintenance. The overall response rate (ORR) was 69% in the VMP arm, 73% in the VD arm, and 80% in the VTD arm. The median progression-free survival (PFS) after a 21.8 month followup did not differ between the arms (13.8 months in VD, 14.7 months in VTD, and 17.3 months for VMP).

In a companion evaluation of quality of life (QOL), the QOL was reduced during the induction phase with the triplet regimens but returned to near baseline during the maintenance phase with all 3 regimens. The decrease in QOL during induction was most pronounced with the VTD regimen, which was also the least well tolerated of these regimens. Taken together, these data suggest the benefit of the simple VD regimen for induction followed by bortezomib maintenance in the community setting.

**Discussion**

**What are the key takeaways related to induction regimens?**

**Dr. Giralt:** We learned some key facts from VISTA. I often get the question: “Well, why do I need to start with bortezomib? Why not just give melphalan/prednisone and only give bortezomib on failure?” We can now say the VISTA trial clearly showed the benefit of giving bortezomib upfront. Progression-free survival and overall survival is improved when you give your best drugs upfront.

**Dr. Palumbo:** If you use a triplet, the CR rate is significantly higher and, the higher the CR rate, the better the outcome. So you cannot use a lower-intensity induction.

**Dr. Giralt:** Also from VISTA is continued therapy with attenuated doses of bortezomib with steroids which increases your disease control to an average of 3 years.

**Dr. Palumbo:** UPFRONT tells us several things. When 50% of patients have comorbidities and you add a maintenance approach as a confounding factor, the type of induction might become less relevant. So, here, we did not see any difference between the 3 regimens. The trial is excellent because it is showing that when you start to have more comorbidities, gentle is better, and when you start to use a maintenance approach, the role of induction is probably less important.

**Dr. Landau:** The data from UPFRONT supersedes, in my opinion, the VISTA data because VD is an acceptable upfront regimen.
Dr. Giralt: So this study supports use of VD upfront?

Dr. Landau: Yes, as well as doublet rather than triplet therapy. And also, the maintenance was single agent bortezomib instead of VT or VP. The quality of life was clearly worse for the triplets.

Dr. Giralt: The basic take-home message from this is that VD probably should be the first line for community physicians. For elderly patients, the doublets of bortezomib, dexamethasone or lenalidomide, dexamethasone are reasonable choices.

Dr. Palumbo: Prolonged therapy reduces the need for intensive induction therapy up front in this patient population.

Any important updates in transplant-eligible patients?

Dr. Giralt: At the ASH meeting this year there were no updates on the large, randomized, phase 3 trials that showed that bortezomib-based inductions should be considered a standard of care for patients who are going to transplant. In the US, lenalidomide/dexamethasone remains a valid alternative, although lenalidomide-based inductions have not been compared to bortezomib-based inductions in the transplant situation.

But there was a study that addressed an important transplant issue. Dr. Palumbo’s poster, in which patients who were randomized to an upfront transplant were compared to patients getting lenalidomide, prednisone, and melphalan over a prolonged period of time, showed a significant advantage in PFS for patients who underwent the tandem autologous transplant (2-year PFS 73% with tandem transplant vs. 54% in the MPR arm (HR=0.51, P<.001).26

Dr. Landau: Transplant is not dead. Dr. Palumbo’s data shows the benefit, at least in the absence of bortezomib-based therapy.

Dr. Giralt: I would actually say that high-dose melphalan consolidation should continue to be considered the standard of care for patients who are young and fit for this treatment because it is associated with the best PFS.

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—Sergio A. Giralt, MD
With improvements in treatment practices, multiple myeloma (MM) is becoming a more chronic disease leading to many questions about maintenance therapy and second primary malignancies (SPMs).

**Maintenance**

During this year’s ASH symposium, Dr. Palumbo updated the results of his seminal, randomized trial of MPR–R maintenance vs. melphalan-prednisone-lenalidomide (MPR) vs. melphalan/prednisone (MP), with a focus on the results in the elderly patients (≥65 years of age, N=459, MM-015). In this older population, the ORR was 80% for MPR–R, 73% for MPR, and 47% for MP, which were statistically different. The duration of response (DOR) was 12 months for MP, 15 months for MPR, and 31 months for MPR–R (HR 0.30, 95% CI 0.20-0.45, \(P<.001\) MPR–R vs. MP). At 4 years, the projected overall survival (OS) rate was 49% for MP, 58% for MPR, and 59% for MPR–R (HR 0.898, \(P=.579\)).

According to Dr. Palumbo, MPR required fine tuning in patients over the age of 75 to get an appropriate dose reduction. For this study, MPR induction was effective in patients from 65 to 75 years of age, while it was not effective in patients over the age of 75 because of excessive myelotoxicity. The result was that the discontinuation rate was too high and the cumulative dose intensity of MPR induction was 50%, meaning loss of the benefit of induction. So, while maintenance is equally effective in patients younger and older than 75 years of age, resulting in major improvement in PFS in both patient groups, there was no general improvement in OS. However, Dr. Palumbo noted that the OS rate was not so different from the VISTA trial utilizing melphalan, prednisone, and bortezomib, although the response to MP was much better in the MM-015 trial than was seen in the VISTA trial. At 4 years followup, the investigators are starting to see a survival trend difference in the group of patients from 65 to 75 years of age.

The other maintenance trial presented at ASH was the update from the GEM/Pethema group that looked at bortezomib maintenance (1.3 mg/m² on days 1, 4, 8, and 11) every 3 months plus either prednisone 50 mg every other day (VP) or oral thalidomide 50 mg daily (VT) for up to 3 years after bortezomib/melphalan/prednisone (VMP) or bortezomib/thalidomide/dexamethasone (VTD) induction in elderly patients. The median progressive-free survival (PFS) for all patients receiving maintenance was 35 months. There may have been a slight benefit to VT vs. VP (median PFS from randomization to maintenance 30 months vs. 24 months), which may have been related to better tolerability. This difference was present regardless of the induction regimen. The complete remissions (CR) rate increased from about 24% to 42% with maintenance regimens.\(^27\)

In summary, Dr. Palumbo concluded that maintenance is changing the treatment paradigm of myeloma, not only with lenalidomide but also with the bortezomib maintenance approach. He notes that in the presence of maintenance, the remission duration is increased dramatically—with PFS up to 35 months, which is consistently improved over induction alone, which is often closer to 15 months. In addition, these improvements are seen regardless of the induction regimen and represent a major change in the treatment paradigms.

**Discussion**

**What are the implications of these maintenance studies?**

Dr. Giralt: My current algorithm for maintenance for patients who have evidence of persistent disease (not in complete remission) is to put them on lenalidomide maintenance until progression. For patients with very low-risk disease who have a complete response by immunofixation, in general, I have opted to watch and wait. What have you been doing?
Dr. Giralt: What are the data on the transplant-eligible patient? There are two large trials that have shown that lenalidomide maintenance almost doubles PFS. One trial has not shown a survival benefit. The other one has shown a trend towards a survival benefit. Both trials, however, have shown that the benefit is across the board. These findings are challenging, because if one would go face value with what the trials have shown, one would say, “Everybody should get maintenance”. Now, we have to recognize that neither of these trials have yet been published and that the followup for both trials is relatively limited, still less than 2 years. So I think it would be reasonable that, in patients with low-risk disease who have achieved a good remission, to have a conversation with the patient. Report that: “This is what the trials show. We do not know what the risk-benefit ratio is for patients who have low-tumor burden and good-risk disease because it could be the same. We could save 3 years of treatment by just watching and observing carefully.” For patients who still have persistent disease after transplant, all evidence would suggest that these patients have a higher chance of converting to a complete remission and they would benefit from continued therapy with low-dose lenalidomide. All patients should be counseled about the risk of second primary cancers.

What have we learned specifically about management issues in the elderly?

Dr. Palumbo: Combination therapy is definitely more toxic to in the elderly. Stick to the VMP as induction.

Dr. Giralt: Use VMP as induction but in patients over 75 years of age, dosing has to be done almost on an individualized basis. Start therapy and escalate dosage according to tolerance because the tolerance of these agents in patients over 75 years of age, particularly the neurotoxic agents, thalidomide and bortezomib is not good. For the community physician, patients over 75 years of age probably should start at a lower dose and tolerance should be assessed before escalation, and that is probably good guidance for any agent of the population.

Second Primary Malignancies

Second Primary Malignancies (SPMs) were a key topic at the 2010 ASH annual meeting and there was much interest in the analyses presented. In the normal population, the risk of SPM is 1.5% per year of life over the age of 65. The VISTA trial that included an alkylating agent and bortezomib, showed the risk of SPM is 1.66 per 100 patient years of followup. With the combination of melphalan and lenalidomide followed by lenalidomide maintenance, the risk of SPM is 3.0 per 100 patient years of followup. So the risk of SPM for combination, including melphalan and lenalidomide, is double in comparison to melphalan and bortezomib. Dr. Palumbo cautioned that this is based on only 4 years of followup, and the impact with longer-term followup is unknown. Also, all of these data are based on 12 cases after 500 patients, so if by chance 3 more patients develop prostate cancer, the incidence would dramatically increase.

Dr. Palumbo also noted a discrepancy among different studies. In the French experience there was a peak of B-cell tumors that was not confirmed in the American experience and in other studies. In the MM-015 trial, there is a peak of myelodysplastic syndrome (MDS) that has not been confirmed in other studies. Thus, with such few events in the study population, it is very difficult to make a final conclusion. Lastly, everything should be put into perspective and the risk of dying from infection after chemotherapy is 2 to 3 times higher than the risk of developing a SPM. Further, the risk of dying from MM is considerably higher than the risk of a secondary cancer.

As reported in the Palumbo series of 2,200 patients treated with alkylating agent and lenalidomide or bortezomib, the risk of SPM is 2% and the risk of dying from toxicity related to treatment is 8%. So, melphalan plus lenalidomide carries twice the risk of bortezomib; lenalidomide without melphalan seems to be equal to bortezomib. Longer followup is needed and the risk is much less than many under evaluated risks, such as dying from infection or other toxicities due to treatment.

Discussion

Dr. Giralt: Concerning second primary cancers, for the community physician, the message is that for patients getting
lenalidomide/dexamethasone for RRMM, it does not seem to be a problem. But for patients getting prolonged lenalidomide therapy in the context of either maintenance after primary therapy with melphalan/prednisone or maintenance after high-dose melphalan therapy, that seems to be where all the signals are. The risk is there, but the benefits outweigh the risk. The risk of disease progression is so high that the benefit from reducing the risk of disease progression far outweighs any risk of second primary cancers.

Dr. Palumbo: There is no significant signal today when lenalidomide and dexamethasone are combined. The signal is only present when lenalidomide is combined with melphalan. At five years, the risk of SPM is 5%; the risk of progressing from myeloma is 75%; so the risk of progressing from myeloma is usually 10 to 15 times higher than the risk of SPM, and this is the benefit risk ratio.

Dr. Giralt: So the signal exists, and is positive for lenalidomide, but only in the context of melphalan induction or melphalan consolidation?

Dr. Palumbo: It’s an issue every time you have melphalan around.

Dr. Giralt: So the signal exists, and is positive for lenalidomide, but only in the context of melphalan induction or melphalan consolidation?

Dr. Palumbo: Not usually. If a patient who was heavily pretreated, did not appear to need maintenance therapy, then I would refrain from using maintenance therapy based on this data. But I have the discussion with every patient.

Dr. Giralt: So the signal exists, and is positive for lenalidomide, but only in the context of melphalan induction or melphalan consolidation?

Dr. Palumbo: It’s an issue every time you have melphalan around.

Dr. Giralt: We recommend that these patients continue to be assessed on a routine basis for second primary cancers. We do not think that we should do screening colonoscopies but that, as appropriate for their age, they should have screening colonoscopies to monitor for these type of issues. Common sense would also say that before going on maintenance, patients should undergo a bone marrow assessment, and if there is evidence of dysplasia, or if there is evidence of cytogenetic abnormalities that would suggest potential MDS clones, these patients should probably not go on maintenance therapy but be observed carefully.
How do you interpret the data related to patients with high-risk cytogenetics? What is your current approach with these patients?

Dr. Landau: I was very disappointed in the updated VISTA trial. Initially, this study was the first data to suggest that bortezomib could really overcome poor risk cytogenetic abnormalities and result in a survival benefit. I was disappointed to see that dropped out over time. It must be recognized that the cytogenetics come into play with survival outcomes and not response rates. So when reading the literature, one must appreciate that reporting similar response rates in high-risk cytogenetic subgroups compared with standard risk patients, is probably meaningless data. The issue is the patients with high-risk cytogenetics respond, but relapse early and die of aggressive disease at relapse.

Dr. Giralt: I think it is a function of not being able to overcome resistance. What we are seeing is people who have poor cytogenetic features, while they are in remission. We are just not keeping them there. Is it that we do not have the right maintenance therapy? Is this a question of consolidation that we are not giving a significant treatment after observing the minimal residual disease getting down to a point where the patient’s immune system can take care of it? Or is this a question of emergence of a resistant clone? So, say you had 1,000 cells, you are left with 10 cells that are very resistant, and those will come back very quickly, and then they are very difficult to get rid of. What can you do to prevent those 10 cells from growing? Many of us are looking forward to seeing some of these new immune therapeutic maneuvers, the monoclonal antibodies, the new targeted therapies, or even allogeneic transplant as a way of trying to prevent the emergence of these resistant clones that are all cytogenetically defined.

Dr. Landau: The Mayo data presented at ASH addressed this issue. They administered a dendritic cell, anti-idiotype vaccine posttransplant. The vaccine resulted in a survival benefit, despite similar response frequency. I think that the immunotherapy may get at the core of the problem. It may not change the response but it is not the response that matters in these patients, it is the long-term disease control.32

Dr. Giralt: We will get the data to answer that from the DFCI IMF trials. There will be an early vs. late transplant in patients with cytogenetic abnormalities.

Anything else to comment on related to risk stratification and use of molecular markers?

Dr. Giralt: While we know that achieving a flow cytometric CR is beneficial; what we do not know is whether trying to induce patients into a flow cytometric CR will make a difference. So what do you do with a patient taking lenalidomide/dexamethasone who is on maintenance and is not in a flow cytometric CR? Do you give them another treatment or do you just watch them and only treat in the moment that you have evidence of disease burden increasing? We do not know that. We just know that a marker of these people may do worse. We do not know whether it should change your patterns of practice.

Dr. Landau: Flow cytometry is relatively inaccessible and not necessarily reliable in the community setting.

Dr. Giralt: But in the US, flow cytometry is still working its way through to become an easily accessible, reproducible, and validated test, but is currently still limited to only specialized centers. But regarding the question, should I be obtaining cytogenetic assessments? The answer is definitely yes. Because this assessment will allow you to restratify and potentially identify patients for clinical trials that may be beneficial.

Dr. Landau: Patients need to undergo cytogenetic evaluation, both at diagnosis and at relapse.
Any commentary on supportive care issues, particularly as these new therapies become available in the community?

Dr. Giralt: I think that is why the UPFRONT trial was so relevant because this is a true community practice study and also, as Dr. Palumbo pointed out, this trial comprised of patients who present with comorbidities. I think at the end of the day clinicians need to recognize that clinical trials inform practice but that clinical practice is not necessarily reflective of what happens in clinical trials. There has to be some degree of judgment when treating the individual patient outside of a clinical trial because we have to balance the risks and benefits of what we are doing to the patients. I think the other comment on it is, Dr. Niesvizky and his colleagues from UPFRONT should be commended because we need more trials that will inform how and what we are learning in phase II trials are going to be applicable in the community.

Dr. Landau: For the community physician, it is important to know that very effective agents are available, but physicians have to make individual decisions on individual patients. With effective agents, when there is toxicity, dose reductions are acceptable. Bortezomib should not be given if a patient has grade III peripheral neuropathy. Any signal of peripheral neuropathy warrants dose reduction, withholding the drugs, changing the schedule, or changing the administration. The goal is to change myeloma into a chronic disease and that requires patients to tolerate our drugs.

Dr. Giralt: Unfortunately, myeloma is still not necessarily a curable disease so we have to continue to look at quality of life. The biggest problem I see in community physicians is they look at a regimen that was given in a clinical trial and they stick to it. If people are not tolerating dexamethasone, they need to reduce the dose. If people are getting painful neuropathy, they have to withhold the drug. They can not keep giving it just to get that response. Consult somebody, consult the academic physicians in that setting because I think we are a lot more comfortable going through these trials of dose reductions and changing schedules. This is important for the community physician. Peripheral neuropathy is not a price patients need to pay anymore. We have subcutaneous and weekly bortezomib, as well as carfilzomib becoming available and other alternative agents. Subcutaneous bortezomib has been shown to be an appropriate alternative strategy of administering bortezomib with similar response rates but a significant reduction in the risk of emerging peripheral neuropathy.

Dr. Landau: There are a lot more data for the use of weekly bortezomib than there are for subcutaneous bortezomib, in terms of both the reduction of peripheral neuropathy and similar efficacy.

In 2 to 5 years, how do you think your management of myeloma is going to be different than it is currently?

Dr. Landau: I am excited to say that I think we are going to have more options for the relapsed/refractory patients that will become available and be a standard of care. We are moving forward in terms of our induction transplant maintenance, and currently we are conducting the very important BMT CTN study evaluating the role of post-transplant consolidation vs. maintenance vs. tandem transplantation. This study will be very important in guiding us in the treatment of transplant-eligible patients.

Other than that, the standard of care will remain induction, followed by transplant, followed by maintenance. I am hopeful that we will see a survival benefit in the maintenance studies over time. The issue is going to be that these patients who are now relapsing are refractory to our best therapies. Therefore, I am encouraged that at ASH this year we have heard about new agents with activity in this patient population. Availability of effective therapy in that setting has the potential to make a difference in terms of survival.

Dr. Palumbo: The major changes will be the use of maintenance treatment with both lenalidomide and proteasome inhibitors. Also, the use of novel, next-generation proteasome inhibitors (carfilzomib/oral agents) that will compete with bortezomib for induction and salvage. We will see the introduction of the myeloma first antibody therapy with anti-CS1. From an endpoint perspective, I also think we will get a better definition of stringent CR. Finally, with more active treatment, we will be better able to treat standard-risk patients with a curative intent.

Dr. Giralt: So in two years, my belief is that we will have more drugs. We will have potentially better assays to risk stratify and to monitor the disease. Inducing options are going to be the three treatment categories: IMiD, a proteasome inhibitor, and steroids which may be reduced or eliminated, but will probably still be an option. People will get induction over two to four cycles, hopefully oral, so that there will be minimal disruption to life and minimal treatment burden. The transplant decision will be made based upon the response in the restratification so you will have people who have very good responses and all that is needed is maintenance; have good responses and they will get consolidated with transplant; and then those who definitely need...
didn’t have the transplant will be offered it. Being forward thinking, you would think this is where we want to go and then people will be placed on prolonged therapy until a certain threshold is achieved and then they will be left off therapy and monitored.

Patients with myeloma today have a lot of reasons to be hopeful.

Our results and the outcomes have improved significantly over the last decade and we continue to see new drugs come through the line that will help the patients who are relapsing today and hopefully prevent patients of tomorrow from having to deal with their disease again.

References


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<thead>
<tr>
<th>Abbreviation Key</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
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<td>ASH</td>
<td>American Society of Hematology Annual Meeting and Exposition</td>
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<td>CBR</td>
<td>clinical benefit rate</td>
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<td>CLaPD</td>
<td>clarithromycin-pomalidomide-dexamethasone</td>
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<td>CLL</td>
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<td>complete remission</td>
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<td>US Food and Drug Administration</td>
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<td>MTD</td>
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<td>NHL</td>
<td>non-Hodgkin’s lymphoma ORR overall response rate</td>
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<td>OS</td>
<td>overall survival</td>
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<td>PCP</td>
<td>pomalidomide plus cyclophosphamide and prednisone</td>
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<td>PFS</td>
<td>progression-free survival</td>
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<td>PN</td>
<td>peripheral neuropathy</td>
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<td>QOL</td>
<td>quality of life</td>
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<td>RRMM</td>
<td>relapsed/refractory multiple myeloma</td>
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<td>sCR</td>
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<td>SPM</td>
<td>second primary malignancy</td>
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1. Double-refractory multiple myeloma is
   A. the term used to describe myeloma that is refractory to both bortezomib and dexamethasone.
   B. associated with a median overall survival of approximately 9 months.
   C. not effectively managed with any investigational agents.
   D. no longer an issue in the era of novel agents.

2. Which of the following investigational agents does not have appreciable single-agent activity?
   A. Carfilzomib
   B. MLN-9708
   C. Elotuzumab
   D. Pomalidomide

3. Vorinostat
   A. works synergistically with bortezomib.
   B. is associated with self-limiting dyspnea.
   C. has a mechanism of action that is similar to that of melphalan.
   D. has little activity in double-refractory patients.

4. Which of the following is true about novel/investigational agents and peripheral neuropathy (PN)?
   A. Weekly bortezomib has similar PN incidence as twice-weekly bortezomib.
   B. Subcutaneous bortezomib has reduced PN compared with twice-weekly i.v. bortezomib.
   C. Carfilzomib has substantial PN rates, but the severity is low.
   D. Peripheral neuropathy is a marker of efficacy for proteasome inhibitors, patients need to accept that fact and learn to deal with it.

5. Which of the following was a finding from the 5-year update of the VISTA trial?
   A. Bortezomib given with melphalan/prednisone (VMP) at induction is more effective than bortezomib that is held in reserve and used at relapse after melphalan/prednisone (MP).
   B. The OS benefit of VMP over MP seen at 3 years was no longer present at the 5-year follow-up.
   C. VMP is more effective than MP, particularly in the high-risk cytogenetic cohort.
   D. VMP carries a similar level of risk for second primary malignancy as lenalidomide/melphalan/prednisone (RMP).

6. Which of the following is a correct association for investigational agents?
   A. Pomalidomide: immunomodulatory agent
   B. Bendamustine: first monoclonal antibody for use in MM
   C. Elotuzumab: directed against ubiquitin protein
   D. Panobinostat: alkylating agent along the lines of melphalan

7. Which of the following is true about novel therapies and second primary malignancies in MM?
   A. Rates are highest in patients receiving lenalidomide plus dexamethasone.
   B. Rates with lenalidomide are similar to that caused by chemotherapy toxicity.
   C. Rates with bortezomib induction are substantially higher than those seen in an age-matched control population.
   D. The risk of second primary malignancy is much lower than the risk of dying from disease progression.

8. Which of the following is true about the role of transplant in multiple myeloma?
   A. Patients receiving tandem transplants fare similarly as patients receiving only long-term lenalidomide-based therapy.
   B. Patients with cytogenetic abnormalities may relapse quickly after transplantation.
   C. Standard induction regimens for transplant-eligible patients should not contain bortezomib.
   D. Peripheral neuropathy is a marker of efficacy for proteasome inhibitors, patients need to accept that fact and learn to deal with it.

9. Maintenance therapy in multiple myeloma
   A. can only be used effectively in transplant patients.
   B. is effective with lenalidomide-based but not with bortezomib-based regimens.
   C. with lenalidomide maintenance, currently provides a statistically significant improvement in OS vs. no maintenance.
   D. prolongs PFS, typically to values >30 months.

10. Which of the following is true about induction/maintenance regimens for the transplant-ineligible populations and the elderly?
    A. Elderly patients (>75) seem to tolerate full-dose MPR-R as well as younger patients.
    B. Triplet induction regimens, such as VMP and VTD, are much more effective than VD, especially when followed by maintenance in the community setting.
    C. Thalidomide is very well tolerated in elderly patients.
    D. Triplet regimens, such as VMP and VTD, are associated with reduced QOL during the induction phase.
Multiple Myeloma: Therapeutic Advances and Comprehensive Care in 2012

**PRINT OR TYPE**

**EVALUATION** (must be completed for your CME Quiz to be scored)

Using the scale below, circle the number that corresponds with your opinion for each item.

1 = Poor    2 = Fair    3 = Good    4 = Very Good    5 = Excellent    6 = Does Not Apply

1. Rate the clinical usefulness of the publication to your daily practice.  1 2 3 4 5 6
2. Rate the effectiveness of the teaching/learning methods.  1 2 3 4 5 6
3. The activity was presented objectively and was free of commercial bias. [Please use the “additional comments” field below to provide further information.]
   1 = Strongly Agree    2 = Agree    3 = No Opinion    4 = Disagree    5 = Strongly Disagree
   6 = Does Not Apply    7 = Already Do In Practice
4. Based on the information I learned during this activity, I feel more confident in treating patients within my practice.  1 2 3 4 5 6 7
5. Knowledge acquired from this activity will be utilized to improve outcomes in my patients.  1 2 3 4 5 6 7
6. Future activities concerning this subject matter are necessary.  1 2 3 4 5 6
7. CME Registration Forms will not be accepted after the expiration date. Return the CME Registration Form before the test expires to:
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8. These are the barriers I face in my current practice setting that may impact patient outcomes:
   A. Lack of evidence-based guidelines  1 2 3 4 5
   B. Lack of applicable guidelines for my current practice/patients  1 2 3 4 5
   C. Lack of time  1 2 3 4 5
   D. Other  1 2 3 4 5
9. This activity supported achievement of each of the learning objectives.  1 2 3 4 5
10. I see this percent of patients per month with multiple myeloma:  1 2 3 4 5 6 7
A. < 10%  1 2 3 4 5
B. 10% to 25%  1 2 3 4 5
C. 25% to 50%  1 2 3 4 5
D. > 50%  1 2 3 4 5

**CME ACTIVITY REQUEST**

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