Dear Colleague:

It is my distinct pleasure to offer this newsletter entitled “Considerations in Multiple Myeloma: Treatment-Naive Patients,” the second issue in a series of newsletters featuring topics relevant to your multidisciplinary team approach to caring for patients with multiple myeloma (MM).

A faculty of hematologists/oncologists, oncology nurses, and oncology pharmacists help focus the discussion on one topic for each newsletter. While the first issue focused on patients with renal dysfunction, this issue discusses initial treatment of newly diagnosed patients. Topics in upcoming issues will include difficult-to-treat populations, health economics, and side effect management.

It is my sincere hope that the information presented here is of value to you in your care of patients with MM.

Sincerely,

Sagar Lonial, MD
Associate Professor of Hematology and Oncology
Emory University

LETTER TO OUR READERS

Sagar Lonial, MD
Editor in Chief
Emory University

MULTIDISCIPLINARY TEAM PRESENTATIONS BY

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Considerations in Multiple Myeloma: Treatment-Naive Patients
Target Audience
This educational publication is designed for physicians, nurses, and pharmacists who wish to enhance their knowledge concerning the management of patients with newly diagnosed multiple myeloma.

Learning Objectives
At the completion of this educational activity, participants should be able to
• Discuss the use of novel agents thalidomide, lenalidomide, and bortezomib in the initial treatment of patients newly diagnosed with multiple myeloma (MM) who are candidates for stem cell transplant
• Discuss the use of these agents in combination with melphalan and prednisone for the initial treatment of patients newly diagnosed with MM who are ineligible for stem cell transplant
• Review the results of studies and study updates presented at the 2007 annual meeting of the American Society of Hematology using these agents in various combinations

Accreditation
Physicians
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of CME Consultants and Center of Excellence Media. CME Consultants is accredited by the ACCME to provide continuing medical education for physicians.

CME Consultants designates this educational activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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Faculty Disclosures

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<thead>
<tr>
<th>Name</th>
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<tr>
<td>Tiffany Richards, MS, ANP, AOCNP*</td>
<td>Celgene</td>
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<td>Rowena Schwartz, PharmD</td>
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<td>Sagar Lonial, MD*</td>
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*Please note non-FDA approved uses of pharmaceutical products or medical devices will be included in this material.

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<td>Karen Cooksey</td>
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Mission Statement

Multidisciplinary Cancer Care newsletters provide a forum for sharing expert interdisciplinary treatment perspectives on patient care with the ultimate goal of promoting ongoing professional education to physicians, nurses, and pharmacists in the hematology/oncology community.

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**For Patients Who Are Candidates for Transplantation**

For patients who are eligible for autologous stem cell transplant (ASCT), initial chemotherapy (induction therapy) is given before the transplant. Until recently, the most commonly used induction therapy was the combination of vincristine, Adriamycin® (doxorubicin), and dexamethasone (VAD).1 The combination of thalidomide and dexamethasone is now used frequently, especially in the United States. In addition, newer agents approved for use as second-line therapy, such as bortezomib and lenalidomide, are now being integrated into induction therapy in combination with dexamethasone and other agents. These combinations include:

- Thalidomide and dexamethasone (TD)
- Revlimid® (lenalidomide) and dexamethasone (Rev-Dex)
- Velcade® (bortezomib) and dexamethasone (Vel-Dex)
- Velcade® (bortezomib), thalidomide, and dexamethasone (VTD)
- Velcade® (bortezomib), Revlimid® (lenalidomide), and dexamethasone (Vel-Rev-Dex)
- Biaxin® (clarithromycin), Revlimid® (lenalidomide), and dexamethasone (BiRD)

**Thalidomide-Dexamethasone (TD)**

In the last few years, TD has emerged as the most commonly used induction regimen for the treatment of newly diagnosed multiple myeloma (MM) in the United States. In an Eastern Cooperative Oncology Group (ECOG) randomized trial of 202 patients, the best response within four cycles was significantly higher with TD compared with dexamethasone alone (63% vs 41%, respectively; \( P=0.002 \)).7 Based on this trial, in May 2006 the United States Food and Drug Administration (FDA) granted accelerated approval for TD for the treatment of newly diagnosed myeloma. Preliminary results from a separate randomized, double-blind, placebo-controlled study comparing TD vs dexamethasone alone as primary therapy in 470 patients with newly diagnosed myeloma confirmed these findings.7

**Lenalidomide-Dexamethasone (Rev-Dex)**

Lenalidomide plus dexamethasone showed efficacy in patients with newly diagnosed MM in a phase 2 trial.4 At the 2007 annual meeting of the American Society of Hematology (ASH), Rajkumar and colleagues presented the results of a phase 3 ECOG trial in which lenalidomide plus standard, high-dose dexamethasone (ie, 40 mg orally on days 1-4, 9-12, and 17-20 every 28 days) was compared with lenalidomide plus low-dose dexamethasone (40 mg orally on days 1, 8, 15, and 22 every 28 days) in newly diagnosed, untreated, symptomatic MM patients (N=445) whose median age was 65 years.7 Responses are shown in Figure 1.

Overall survival (OS) at the second preplanned interim analysis was significantly higher with lenalidomide plus low-dose dexamethasone than with lenalidomide plus high-dose dexamethasone (\( P<0.001 \)). The 1-year survival rate was 96% for the group that received low-dose dexamethasone vs 87% for the group that received high-dose dexamethasone; the 18-month survival rates were 91% and 80%, respectively. At 1

![Figure 1. Response rates within four cycles with lenalidomide plus high-dose or low-dose dexamethasone (Rev-Dex).](image-url)

**Abbreviations:** CR, complete response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease.
year, OS differences in favor of the low-dose dexamethasone arm were seen in patients younger than 65 years (P=0.022; 97% vs 92%, respectively), as well as in patients 65 years or older (P=0.002; 94% vs 83%, respectively).

At this interim analysis presented at ASH 2007, there was a nonsignificant trend toward improved progression-free survival (PFS) with lenalidomide plus low-dose dexamethasone (21.9 months) vs lenalidomide plus high-dose dexamethasone (19.3 months; P=0.0637).

Time to progression (TTP) was 22.6 months in the lenalidomide plus low-dose dexamethasone group and 21.8 months in the lenalidomide plus high-dose dexamethasone group (P=0.2117).

The rate of major grade 3 or higher toxicities, including deep vein thrombosis (DVT)/pulmonary embolism and infections, was significantly higher in the high-dose dexamethasone arm.

The authors concluded that lenalidomide plus low-dose dexamethasone is associated with superior OS compared with lenalidomide plus high-dose dexamethasone in newly diagnosed MM, and that the increased mortality in the high-dose group is due to disease progression (myeloma deaths) as well as to increased toxicity.

Also at ASH 2007, Zonder and colleagues presented the results of a Southwest Oncology Group (SWOG)-conducted trial comparing lenalidomide plus high-dose dexamethasone vs high-dose dexamethasone alone as treatment for newly diagnosed MM.

The original study design called for enrollment of 500 patients with newly diagnosed MM, with an interim analysis after accrual of 300 patients. However, the trial was closed by the Data Safety Monitoring Committee after 198 patients were enrolled.

Patients were randomized to lenalidomide 25 mg/day (28 of 35 days for three induction cycles, then 21 of 28 days as maintenance thereafter) plus high-dose dexamethasone (40 mg on days 1-4, 9-12, 17-20 as induction, then on days 1-4, 15-18 as maintenance) or high-dose dexamethasone alone (with the same induction and maintenance schedules) plus placebo. Therapy was unblinded for disease progression; patients on high-dose dexamethasone could cross over to lenalidomide plus high-dose dexamethasone. After a high initial rate of DVT was seen in patients receiving the combination of lenalidomide plus high-dose dexamethasone, aspirin (ASA) 325 mg/day was mandated.

Several presentations at ASH 2007 reported the results of bortezomib as part of a pretransplant regimen.

Between October 2004 and March 2007, 100 patients were randomized to lenalidomide plus high-dose dexamethasone (Rev-Dex) and 98 patients to high-dose dexamethasone plus placebo (Dex). At the time of the interim analysis, 61 patients on Rev-Dex and 72 patients on Dex were assessable for response. Estimated 1-year PFS was 77% (Rev-Dex) vs 55% (Dex) (P=0.002). Complete response (CR) was 22.1% vs 3.8% on the Rev-Dex and Dex arms, respectively (P=0.001). OS was high in both arms (93% vs 91% at 1 year; P=NS). Forty patients on the Rev-Dex arm crossed over to the Dex arm. Of these, 23 were assessable for response; CR was 14.8%.

Grade 3-4 neutropenia was more frequent among patients receiving Rev-Dex (13.5% vs 2.4%; P=0.010), as were infections (Rev-Dex arm: n=38, grade 3-4=13, grade 5 (lethal)=1; Dex arm: n=23, grade 3-4=8, grade 5=0; P=0.003). There were 20 DVT events in the Rev-Dex arm (14 on ASA prophylaxis) before crossover and 5 after crossover, and 12 in the Dex arm (all on ASA). Thus, 25 DVT events occurred during either blinded or open-label lenalidomide plus high-dose dexamethasone vs 7 on high-dose dexamethasone alone (P=0.089).

**Bortezomib-Based Regimens**

In newly diagnosed myeloma, high response rates (approximately 70%-90%) have been observed with bortezomib plus dexamethasone (Vel-Dex), bortezomib-thalidomide-dexamethasone (VTD), and other bortezomib-based combinations. Several presentations at ASH 2007 reported the results of bortezomib as part of a pretransplant regimen.

**Bortezomib With High-Dose Dexamethasone (Vel-Dex) as Induction Therapy.** At ASH 2007, Corso et al presented interim results from a phase 2 multicenter study to investigate the efficacy of bortezomib with high-dose dexamethasone (Vel-Dex) as induction therapy in MM patients who are candidates for high-dose therapy.

Thirty-nine evaluable treatment-naive patients younger than 65 years of age received four courses of Vel-Dex (bortezomib 1.3 mg/m² IV on days 1, 4, 8, and 11; oral dexamethasone 40 mg on days 1-4 and 8-11 every 3 weeks), followed by two courses of dexamethasone-cyclophosphamide-etoposide-platinum (DCEP) 4 weeks apart with stem cell collection, and a single autologous transplant with melphalan 200 mg/m².

Overall response rate (ORR) was achieved by 85% of patients, with 67% achieving major responses (CR 33%, nCR 26%, VGPR 8%), 18% achieving partial response (PR), 7% achieving stable disease, and 8% experiencing progression.

Grade 1 or 2 adverse events (AEs) were: infection (19), constipation (16), peripheral neuropathy (13), diarrhea (9), gastritis (6), and nausea (5). Grade 3 AEs were: infection (9, with 5 varicella-zoster infections), peripheral neuropathy (4), and cardiac arrhythmia (2). A single fatal AE (fetal sepsis) occurred.

Adequate numbers of stem cells were collected from all 25 patients who had completed the stem cell mobilization phase at the time of this interim report.

The study authors concluded that Vel-Dex as first-line therapy produces high response rates in MM patients, with generally predictable and manageable toxicities.
Multidisciplinary Cancer Care

Vel-Dex appears to be an effective and safe pretransplant treatment for younger MM patients.

**Bortezomib-Dexamethasone (Vel-Dex) vs Vincristine-Doxorubicin-Dexamethasone (VAD).** At ASH 2007, Harousseau et al presented results from a randomized phase 2 trial comparing bortezomib-dexamethasone (Vel-Dex) with vincristine-doxorubicin-dexamethasone (VAD) as induction treatment prior to ASCT in 482 patients younger than 65 years with newly diagnosed MM.10

The primary objective was CR (defined by negative immunofixation) plus nCR (defined by negative electrophoresis) after four cycles. The secondary objective was to evaluate the impact of consolidation chemotherapy with two cycles of DCEP.

Patients treated with Vel-Dex (n=240) had a significantly higher postinduction CR/nCR rate (21.3%) than did patients treated with VAD (n=242) (8.3%, \(P<0.0001\)). Patients treated with Vel-Dex also had a significantly higher postinduction CR/VGPR rate (46.7%) than did patients treated with VAD (18.6%, \(P<0.0001\)). This benefit translates to higher response rates after ASCT. The CR/nCR rate for patients who received Vel-Dex compared with those who received VAD was 35% compared with 22.6%, respectively.

Subset analyses were conducted in patients with abnormal cytogenetics. In patients with chromosome 13 deletion, the CR+nCR rate was 43% in patients treated with VTD and 4% in patients treated with TD (\(P<0.001\)). In patients with t(4;14) translocation, the CR+nCR rate was 47% in patients treated with VTD and 8% in patients treated with TD (\(P=0.002\)).

A total of 74 patients in the VTD arm and 79 patients in the TD arm went on to receive ASCT. After ASCT, statistically significantly more patients in the VTD group achieved response of at least VGPR compared with those in the TD group (77% vs 54%, respectively; \(P=0.003\)).

Grade ≥2 and grade ≥3 AEs were similar in both arms, with the exception of grade ≥3 skin rash (6.5% in the VTD arm compared with 1% in the TD arm; \(P=0.04\)). Grade 3 peripheral neuropathy was reported in 7% of patients who received VTD and in 2% of patients who received TD (\(P=0.03\)). The incidence of deep vein thrombosis (DVT) was significantly lower for patients in the VTD arm compared with those in the TD arm (3.0% vs 6.5%, respectively; \(P=0.01\)).
One patient in each arm discontinued treatment due to AEs. The study authors conclude on the basis of interim results of this study that VTD is a highly active and well-tolerated induction regimen, resulting in a significantly higher response rate compared with TD, both before and after ASCT.

**Bortezomib-Lenalidomide-Dexamethasone (Vel-Rev-Dex).** At ASH 2007, Richardson et al presented preliminary data from their phase 1/2 experience with the combination of bortezomib, lenalidomide, and low-dose dexamethasone. In the phase 1 study, four dose levels (1-4) were planned initially, and a fifth dose level (level 4M) with a reduced dexamethasone starting dose was introduced later based on safety data (Table).

Richardson reported that patients have received a median of six cycles; 16 patients (32%) have completed at least eight cycles; and 7 patients have proceeded to stem cell collection. Two incidents of dose-limiting toxicity (ie, grade 3 hyperglycemia due to high-dose dexamethasone) were seen at dose level 4; and the adjusted maximum planned dose, dose level 4M (lenalidomide 25 mg, bortezomib 1.3 mg/m², and dexamethasone 20 mg), has been reached. Phase 1 enrollment is complete; phase 2 enrollment is ongoing at dose level 4M.

Dose reductions for lenalidomide have occurred in 12 patients (8 in dose levels 1-4), for bortezomib in 11 patients (8 in dose levels 1-4), and for dexamethasone in 18 patients (15 in dose levels 1-4). Toxicities to date have been manageable. Only two grade 3 or higher deep vein thromboses (one grade 4) have occurred. Other grade 4 toxicities included two cases of thrombocytopenia and two cases of neutropenia; no grade 3 or higher peripheral neuropathy has been seen. No treatment-related mortality occurred.

The overall response rate (CR/nCR+VGPR+PR: subject to confirmation) across all dose cohorts is currently 98% (95% CI, 87.4%-99.9%) in 42 evaluable patients, including 29% CR/nCR.

### **Biaxin® (clarithromycin), Revlimid® (lenalidomide), and dexamethasone (BiRD)**

The lenalidomide-dexamethasone therapeutic backbone has also been combined with the alkylating agent clarithromycin. In a recent issue of Blood, Niesvizky and colleagues reported the results of the use of the combination regimen they called BiRD, which consisted of lenalidomide plus dexamethasone plus clarithromycin, as frontline therapy for symptomatic, newly diagnosed MM. Patients received BiRD in 28-day cycles. Dexamethasone (40 mg) was given orally once weekly, clarithromycin (500 mg) was given orally twice daily, and lenalidomide (25 mg) was given orally daily on days 1 to 21.

Of the 72 patients enrolled, 65 had an objective response (90.3%). A combined stringent and conventional CR rate of 38.9% was achieved, and 73.6% of the patients achieved at least a 90% decrease in M-protein levels. This regimen did not interfere with hematopoietic stem-cell harvest. Fifty-two patients who did not go on to receive transplants received continued therapy (CR, 37%; VGPR, 33%). The major adverse events were thromboembolic events, corticosteroid-related morbidity, and cytopenias.

At ASH 2007, Mark et al provided an update on this study. In this update, Mark reported that 24 (33%) of the 72 patients developed one or more atypical serum immunofixation patterns (ASIPs) with either a monoclonal or oligoclonal banding pattern during the course of MM induction therapy with the BiRD regimen, consisting of the combination of lenalidomide-dexamethasone plus clarithromycin.

Patients with ASIPs had significantly better response to lenalidomide-dexamethasone plus clarithromycin compared with non-ASIP patients ($P=0.00002$), with CR+sCR rate of 71% vs 23%, and a VGPR or better rate of 96% vs 61%.

The authors proposed that ASP development during MM therapy with a lenalidomide-based regimen heralds a robust tumor reduction with a hitherto unprecedented CR rate.

### For Patients Who Are Not Eligible for Transplantation

Advances in multiple myeloma (MM) research have expanded the treatment options for patients who are not candidates for stem cell transplantation. At one time, the most common initial treatment was the combination of melphalan and prednisone (MP). However, studies have shown that new combination regimens provide good outcomes, particularly for older patients and for those who are at a high risk of poor prognosis. These combinations include:

- **Melphalan, prednisone, and thalidomide (MPT)**
  - Melphalan, prednisone, and Velcade® (bortezomib) (MPV)
  - Melphalan, prednisone, and Revlimid® (lenalidomide) (MPR)
  - Velcade® (bortezomib), thalidomide, and dexamethasone (VTD)

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**Table. Dose Levels in the Phase 1 Study**

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<th>Lenalidomide</th>
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<tr>
<td>1</td>
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*20 mg, cycles 5-8.
Melphalan-Prednisone-Thalidomide (MPT)

Three recent randomized trials have compared MP with MPT.15-17 Palumbo et al15 randomized patients either to standard-dose MP for 6 months or to MPT for 6 months followed by maintenance thalidomide. There was a trend toward an improved 3-year overall survival with MPT. Facon et al16 randomized 447 patients (aged 65-75 years) to MP vs MPT vs tandem ASCT with reduced-dose melphalan (100 mg/m²). Significantly higher response and progression-free survival rates were observed with MPT compared with either MP or tandem ASCT. More importantly, the trial demonstrated a significant survival advantage with MPT (median overall survival not reached at 52 months, 33 months, and 38 months, respectively; P<0.001).

At ASH 2007, Hulin et al confirmed a survival advantage with MPT compared with MP in a randomized trial in elderly patients.8 In this study, 232 patients 75 years or older with untreated MM were randomized to receive melphalan 0.2 mg/kg/day plus prednisone 2 mg/kg/day on days 1 to 4, plus either placebo or daily thalidomide 100 mg/day; data from 229 patients were analyzed. Therapy was continued for 12 courses every 6 weeks.

The median overall survival time was 45.3 months with MPT compared with 27.7 months with MP (P=0.03). The median PFS time was 24.1 months with MPT compared with 19 months with MP (P=0.001). Rates of at least PR, VGPR, and CR were 62%, 22%, and 7% for patients receiving MPT compared with 31%, 7%, and 1% for patients receiving MP, respectively (P<0.001).

After experiencing disease relapse in the MP arm, 77% of patients received thalidomide. Survival time after progression was similar in the two groups, 9.8 months after MP and 9.3 months after MPT.

Forty-two percent of patients in the MPT arm stopped treatment due to toxicity, compared with 11% in the MP arm. The major reasons for stopping treatment in the MPT arm were peripheral neuropathy (12/48 patients), neutropenia (7/48 patients), and DVT (7/48 patients). Some grade 2-4 toxicities were significantly increased with MPT compared with MP, including peripheral neuropathy (20% vs 5%) and neutropenia (23% vs 9%). There were no significant differences in rates for DVT in patients receiving MPT (6%) compared with patients receiving MP (4%) or in rates for somnolence (6% vs 3%, respectively).

Melphalan-Prednisone-Bortezomib (MPV)

Mateos et al19 studied the novel combination of MPV in newly diagnosed myeloma in patients 65 years of age or older. Therapy was associated with a response rate of 89%, including 32% complete response rate.

At ASH 2007, San Miguel et al presented results of the Velcade as Initial Standard Treatment in Myeloma Assessment (VISTA) trial, a randomized, international, multicenter, phase 3 trial (N=680) of the use of melphalan-prednisone-bortezomib (MPV) compared with melphalan-prednisone (MP) for frontline therapy in myeloma patients not eligible for autologous stem cell transplantation (ASCT).20 This study was closed by a data monitoring committee in September 2007 in view of superior response rates and survival associated with MPV. The response to treatment was significantly higher for patients in the MPV arm compared with patients in the MP arm. The ORRs in the two arms were 82% and 50%, respectively (P<0.000001). The CR rates (determined by immunofixation) in the two arms were 35% and 5%, respectively (P<0.000001).

Rapid and durable responses were seen with MPV. The time to response for all responders was 1.4 months and 4.2 months for patients in the MPV and MP arms, respectively. The time to CR was 4.2 months and 5.3 months for patients in the MPV and MP arms, respectively. In other words, response was relatively rapid, but a complete response required several cycles.

The duration of response for all responders was 19.9 months and 13.1 months for patients in the MPV and MP arms, respectively, and the duration of response for patients with CR was 24.0 months and 12.8 months for patients in the MPV and MP arms, respectively. Thus, the 2-year duration of CR experienced by patients receiving MPV was significantly longer than the duration of CR in patients receiving MP.

Patients in the MPV arm had a 52% reduced risk of progression compared with patients in the MP arm. The median TTP was 24 months compared with 16.6 months for patients in the MPV and MP arms, respectively (P<0.000001). In subgroup analyses, patients in the MPV arm experienced a significantly improved 3-year overall survival compared with patients in the MP arm, which translated into a benefit in OS, with a 40% reduction in risk of death for patients in the MPV arm. The projected OS at 2 years is 82.6% for patients in the MPV arm compared with 69% for patients in the MP arm.

Neither the TTP nor OS was affected by patient age (younger than 75 years or older), sex, race, β2-microglobulin levels, albumin levels, geographical region, clinical stage, and cytogenetics revealed that MPV was significantly superior to MP for all subgroups. This benefit in TTP translated into a benefit in OS, with a 40% reduction in risk of death for patients in the MPV arm. The projected OS at 2 years is 82.6% for patients in the MPV arm compared with 69% for patients in the MP arm.

Serious AEs were observed in 46% of patients in the MPV arm compared with 36% of patients in the MP arm. There were no significant differences between the two groups of patients in grade 3-4 neutropenia, thrombocytopenia, and anemia. There was a higher incidence of gastrointestinal grade 3 AEs in patients treated with MPV (19%) compared with patients treated with MP (5%). There was also a higher incidence of peripheral sensory neuropathy in patients treated for 2 months.
with MPV (13%) than in patients treated with MP (0%). Peripheral sensory neuropathy resolved or improved in 75% of the cases in a median of 64 days. The incidence of DVT was 1% in both study arms. In each arm, 14% of patients discontinued therapy due to adverse events. The percentage of treatment-related deaths was low in both arms: 1% for patients receiving MPV and 2% for patients receiving MP.

MPV was well tolerated; patients receiving MPV remained on therapy for a median of 46 weeks (8 cycles) compared with 39 weeks (7 cycles) for patients receiving MP. Patients received the same percentage of planned MP dose intensity in both arms of the trial.

The study authors concluded that, in the largest MP-based phase 3 study to date, MPV significantly prolongs survival and is superior for all prespecified efficacy end points. Responses were rapid and durable, with a CR rate of 35%. TTP, time to next therapy, the treatment-free interval, and OS were all prolonged. MPV was well tolerated, and discontinuations due to AEs were low and identical for both arms. These results established MPV as an option as a new standard of care for MM patients not eligible for ASCT.

Melphalan-Prednisone-Lenalidomide (MPR)

Palumbo et al11 tested MPR in 54 newly diagnosed patients older than 65 years. At the maximum-tolerated dose, the ORR was 81%, with 48% of patients achieving at least very good partial response or better and 24% of patients achieving complete response. No reports of studies with MPR were presented at ASH 2007.

References

18. Hulin C, Facon T, Rodon P, et al. Melphalan-prednisone-thalidomide (MP-T) demonstrates a significant survival advantage in elderly patients ≥75 years with multiple myeloma compared with melphalan-prednisone (MP) in a randomized, double-blind, placebo-controlled trial, IFM 01-01. Presented at: 49th Annual Meeting of the American Society of Hematology; December 8-11, 2007; Atlanta, GA. Abstract 75.
The role of nurses in the treatment and management of patients with newly diagnosed multiple myeloma (MM) continues to expand with the recent increase in the availability of novel agents, including thalidomide, bortezomib, and lenalidomide. Additionally, because the median age at myeloma diagnosis is 66 years of age and older patients may be less tolerant of therapy, nurses should be encouraged to be vigilant in monitoring patients and intervening when disease complications or treatment related toxicities occur.

**Patient Education**

Patients who are newly diagnosed with myeloma present a particular challenge for the healthcare team because these patients are often struggling to cope with the new diagnosis in addition to learning about disease features, monitoring, and treatment recommendations. Newly diagnosed patients require education regarding their disease and its complications and information related to drug toxicity. At the time of the initial visit, patient education should focus on the nature of the disease as well as on information related to the laboratory, radiographic, and pathologic testing used in establishing the diagnosis of multiple myeloma.

**Disease Complications**

**Renal failure**

Approximately 20% of patients diagnosed with MM will present with renal failure. Renal failure in patients with multiple myeloma occurs when the proximal tubules are unable to reabsorb light chains and the ability of the kidneys to metabolize the light chains is exceeded. The immunoglobulin light chains form obstructing casts after they combine with the Tamm-Horsfall mucoprotein (THP) in the distal segment of the nephron. With prompt myeloma treatment, renal failure may be reversible since treatment decreases the amount of light chains produced by the myeloma cells. In patients with acute renal failure who receive high-dose steroids, approximately three-quarters will have reversal of their kidney function within a median of 1.9 months.

Nursing management of patients with renal failure should include immediate recognition of impaired creatinine, avoidance of intravenous contrast and nonsteroidal anti-inflammatory drugs (NSAIDs), and adequate hydration. In patients with renal impairment who are receiving lenalidomide-based therapies, close monitoring of blood counts is advised because of the increased risk of myelosuppression. In addition, lenalidomide dose modifications exist for those patients with a creatinine clearance less than 50 mL/min; these modifications, however, are based on pharmacokinetic studies of healthy volunteers with renal failure. At the time of publication, data are not available for patients with myeloma and impaired renal function, therefore care should be exercised in this patient population. No dose adjustments of bortezomib or thalidomide are necessary in this population.

**Lytic lesions**

Approximately 70% of patients will present with lytic bone lesions at the time of diagnosis. Often these are painless, but if associated with a fracture they may cause disabling pain and poor mobility. Patient education should focus on three areas, including use of bisphosphonate therapy, pain management, and the impact the disease may have on bone health. Patients who present with lytic bone lesions may benefit from monthly infusions of bisphosphonates with either pamidronate or zolendronic acid. Bisphosphonates inhibit osteoclasts, as well as bind to bone surfaces, inhibit IL-6, and induce apoptosis of osteoclasts. In patients with impaired kidney function or those who develop a 50% increase in their creatinine level, the bisphosphonate should be withheld.

In recent years, data on the risk of osteonecrosis of the jaw has emerged with subsequent guidelines for the administration of bisphosphonates. Current recommendations are for patients to undergo a dental evaluation prior to initiating either zolendronic acid or pamidronate. In addition, invasive dental procedures should be performed prior to initiation of bisphosphonate therapy. Nurses play a key role in educating patients about the signs and symptoms of osteonecrosis, risk factors, the importance of dental hygiene, and evaluating kidney function prior to each bisphosphonate dose.

**Hypercalcemia**

Hypercalcemia occurs in response to increased bone resorption and may be aggravated in patients with impaired kidney function due to decreased renal calcium excretion. When evaluating calcium levels, the corrected calcium formula should be utilized because albumin binds to calcium and may cause serum calcium levels to be underestimated. Objective and subjective findings may include dry mouth, nausea/vomiting, constipation, polyuria, fatigue, confusion, hyperreflexia, and cognitive impairment.

Reversal of hypercalcemia requires initiating myeloma treatment in addition to supportive therapy. Administering intravenous fluids concurrently with institution of effective chemotherapy, including steroids, should result in rapid improvement of calcium levels. However, if the ionized calcium level does not improve within 24 to 48 hours, a bisphosphonate such as pamidronate or zolendronic acid may be administered. In those patients with impaired kidney function, zolendronic acid should be avoided, and pamidronate given with appropriate dose reduction is recommended.

**Disease Complications**

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IMPLICATIONS FOR NURSES

**Table 1. Peripheral Neuropathy Dose Reduction Guidelines for Bortezomib/Thalidomide**

<table>
<thead>
<tr>
<th>Neuropathy Grade</th>
<th>Thalidomide Dose Reduction</th>
<th>Bortezomib Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>No reduction</td>
<td>If grade 1 without pain, no dose reduction required</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Reduce by 50%</td>
<td>If grade 1 with pain or grade 2, reduce bortezomib to 1.0 mg/m²</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Discontinue thalidomide until toxicity resolves then restart at reduced dose</td>
<td>If grade 2 with pain or grade 3, hold bortezomib until neuropathy resolves to baseline and restart at 0.7 mg/m² once weekly</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue bortezomib</td>
<td></td>
</tr>
</tbody>
</table>


**Vertebral body fractures**

Vertebral body fractures can be difficult to manage because of the associated pain and decreased mobility, which impacts the patient’s quality of life. Bone pain may arise from both peripheral and central effects, including pressure of the surrounding structures, nerve injury from direct compression, and changes in the opioid pain receptor system. In addition, bone pain assessment has many components, including the determination of persistent pain at rest, spontaneous pain at rest, and pain associated with movement.

Pain management may include the use of vertebroplasty/kyphoplasty and/or the use of analgesics. Treatment of bone pain remains multifactorial, including the use of systemic opioids, NSAIDs, antineuropathic agents (pregabalin, gabapentin, amitryptiline, etc), effective disease treatment, anesthesia techniques, and rarely surgical intervention. In patients with renal impairment, NSAIDs should be avoided as they may worsen kidney function. Nurses play a crucial role in educating patients about pain medication side effects, particularly those observed with opioids. Patients should be told about the potential for nausea/vomiting within the first few weeks of therapy with opioids. Antiemetics can be utilized in order to control nausea until it subsides.

In addition, pain medications may cause impairment of visceral motor function leading to constipation and/or bladder distention. Patient education should focus on the importance of a bowel management program and the use of stool softeners in combination with laxatives. In addition, patients should be instructed to contact their healthcare provider if they develop difficulty urinating and/or obstipation.

Following vertebroplasty/kyphoplasty, improvements in pain scale scores, mobility, and quality of life have been reported. Vertebral body fracture under fluoroscopy. While vertebroplasty improves pain scores, vertebral body height is not restored, and cement leakage has been reported. Kyphoplasty involves placement of a balloon tamp into the vertebral body. The balloon is then inflated and the cavity filled with methyl methacrylate. Kyphoplasty improves pain, mobility, and restoration of vertebral body height, and has a lower incidence of cement leakage.

**Treatment Complications**

**Peripheral neuropathy**

In a prospective study, previously untreated myeloma patients were evaluated with neuroconductive studies prior to initiating treatment. Of those evaluated, 53% were found to have subclinical small-fiber neuropathy, and 9% had subclinical large-fiber neuropathy. While the causative factor of the neuropathy is unclear, its presence may explain why patients with multiple myeloma are more susceptible to neurotoxicity. Bortezomib, thalidomide, lenalidomide, and vincristine may cause grade 3–4 neuropathy in patients, but with prompt dose modifications for symptomatic patients, neurotoxicity may be minimized (Table 1). Bortezomib induces neuropathy in approximately one-third of patients; of those, 70% will have reversal of their symptoms if appropriate dose reductions occur. Neurapraxia, motor symptoms, and/or loss of position sense leading to disturbances in gait. Bortezomib was combined with lenalidomide and dexamethasone, the incidence of neuropathy was low, with no grade 3–4 events reported. Whether lenalidomide offers a protective benefit or the lower incidence of grade 3–4 neuropathy is related to a lower dose of bortezomib is not clear at this point.

In studies of thalidomide-based regimens, approximately 14% to 70% of patients will experience neuropathy. Thalidomide is thought to cause an axonal sensory or sensorimotor neuropathy that begins in the fingers and toes and gradually extends proximally. Patients may report sensory symptoms (paresthesias), motor symptoms, and/or loss of position sense leading to disturbances in gait. Whereas bortezomib-associated neuropathy is thought to emerge within the first five cycles of therapy and then reach a plateau, thalidomide-associated neurotoxicity is believed to be related to a cumulative effect. Therefore, some
authors have recommended that thalidomide should not be given for more than 6 months. Prompt recognition of impairment and discontinuation of thalidomide will often reverse neuropathy within the first 3 weeks. However, if thalidomide is continued the neuropathy may worsen and become irreversible.

Vincristine, which is included in VAD therapy, may induce neuropathy in 12% of patients. The neuropathy associated with vincristine is predominantly an axonal sensory and motor neuropathy, which affects the small sensory fibers. Patients may lose deep tendon reflexes and/or develop paresthesias and foot or wrist drop. Vincristine should be discontinued early with recognition of neuropathic signs or symptoms. Often the abnormalities will resolve upon discontinuation; however, loss of the deep tendon reflexes may persist.

Lenalidomide, an analogue to thalidomide, induces substantially less neurotoxicity than thalidomide. In two phase 3 trials of lenalidomide/dexamethasone vs placebo/dexamethasone, less than 2% of patients developed grade 3-4 neuropathy. Lenalidomide-associated neuropathy will often resolve during the week prior to the start of the next course of therapy.

Patients receiving bortezomib-, thalidomide-, vincristine-, or lenalidomide-based regimens require education regarding the signs and symptoms of peripheral neuropathy and the importance of informing their healthcare team when signs or symptoms occur. Informing patients of the efficacy of chemotherapy despite dose reductions (particularly for bortezomib at the 1 mg/m² dose) may alleviate concerns of receiving inadequate doses of chemotherapy. In addition, it is important to educate the patient that dose reductions improve symptoms and therefore allow for continued treatment with improved quality of life and without dose interruption. For those patients who develop moderate to severe neuropathic symptoms, medications such as pregabalin or duloxetine, which are FDA approved for the treatment of diabetic neuropathy, may be of some benefit in the treatment of chemotherapy-induced neuropathy.

Myelosuppression

The incidence of myelosuppression observed with these novel agents is variable and dependent on the type of chemotherapy combination. Generally bortezomib-based regimens have a 12% to 50% incidence of myelosuppression, whereas lenalidomide and thalidomide have an incidence of approximately 38% to 69% and 14%, respectively.

The main hematologic toxicity of bortezomib is thrombocytopenia. The toxicity profile of bortezomib is predictable, with platelets dropping by 60% of their baseline value; toxicity is thought to be related to suppression of platelet budding. Generally, the platelets will reach nadir by days 11 to 14 and recover by day 21. Patients presenting with thrombocytopenia may require close monitoring of counts and transfusion of platelets during the first few cycles of therapy, until the marrow infiltration by myeloma is reduced. However, in patients with initially normal platelet level, the bortezomib dose should be withheld if the platelet count is less than 25,000.

Lenalidomide in combination with dexamethasone has less hematologic toxicity in previously untreated patients compared with their relapsed/refractory counterparts (rates of 12%-21% compared with 38%-69%, respectively). In patients with impaired kidney function, increased incidence of myelosuppression has been reported in both the previously treated and the newly diagnosed.

Thalidomide has a lower incidence of hematologic toxicity than bortezomib or lenalidomide, with toxicity occurring in approximately 3% to 15% of patients. When combined with additional cytotoxic agents, the incidence increases. The main hematologic toxicity observed with thalidomide is neutropenia; however, most patients are able to tolerate lower doses without difficulty.

In patients receiving any of the novel agents, regular close monitoring of blood

| Table 2. Dose Modification Guidelines for Myelosuppression With Lenalidomide |
|---------------------------------|--------------------------------------------------------------------------------|
| **Platelets <30,000/mm³**       | Hold lenalidomide until platelets >30,000/mm³, may resume at 15 mg daily     |
| **ANC <1000/mm³ and no additional toxicity** | Hold lenalidomide and administer GCSF, follow CBC                                      |
| **Repeat platelet <30,000/mm³** | Hold lenalidomide until platelets >30,000/mm³, then dose reduce by 5 mg               |
| **ANC <1000 with additional toxicity** | Hold GCSF until ANC >1000/mm³, dose reduce lenalidomide by 5 mg                   |

counts is recommended. For those patients receiving lenalidomide, blood counts should be evaluated every 2 weeks, and appropriate dose modifications for thrombocytopenia or neutropenia are recommended (Table 2). In addition, in those patients with impaired renal function, dose adjustment guidelines are recommended when creatinine clearance is less than 50 mL/min. In this subgroup of patients, close monitoring of blood counts weekly is advised with appropriate dose modifications for hematologic toxicity (Table 2). In those patients receiving bortezomib-based regimens, monitoring of blood counts prior to each dose is recommended. Because of the predictable nature of thrombocytopenia with bortezomib, patients may require transfusion support rather than dose reductions with the first few cycles. In patients receiving thalidomide combinations, dose modification may be required for an absolute neutrophil count less than 1000 units.

Thromboembolism

Thromboembolic events in patients receiving lenalidomide or thalidomide in combination with dexamethasone occur in approximately 15% to 25% of patients. While single-agent thalidomide or lenalidomide does not require thromboprophylaxis, anticoagulation is recommended when these agents are combined with dexamethasone. The type of thromboprophylaxis should be based upon patient risk factors, including age, obesity, comorbidities, and tumor mass, as well as the type of therapy. Therefore, patients should be educated about signs and symptoms of deep venous thrombosis and pulmonary emboli, including unilateral swelling, calf tenderness, or acute onset of dyspnea. If a thrombotic event is suspected, the appropriate imaging tests should be obtained.

Nurses act as the frontline caregivers for patients diagnosed with myeloma. They are often the first healthcare professionals that patients contact when they are developing new symptoms or are having difficulty tolerating therapy. Therefore, it is imperative that nurses familiarize themselves with the main side effects of chemotherapy as well as with the complications that may arise from the myeloma. Prompt recognition of toxicities or complications ensures that patients receive appropriate medical management while maintaining a high quality of life.

References

**IMPLICATIONS FOR NURSES**


**FRONTLINE THERAPY IN MULTIPLE MYELOMA: IMPLICATIONS FOR PHARMACISTS**

*Revena Schwartz, PharmD, BCOP, Johns Hopkins Hospital*

It is increasingly clear that multiple myeloma (MM) is a heterogeneous disease, and treatment decisions should be determined on both disease and patient factors. Currently, initiation of therapy in MM is determined by the stage of myeloma. The uses of adjunct therapy are often dependent on the extent of disease to specific sites (eg, bisphosphonates for myeloma bone disease). With better understanding of the prognosis implication of cytogentic and biology of disease, it appears that these factors should also be important considerations for treatment.

The only curative treatment for MM, at this time, is high-dose chemotherapy (HDC) followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT). Unfortunately, the risk of allo-HSCT limits its use in most patients with MM. Therefore, the treatment goals for most individuals with MM are disease control and increased survival. Additionally, an important goal is to minimize disease-related complications and toxicities of treatment to optimize quality of life.

Historically, the best disease control in MM has been seen in patients who first receive induction chemotherapy, then HDC, followed by autologous hematopoietic stem cell transplantation (auto-HSCT). Therefore, a major treatment consideration for an individual with MM is the determination of the patient’s ability to receive autoHSCT. It is possible that as more effective frontline treatment options are developed, the role of auto-HSCT may change and the eligibility of a patient for transplantation may become less of an issue.

**Induction therapy**

Induction therapy as frontline therapy, for individuals that are candidates for HDC with autoHSCT, has continued to evolve. Chemotherapy, such as vincristine and doxorubicin combined with dexamethasone were, until recently, standard of care for induction therapy. At this time, alkylation agents such as melphalan, once considered standard initial MM treatment, are not used as induction therapy because they have been shown to compromise stem-cell reserve prior to bone marrow harvest. In the last decade, the progress in the understanding of the pathogenesis and biology of MM has resulted in new treatment (nonchemotherapy) approaches. Agents that have demonstrated activity in patients after disease progresses following autoHSCT (recurrent or relapsed disease) have now moved to frontline as induction therapy. Induction strategies for individuals with myeloma are outlined in the Table.

Thalidomide, an oral immunomodulatory agent, is effective across the spectrum of MM, including use as a single agent or in combination for frontline therapy. Thalidomide’s mechanism of action in MM is not fully understood. Proposed mechanisms include the inhibition of tumor necrosis factor α (TNFα), prevention of free-radical-mediated DNA damage, suppression of angiogenesis, increase in cell-mediated cytotoxic effects, and alteration of the expression of cellular adhesion molecules. Thalidomide may also inhibit the activity of NF-kB and the enzymes cyclooxygenase-1 and cyclooxygenase-2.

The initial dose of thalidomide is usually 200 mg daily at bedtime, taken with water, and increased as tolerated to 400 mg per day after 2 to 4 weeks. The side effects of thalidomide are typically dose...
Lenalidomide 25 mg is given orally, with water, daily for 21 days of each 28-day cycle in combination with dexamethasone (dexamethasone 40 mg orally on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 therapy cycles, followed by dexamethasone 40 mg daily on days 1-4 of each 28-day cycle on subsequent cycles. The challenge of this regimen is coordinating oral therapy with patient and caregivers. Drug interactions with lenalidomide and/or dexamethasone are challenging to manage since the drug is given intermittently throughout the course. Lenalidomide is renally eliminated as unchanged drug, and therefore dose adjustments should be considered in patients with creatinine clearance less than 50 mL/min.9

Lenalidomide is a thalidomide analogue but seems to have a better safety profile and does not cause significant somnolence, constipation, or peripheral neuropathy. Unlike thalidomide, lenalidomide is associated with myelosuppression. The most common adverse effects in early trials in MM were thrombocytopenia and neutropenia. Dose interruption or modification is recommended for patients with a platelet count less than 30,000/mL and/or neutrophil count less than 1000/mL.10

VTE has been reported in patients with MM managed with lenalidomide. As with thalidomide, VTE is more common in patients receiving lenalidomide in combination with dexamethasone. The most appropriate prophylaxis strategy is not known, but recommendations for practice are available.6 Similar to thalidomide, lenalidomide use requires all prescribers, patients, and pharmacists to comply with the conditions of the RevAssist® program when prescribing, dispensing, or receiving lenalidomide, due to the potential risk for teratogenicity. 

**Bortezomib**

Bortezomib is a first-in-class proteasome inhibitor. Bortezomib targets the 26S proteasome, a multicatalytic protease complex involved in intracellular protein degradation. The inhibition of this proteasome disrupts the hemostasis of cellular proteins that are important for the regulation of cellular function, including cell-cycle progression, signal transduction, gene expression, apoptosis, immune response, and angiogenesis.4 Bortezomib inhibits transcription factor NF-κB activation which up-regulates transcription of proteins that promote cell survival and growth, decreases apoptosis susceptibility, influences the expression of adhesion molecules, and induces drug resistance in myeloma cells.7 Bortezomib also acts in the bone marrow microenvironment by inhibiting the binding of myeloma cells to bone marrow stromal cells and bone marrow-activated angiogenesis.

The dose of bortezomib is 1.3 mg/m² administered as a 3- to 5-second bolus intravenous injection on days 1, 4, 8, and 11 of every 21-day cycle. The most common adverse events associated with bortezomib are thrombocytopenia and peripheral neuropathy.10 Platelet counts decrease and recover predictably during each treatment cycle with no evidence of cumulative toxicity.11 Patients with a baseline platelet count of less than 70,000/mL have been shown to be at higher risk for significant thrombocytopenia. The dose of bortezomib is adjusted for thrombocytopenia.11 Peripheral neuropathy occurs in about 40% of patients receiving bortezomib. The incidence of peripheral neuropathy does not appear to be influenced by baseline neuropathy or previous therapy with neurotoxic agents. Again, dose modifications should be considered in patients with treatment-related neuropathy. Other bone marrow toxicities include neuropenia and anemia. Other common nonhematologic toxicities include nausea and vomiting, diarrhea, constipation, anorexia, pyrexia, fatigue, edema, cough, and headache.

The role of bortezomib in the treatment of myeloma continues to evolve.12 Bortezomib-based combinations have been shown to be effective in refractory disease, and most recently as frontline therapy. The high complete response
rates are especially encouraging, and the potential impact of disease control on overall survival is being evaluated. There does not seem to be a negative impact on stem cell harvest or engraftment in patients who receive bortezomib as part of their induction regimen, and bortezomib can be used safely in patients who will receive HDC and autoHSCT.

**Frontline therapy: Individuals who are not candidates for stem cell transplant**

Historically, combination chemotherapy with melphalan and prednisone (MP) has been the standard treatment option for individuals who are not HSCT candidates. Single-agent dexamethasone has also been used in select patients. At this time, many of the agents used in induction therapy prior to HSCT are being used as frontline therapy in those individuals who are not candidates for stem cell transplant. Clinical trials continue to evaluate available treatment combinations and to compare them to what was once the standard approach of melphalan and prednisone. Frontline treatment regimens used in patients who are not considered transplant candidates have been reported (see Table).

With the promising results from recent trials, it appears there are a number of treatment options available for individuals who are not able to undergo transplantation. The choice should be made based on patient specific factors such as toxicity, cost, convenience, and patient preference. As many of these regimens require oral therapy, it is necessary to assess the ability of the patient and/or caregiver to understand the regimen and the importance of adherence.

**Conclusion**

Strategies for initial induction therapy continue to be evaluated and redefined, with a goal to optimize efficacy and impact survival. Additionally, it is important to determine the role of specific agents and/or combinations in select patient subsets. It is becoming increasingly more clear that disease related aspects (eg, genetic profiles, cytogenetic abnormalities) define patients who have more aggressive myeloma. Newer agents may demonstrate increased activity in a subset of patients with these aggressive cancers.

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**References**


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**Table. Frontline Therapy for Multiple Myeloma**

<table>
<thead>
<tr>
<th>Transplant Candidates</th>
<th>Nontransplant Candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine/doxorubicin/dexamethasone (VAD)</td>
<td>Melphalan and prednisone (MP)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Melphalan and prednisone and thalidomide (MPT)</td>
</tr>
<tr>
<td>Thalidomide+dexamethasone</td>
<td>Melphalan and prednisone and bortezomib (MPB)</td>
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<tr>
<td>Liposomal doxorubicin and vincristine and dexamethasone (DVD)</td>
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<td>Dexamethasone</td>
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<td>Liposomal doxorubicin and vincristine and dexamethasone (DVD)</td>
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</tbody>
</table>
Considerations in Multiple Myeloma: Treatment-Naive Patients

For each question, select the one statement that provides the best answer. Please enter your answers on the Posttest Answer Key on back cover.

1. Which of the following statements is TRUE regarding initial treatment for multiple myeloma (MM) patients who are candidates for autologous stem cell transplant (ASCT)?
   a. Newer agents approved for use as second-line therapy, such as bortezomib and lenalidomide, are now being integrated into induction therapy in combination with dexamethasone and other agents.
   b. Until recently, the most commonly used induction therapy was the combination of vincristine, Adriamycin® (doxorubicin), and dexamethasone (VAD).
   c. The combination of thalidomide and dexamethasone is now used frequently, especially in the United States.
   d. All of the above

2. Which of the following statements is TRUE regarding initial treatment for newly diagnosed MM patients with lenalidomide plus dexamethasone, according to results of a phase 2 trial conducted by the Eastern Cooperative Oncology Group (ECOG)?
   a. Overall survival (OS) was significantly higher with lenalidomide plus low-dose dexamethasone than with lenalidomide plus high-dose dexamethasone.
   b. OS was significantly higher with lenalidomide plus high-dose dexamethasone than with lenalidomide plus low-dose dexamethasone.
   c. The rate of major grade 3 or higher toxicities, including deep vein thrombosis (DVT), pulmonary embolism, and infections, was similar in both the low-dose and high-dose dexamethasone arms.
   d. All of the above

3. Which of the following statements is FALSE regarding initial treatment for newly diagnosed MM patients with lenalidomide plus dexamethasone (Rev-Dex), according to results of a phase 3 trial conducted by the Southwest Oncology Group (SWOG)?
   a. After a high initial rate of DVT was seen in patients receiving the combination of lenalidomide plus high-dose dexamethasone, aspirin (ASA) 325 mg/day was mandated.
   b. The complete response (CR) rate was higher in the group of patients who received lenalidomide plus high-dose dexamethasone than in the group that received dexamethasone alone.
   c. The rate of grade 3–4 neutropenia, infections, and DVT was higher in the group of patients who received lenalidomide plus high-dose dexamethasone than in the group that received dexamethasone alone.
   d. None of the above

4. In the interim results from a phase 2 multicenter study of bortezomib with high-dose dexamethasone (Vel-Dex) as induction therapy in newly diagnosed MM patients, which of the following overall response rates was reported?
   a. 65%
   b. 75%
   c. 85%
   d. 95%

5. In the phase 2 trial comparing bortezomib-dexamethasone (Vel-Dex) with vincristine-doxorubicin-dexamethasone (VAD) as induction treatment prior to ASCT in patients younger than 65 years with newly diagnosed MM, which of the following was reported?
   a. Patients treated with Vel-Dex had significantly higher postinduction response rates than did patients treated with VAD.
   b. Patients treated with Vel-Dex had significantly higher response rates after transplantation than did patients treated with VAD.
   c. The number of serious adverse events and the incidence of grade 3–4 adverse events were comparable in the Vel-Dex and VAD arms.
   d. All of the above

6. Which of the following statements is FALSE regarding the results reported from the phase 3 study comparing bortezomib-thalidomide-dexamethasone (VTD) with thalidomide-dexamethasone (TD) as induction therapy before ASCT in newly diagnosed MM patients?
   a. No disease progression was seen in the VTD arm, while 5.5% of patients in the TD arm experienced disease progression.
   b. In patients with chromosome 13 deletion or t(4;14) translocation, higher response rates were seen in patients treated with VTD than in patients treated with TD.
   c. The incidence of deep vein thrombosis (DVT) was significantly lower for patients in the TD arm compared with those in the VTD arm.
   d. Grade 3 peripheral neuropathy was reported in 7% of patients who received VTD and in 2% of patients who received TD.

7. Among the preliminary data reported by Richardson et al from the phase 1/2 study of the combination of bortezomib, lenalidomide, and low-dose dexamethasone, which of the following overall response rates was reported?
   a. 68%
   b. 78%
   c. 88%
   d. 98%

8. Which of the following statements is TRUE regarding use of the combination of lenalidomide plus dexamethasone plus clarithromycin (BiRD), as frontline therapy for symptomatic, newly diagnosed MM?
   a. The major adverse events were thromboembolic events, corticosteroid-related morbidity, and cytopenias.
   b. One-third of the patients in the study developed one or more atypical serum immunofixation patterns (ASIPs) with either a monoclonal or oligoclonal banding pattern during the course of MM induction therapy with the BiRD regimen.
   c. Patients who developed ASIPs during the course of MM induction therapy with the BiRD regimen had significantly better responses compared with non-ASIP patients.
   d. All of the above

9. Which of the following statements is FALSE regarding treatment options for MM patients who are not candidates for stem cell transplantation?
   a. At one time, the most common initial treatment for MM patients who are not candidates for stem cell transplantation was the combination of melphalan and prednisone (MP).
   b. Studies have shown that new combination regimens, using the novel agents thalidomide, lenalidomide, and bortezomib in combination with MP, provide good outcomes in patients newly diagnosed with MM who are ineligible for stem cell transplant.
   c. Significantly higher response rates were observed with melphalan-prednisone-thalidomide (MPT) compared with MP.
   d. None of the above

10. Among the data reported by Hulin et al from the study of MPT vs MP in patients older than 75 years which of the following was reported?
   a. The median OS time was 45.3 months with MPT compared with 27.7 months with MP (P=0.03).
   b. Forty-two percent of patients in the MPT arm stopped treatment due to toxicity, compared with 11% in the MP arm.
   c. The major reasons for stopping treatment in the MPT arm were peripheral neuropathy, neutropenia, and DVT.
   d. All of the above
EVALUATION FORM

Considerations in Multiple Myeloma: Treatment-Naive Patients
Project ID: JE8027215

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
1 = Strongly Disagree  2 = Disagree  3 = Neutral  4 = Agree  5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives
After completing this activity, I am now better able to:

Discuss the use of novel agents thalidomide, lenalidomide, and bortezomib in the initial treatment of patients newly diagnosed with multiple myeloma (MM) who are candidates for stem cell transplant 1 2 3 4 5

Discuss the use of these agents in combination with melphalan and prednisone for the initial treatment of patients newly diagnosed with MM who are ineligible for stem cell transplant 1 2 3 4 5

Review the results of studies and study updates presented at the 2007 annual meeting of the American Society of Hematology using these agents in various combinations 1 2 3 4 5

Overall Effectiveness of the Activity
The content presented:

Was timely and will influence how I practice 1 2 3 4 5

Enhanced my current knowledge base 1 2 3 4 5

Addressed my most pressing questions 1 2 3 4 5

Provided new ideas or information I expect to use 1 2 3 4 5

Addressed competencies identified by my specialty 1 2 3 4 5

Avoided commercial bias or influence 1 2 3 4 5

Impact of the Activity
Name one thing you intend to change in your practice as a result of completing this activity:

____________________________________________________________________________________________________________________________________________________

____________________________________________________________________________________________________________________________________________________

Please list any topics you would like to see addressed in future educational activities:

____________________________________________________________________________________________________________________________________________________

____________________________________________________________________________________________________________________________________________________
EVALUATION FORM

Considerations in Multiple Myeloma: Treatment-Naive Patients
Project ID: JE8027215

Additional comments about this activity:
___________________________________________________________________________________________________________
___________________________________________________________________________________________________________

Follow-up
As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey.
☐ No, I’m not interested in participating in a follow-up survey.

If you wish to receive acknowledgment for completing this activity, please complete the posttest by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

You may also complete the posttest online at www.cmeuniversity.com. Click on “Find Posttest / Evaluation by Course” on the navigation menu, and search by project ID JE8027215. Upon successfully completing the posttest and evaluation, your certificate will be made available immediately.

Posttest Answer Key

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Request for Credit (check box): MD ☐ RN ☐ Pharm ☐ Other ☐

Name _________________________________________________________ Degree ________________________________

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For Physicians Only
I certify my actual time spent to complete this educational activity to be:

☐ I participated in the entire activity and claim 1.0 credits.
☐ I participated in only part of the activity and claim _____ credits.