LETTER FROM THE EDITOR-IN-CHIEF

Over the past several years, significant progress has been made in the management of multiple myeloma (MM). This is due, in large part, to an accumulating knowledge of the biology of the disease, along with the development and clinical investigation of highly effective therapies. The shift in the paradigm of care for MM has resulted in revised criteria for diagnosing, staging, and risk-stratifying patients; new standards of care; and updated guidelines for the management of comorbidities and treatment-related toxicities. However, more progress is needed and many questions remain regarding the application and interpretation of recent clinical advances.

In this fifth annual “Considerations in Multiple Myeloma” newsletter series, we continue to address frequently asked questions related to the diagnosis and treatment of the disease. To provide an interprofessional perspective, questions are answered by physicians, nurses, and pharmacists from leading cancer institutions, who share their insight, knowledge, and professional experience regarding evidence-based care. In this second issue, experts from City of Hope Cancer Center answer questions pertaining to the management of patients in the maintenance setting.

Sincerely,

Sagar Lonial, MD
Professor
Vice Chair of Clinical Affairs
Department of Hematology and Medical Oncology
Winship Cancer Institute
Emory University School of Medicine
Atlanta, GA

Supported by educational grants from Celgene Corporation and Millennium: The Takeda Oncology Company.
The importance of posttransplant is to prevent or at least very good partial chimerism and for those who do not achieve a complete response (CR) with MM? cytogenetics and for those who do not achieve a complete response (CR) to the use of these therapies remain unresolved. In this article, Amrita K. Krishnan, MD, FACP, is a consultant for Celgene Corporation, and is on the speakers’ bureau for Celgene Corporation, Genentech, and Millennium: The Takeda Oncology Company. Christina Beckeman, RN, ANP-C, AOCNP, has nothing to disclose. *Sripriya Shanmugam, PharmD, BCOP, is on the advisory board for Genzyme.

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Recent Advances and Ongoing Controversies in the Maintenance Setting

Amrita Y. Krishnan, MD, FACP
Director, Multiple Myeloma Program
Associate Director, Medical Education and Training, Department of Hematology/HCT
City of Hope Cancer Center, Duarte, CA

Introduction
Despite the development of more effective induction regimens and the increased use of autologous stem cell transplant (ASCt), most patients with multiple myeloma (MM) eventually relapse and succumb to progressive disease. Novel agents that have demonstrated good clinical activity in the frontline and relapsed settings continue to be evaluated as maintenance therapy, with the goal of delaying relapse and extending survival. However, important questions related to the use of these therapies remain unresolved. In this article, Amrita Y. Krishnan, MD, FACP, shares her insight on recent clinical data and ongoing issues in the maintenance setting for myeloma.

When do you consider maintenance therapy for your patients with MM?

I am most likely to recommend maintenance for patients with high-risk cytogenetics and for those who do not achieve a complete response (CR) after ASCT. Unfavorable cytogenetics in both transplant and nontransplant candidates portend a high risk of relapse or disease progression. In addition, an important objective posttransplant is CR or at least very good partial response, as this has been correlated with improved overall survival (OS). Maintenance therapy with novel agents can contribute to these treatment goals, especially in patients who do not achieve a CR with transplant alone.

I am less likely to use maintenance in standard-risk patients who achieve CR, because of concern that the risk of continued drug treatment may outweigh benefit in this population. Of course, there are always exceptions, and the approach to therapy must be individualized to the patient. Many questions remain on the optimal use of maintenance therapy, because we do not yet have unequivocal evidence that it prolongs OS in specific MM subgroups.

What evidence has influenced your approach to maintenance therapy?

In patients with high-risk cytogenetics who exhibit the translocation t(4;14), I tend to use bortezomib. The HOVON-65/GMMG-HD4 trial showed a benefit in progression-free survival (PFS) in patients with t(4;14) who received this agent as maintenance. There is controversy, however, because HOVON-65/GMMG-HD4 did not prove that it was the maintenance that produced this clinical benefit, since patients received bortezomib during induction as well in one arm of the study, whereas the other arm did not receive bortezomib during induction or maintenance (Figure). There has also been debate regarding the efficacy of bortezomib maintenance in patients with deletion 17p (del(17p)). A study by Aver-Loiseau and colleagues reported that bortezomib-based therapy could not overcome this chromosomal abnormality. However, patients in this trial received bortezomib short-term (4 cycles) with no maintenance. Results of HOVON-
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lenalidomide consolidation in both arms). In this study, lenalidomide main-
tained patients for 2 years.\(^5\) In CALGB 100104, lenalidomide main-
tenance was given until progression. The investigators of this study reported that lenalidomide after initial therapy is associated with significantly longer time to progression and improved survival in the lenalidomide arm versus the placebo arm (Table).\(^9\) IFM 2005-02 also compared single-agent lenalidomide maintenance with placebo post-ASCT (after 2 courses of lenalidomide consolidation in both arms).\(^8\) In this study, lenalidomide mainte-
nance improved median PFS to 41 months versus 23 months with placebo (P<.001), with benefit across cytogenetic subgroups. Three-year and 4-year OS rates were comparable in the lenalidomide versus placebo groups: 80% versus 84% (3-year) and 73% versus 75% (4-year), respectively.

Recent data from the RV-MM-PI-209 trial add further support to the use of lenalidomide maintenance after consolidation.\(^11\) Patients received induction with lenalidomide and low-dose dexamethasone, followed by either melphalan, prednisone, and lenalidomide (MPR) ± lenalidomide main-
tenance or melphalan/ASCT ± lenalidomide maintenance. A comparison of all patients given lenalidomide maintenance (after either MPR or ASCT) versus all patients receiving no maintenance showed that maintenance increased PFS but not OS. The recent MM-D15 trial evaluated lenalidomide maintenance in older, transplant-ineligible patients with myeloma. The investigators of this study reported that lenalidomide after initial therapy with MPR significantly extended PFS compared with melphalan plus pred-
nisone alone or MPR without maintenance.\(^12\)

Thalidomide is not used preferentially for maintenance in the United States, largely due to data showing a high incidence of serious adverse events, reduced quality of life, and potentially poorer outcomes in del(17p) patients.\(^15\,16\) In Europe, however, thalidomide is used more often, because of regulatory limitations on other novel drugs such as lenalidomide.

What are some of the key concerns in using maintenance therapy?

The first concern is risk versus benefit. Are we seeing enough clinical benefit to justify the toxicity and added expense of maintenance therapy? Certainly, data suggest benefits in response and PFS when maintenance is used, but a consistent benefit in OS has not been shown.\(^17\)

Adverse events are also an important consideration. With bortezomib maintenance, grade 3 or 4 peripheral neuropathy may be treatment-limiting.\(^1,3\) With lenalidomide, trials have reported an increased risk of second primary malignancies with maintenance therapy.\(^9,10,12,16\) In CALGB 100104, for example, second cancers were reported in 8% of patients receiving lenalidomide maintenance versus 3% of patients receiving placebo during approximately 3 years of follow-up.\(^9\) The investigators of this study have indicated that they will continue to assess risk factors for development of second primary cancers with further follow-up. Factors such as cost and insurance coverage may also affect the choice of maintenance therapy. These issues can influence patient preference, which we always consider.

How long should patients remain on maintenance therapy with novel agents?

Currently, there is no consensus regarding the optimal duration of maintenance therapy for myeloma. In HOVON-65/GMMG-HD4, patients received bortezomib maintenance for 2 years.\(^3\) In CALGB 100104, lenalido-
mide maintenance was given until progression.\(^2\) The investigators in the IFM 2005-02 trial planned to use lenalidomide until progression but stopped therapy once secondary malignancies arose.\(^10\) In the ongoing phase 3 multicenter BMT CTN 0702 trial, we plan to give lenalidomide maintenance therapy for 3 years.\(^17\)

However, many questions remain unresolved. What is the optimal duration of lenalidomide therapy to improve PFS and possibly OS? Since bortezomib-related neuropathy may shorten maintenance time, can we reduce the incidence and severity of this toxicity and extend the duration of time that patients can stay on maintenance by using subcutaneous bortezomib\(^16\) or an alternate proteasome inhibitor such as carfilzomib or MLN9708?\(^29\,22\)

Hopefully, emerging clinical data and ongoing research will better define the role of novel agents in the maintenance setting and provide answers to these questions. \(\checkmark\)

References


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Improving Patient Outcomes During Maintenance Therapy

Christina Boeckman, RN, ANP-C, AOCNP
Nurse Practitioner
Department of Hematology/HCT, City of Hope Cancer Center
Duarte, CA

Introduction
Along with the clinical benefits seen with maintenance regimens for multiple myeloma (MM), new challenges have arisen, due to the increased risk of adverse events associated with prolonged use of therapy. As a member of the cancer care team, it is the nurse’s responsibility to anticipate which toxicities and complications are likely to occur, to employ the necessary interventions, and to counsel patients accordingly. In this article, Christina Boeckman, RN, ANP-C, AOCNP, discusses effective nursing strategies in the maintenance setting, and shares her perspectives on preventing and managing common adverse events related to the use of novel agents.

Which patient-related factors need to be considered in the maintenance setting?
Age, comorbidities, and performance status must all be considered when a patient is scheduled to receive maintenance therapy. Elderly MM patients frequently have age-related comorbidity conditions that can make managing their disease especially challenging.1 These individuals are more likely to have organ dysfunction (eg, cardiovascular disease, renal impairment) and diabetes, and are more prone to infection and deep vein thrombosis.2 It is crucial to take these factors into account when determining an effective management plan. It is also important to know which agents were used during previous lines of therapy, how patients tolerated these medications, and whether they are experiencing any residual adverse events. In some cases, it may be necessary to avoid the use of specific agents due to preexisting comorbidities or cumulative toxicities.

A patient’s overall performance status should also be evaluated prior to and during maintenance therapy. Nurses must assess whether an individual is able to perform activities of daily living, such as preparing meals, eating, bathing, and dressing. The goal is to achieve a balance between providing effective therapy and maintaining good quality of life.

What strategies do you use to minimize peripheral neuropathy (PN) in patients receiving bortezomib as maintenance therapy?
Neuropathy is a well-known adverse event associated with the use of novel agents such as bortezomib and thalidomide.2 Symptoms may include transient numbness and tingling, paresthesias, and muscle cramping or weakness, or in severe cases, burning pain, organ dysfunction, and paralysis.3 High rates of thalidomide-induced PN have been observed during maintenance therapy.4,5 If treatment with this agent is not interrupted quickly, symptoms may become irreversible.6 As a result, thalidomide is being used less frequently as maintenance. Bortezomib-induced PN, on the other hand, is generally reversible with dose reduction and treatment discontinuation.2 We have...
recently seen an increase in the use of bortezomib in the maintenance setting, and nurses need to be familiar with its toxicity profile and recommended supportive care strategies.

Assessing PN prior to the start of maintenance and throughout the course of therapy is essential.2,3 Verbal and nonverbal questionnaires and pain scales are helpful for these assessments. When patients come to our center for treatment, I ask them if they are experiencing any numbness and tingling in their hands and feet, ringing in their ears, neuropathic pain, or cramping. I also determine if they are having trouble with everyday tasks, such as buttoning their shirts or writing with a pen. Patients must understand the importance of reporting signs and symptoms of PN as soon as they occur, so that the appropriate interventions can be initiated.

When bortezomib-related PN develops, the goal is to alleviate symptoms and prevent progression.2 This can be accomplished through recommended dose modifications based on the degree of neurotoxicity (Table).4,5 For example, if a patient develops grade 3 PN while on bortezomib, we typically hold treatment until symptoms resolve, and then reinitiate therapy at a lower dose and schedule. For patients who have neuropathic pain, we prescribe opioids when necessary; the use of nonsteroidal anti-inflammatory drugs is not advisable due to the likelihood of myeloma-related renal dysfunction. Additional medications that may be used in the treatment of PN symptoms include gabapentin, pregabalin, duloxetine hydrochloride, and tricyclic antidepressants.2 We usually recommend that patients start taking B complex vitamins, folic acid, and alpha lipoic acid, as long as they are not contraindicated with other medications.

How do you assess and treat hematologic toxicities related to lenalidomide therapy in the maintenance setting?

Hematologic toxicities are commonly associated with the use of lenalidomide.1 To effectively manage these adverse events, it is important for myeloma patients to have their blood counts monitored regularly, with the most frequent monitoring performed early in their treatment cycles. We see patients at least every 2 weeks during the first and second cycles of maintenance to assess how they are responding to treatment and to evaluate the need to make dose or schedule adjustments based on their counts. Depending on their performance status and laboratory results, we may lessen the frequency of these evaluations to once per month.

When platelet counts fall to <30,000/mcL, we may need to temporarily discontinue lenalidomide. Treatment can usually be resumed when platelet counts return to ≥30,000/mcL, but it may be necessary to restart them at a reduced dose.2,3 We usually do not initiate transfusion unless platelet counts decline to <20,000/mcL. If the patient’s absolute neutrophil count (ANC) is <1000/mcL, lenalidomide treatment should also be halted until counts return to baseline. In some cases, we may initiate granulocyte colony-stimulating factor if a patient’s ANC remains low for an extended period of time.

Patients also need to be evaluated for bleeding, bruising, dyspnea, fatigue, and infection, and should be educated on how to monitor for these signs and symptoms at home. We tell them to notify us immediately if they experience bleeding that does not stop, frequent bruising, or fever. It is important to instruct patients on effective strategies for infection control, including routine hand washing and the avoidance of crowds, when their blood counts are low. If patients develop signs of infection, we may also need to hold lenalidomide treatment until symptoms resolve.

What is the nurse’s role in helping patients continue with maintenance therapy?

Prior to the initiation of maintenance, it is important to discuss with patients both the risks and benefits of prolonged therapy with novel agents. Some individuals do not understand why they need to undergo further treatment if they have responded well to initial chemotherapy and/or transplantation. It is important to remind these patients that continued use of effective agents may help to delay relapse and disease progression. Although patients will typically be familiar with the toxicity profiles of agents they have already received during frontline therapy, we review this information again prior to the start of maintenance. We also inform patients about the increased risk for secondary malignancies related to prolonged duration of therapy, and encourage them to be diligent about routine health screenings, including mammograms and colonoscopies. We ensure them that we will also monitor for secondary malignancies through laboratory tests and other procedures.

To provide optimal care, nurses must consider patient preferences as well as psychosocial factors in the maintenance setting. Some individuals would rather receive oral lenalidomide, so they do not have to travel back and forth to the center every week for treatment. If we determine that a patient can be compliant with an oral regimen, and they do not have comorbidities or other characteristics that would preclude the use of lenalidomide, we will most likely use this therapy. For other patients, intravenous or subcutaneous bortezomib may be preferential, based on patient- or disease-related factors. Regardless of which type of therapy is prescribed during maintenance, oncology nurses play an important role in improving patient outcomes by establishing good communication with patients, carefully monitoring for signs and symptoms of toxicities, and being prepared to initiate effective supportive care strategies when needed.

References

Table. Bortezomib Dose Modifications Based on Severity of Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Severity of Peripheral Neuropathy</th>
<th>Modification of Dose and Regimen</th>
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<tbody>
<tr>
<td>Grade 1 (paresthesia or loss of reflex) without pain or loss of function</td>
<td>No action</td>
</tr>
<tr>
<td>Grade 1 with pain or grade 2 (interferes with function but not with activities of daily living)</td>
<td>Reduce bortezomib dose from 1.3 to 1.0 mg/m²</td>
</tr>
<tr>
<td>Grade 2 with pain or grade 3 (interferes with activities of daily living)</td>
<td>Withhold bortezomib until toxicity resolves, then reinitiate at a dose of 0.7 mg/m² once weekly</td>
</tr>
<tr>
<td>Grade 4 (permanent sensory loss that interferes with function)</td>
<td>Discontinue bortezomib</td>
</tr>
</tbody>
</table>

Grading based on NCI Common Toxicity Criteria CTCAE V 3.0.

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Dosing and Administration of Novel Agents in the Maintenance Setting

Sepideh Shayani, PharmD, BCOP
Clinical Manager, Pharmacy Services
Department of Pharmaceutical Services
City of Hope Cancer Center
Duarte, CA

Introduction
Over the past decade, maintenance therapy has become an increasingly important component of treatment for patients with multiple myeloma (MM). Recent evidence has shown that newer targeted agents, such as bortezomib and lenalidomide, have the potential to extend duration of response following frontline therapy, and are generally better tolerated and more effective than older, conventional therapies used for this indication. In this article, Sepideh Shayani, PharmD, BCOP, discusses recent advances in the maintenance setting, and answers questions related to the administration of novel agents.

Has a standard dose and schedule been established for bortezomib as maintenance therapy?
To date, a standard dose and schedule has yet to be established for bortezomib maintenance; however, data from recent clinical trials can be helpful in guiding therapeutic decisions. As in the frontline and relapsed/refractory settings, it is essential to strike a balance between efficacy and safety when using novel agents as maintenance, especially since patients will be on therapy for an extended period of time.

In the phase 3 HOVON-65/GMMG-HD4 trial, transplant-eligible patients with MM were randomly assigned to induction therapy with vincristine, doxorubicin, and dexamethasone (VAD) or bortezomib, doxorubicin, and dexamethasone (PAD). This was followed by high-dose melphalan and autologous stem cell transplant (ASCT). Patients started on VAD received thalidomide maintenance at a dose of 50 mg/day for 2 years (arm A) and those randomized to PAD received bortezomib maintenance at a dose of 1.3 mg/m² biweekly for 2 years (arm B).

In this trial, progression-free survival (PFS) was lower with VAD/ASCT/thalidomide compared with PAD/ASCT/bortezomib (42% vs 46% at 36 months, P=0.047). Overall survival was significantly higher in arm B (P=0.048). A total of 67% of patients in arm A and 57% in arm B started maintenance therapy, and 64% and 47% of those patients, respectively, went off protocol due to various factors (Table 1). Grade 3/4 peripheral neuropathy (PN) was observed in 7% of patients in arm A and 16% of patients in arm B.

In the phase 3 GIMEMA trial, patients with MM were randomized to nine 6-week cycles of induction with bortezomib, melphalan, prednisone, and thalidomide (VMP) followed by 2 years of maintenance with bortezomib (1.3 mg/m² every 14 days) plus thalidomide (50 mg/day) (VT) or to nine 6-week cycles of VMP induction without maintenance. Early in this trial, which enrolled patients who were not eligible for transplant due to advanced age or comorbidities, the schedule of bortezomib (1.3 mg/m²) used for induction was reduced from twice weekly to once weekly. In addition, both the VMPT and VMP schedules were changed to nine 5-week cycles.

Results showed a benefit with VMPT/VT compared with VMP alone, in terms of complete response rates (38% vs 24%; P<0.001), PFS (56% vs 41%, P=0.008), and time to next treatment. Importantly, the once-weekly schedule of bortezomib lowered discontinuation rates and prolonged time on therapy. This finding has important clinical implications, especially for the treatment of older patients who may have difficulty tolerating a standard regimen. The schedule adjustment used in this study also significantly reduced the incidence of severe sensory PN from 16% to 3% (P<0.001).

It is essential to strike a balance between efficacy and safety when using novel agents as maintenance, especially since patients will be on therapy for an extended period of time.

Both of these maintenance trials reported encouraging clinical activity with bortezomib. In GIMEMA, once-weekly dosing was more tolerable than twice-weekly dosing, but maintained good clinical activity. In this trial, bortezomib maintenance administered bimonthly also appeared to be an effective strategy. Investigators continue to evaluate various bortezomib dosing and schedule protocols. Hopefully, data from new trials will help to determine a standard of care. In the meantime, following established dosing adjustment guidelines for bortezomib to reduce toxicities such as PN is essential to ensure optimal outcomes. Additionally, subcutaneous administration of bortezomib may improve the adverse event profile associated with this agent. In a recent trial of relapsed/refractory MM, this mode of administration resulted in similar overall response rates but significantly less PN than traditional intravenous dosing. The increased tolerability seen with subcutaneous bortezomib in this population of patients may translate to the maintenance setting.

What dosing and administration schedules are being used for lenalidomide as maintenance?
In the phase 3 IFM 2005-02 trial, patients with MM who had single or double ASCT were treated with 2 cycles of consolidation with lenalidomide (25 mg/day, days 1-21) followed by placebo or lenalidomide maintenance (given at 10 mg/day for the first 3 months and increased to 15 mg/day if tolerated). Treatment was continued until disease progression or development of toxicity, progression, other reasons, or death. Patients with progressive disease were enrolled off protocol due to various factors (Table 1).

Table 1. Discontinuation Rates in the Maintenance Phase of the HOVON-65/GMMG-HD4 Trial

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Progression</th>
<th>Other</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>31%</td>
<td>31%</td>
<td>2%</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>9%</td>
<td>29%</td>
<td>9%</td>
</tr>
</tbody>
</table>

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of intolerance. After a median follow-up of 2 years postrandomization to maintenance, there was a significant improvement in PFS in the lenalidomide arm (41 months vs 23 months, P<.01). The rates of grade 3/4 PN were similar in both groups. Grade 3/4 hematologic events were reported in 58% of patients on lenalidomide versus 23% on placebo, but these were manageable with dose adjustments (down to 5 mg/day). The incidence of second primary cancers was higher in the lenalidomide arm (3.1 vs 1.2 per 100 patient-years, P=.02). Overall, 21% of patients in the lenalidomide arm and 15% in the placebo arm discontinued therapy due to toxicity.6

We are seeing RVD used more frequently as induction therapy in MM, so data from this study should be relevant to clinical practice.

The phase 3 MM-015 trial randomized elderly, transplant-ineligible MM patients to 9 cycles of melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance (MP-R), or to 9 cycles of MPR or MP without maintenance.7,8 In this study, the scheduled dose of lenalidomide (during induction and maintenance) was 10 mg/day, given on days 1 to 21. Patients could receive maintenance until disease progression or development of intolerance. After a median follow-up of 27 months, PFS was significantly longer with lenalidomide maintenance (31 vs 14 vs 13 months for MPR-R, MPR, and MP, respectively; MPR-R vs MP, P<.001).

The most common adverse events were hematologic; these occurred more frequently in patients who received lenalidomide. Grades 3 and 4 hematologic toxicities in this study are shown in Table 2. However, during the maintenance phase of MPR-R, the incidence of new or worsening toxicities was low. Discontinuation due to adverse events in the MPR-R, MPR, and MP arms was observed in 16%, 14%, and 5%, respectively. These rates were higher in patients >75 years of age than in those 65 to 75 years of age, as was the need for dose reductions. Incidence of second primary malignancies was low, corresponding to 3.04, 2.57, and 0.98 per 100 patient-years for MPR-R, MPR, and MP, respectively.8

BMT CTN-0702, a new phase 3 multicenter trial, will evaluate the safety and efficacy of lenalidomide maintenance in 3 cohorts of patients.9 Following ASCT, participants will proceed to either second transplant, consolidation with lenalidomide, dexamethasone, and bortezomib (RVD), or maintenance with lenalidomide. Patients undergoing second transplant and consolidation will also receive maintenance therapy, which will start at 10 mg/day for 3 months and increase to 15 mg/day. We are seeing RVD used more frequently as induction therapy in MM, so data from this study should be relevant to clinical practice.

What strategies are important to ensure optimal outcomes in the maintenance setting?

Certainly, it is important to consider safety and efficacy data from recent studies in the decision-making process. Beyond that, factors such as convenience, cost, reimbursement, and, of course, toxicity profiles of specific agents must be considered so that therapy can be tailored to a patient’s needs. The treatment landscape for MM is constantly evolving; therefore, clinicians must also stay informed of new agents that are being investigated in clinical trials. For example, early data from phase 1/2 trials were recently released on the use of the oral proteasome inhibitor MLN9708 in MM. In both newly diagnosed and relapsed/refractory patients, treatment with this agent resulted in encouraging response rates with good tolerability, especially low rates of PN.10,11 Based on these results, phase 3 trials are under way to further evaluate the safety and efficacy of this agent in myeloma.11

Table 2. Select Grades 3 and 4 Hematologic Toxicities in the MM-015 Trial

<table>
<thead>
<tr>
<th></th>
<th>MP (Gr 3/4)</th>
<th>MPR (Gr 3/4)</th>
<th>MPR-R (Gr 3/4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia (%)</td>
<td>29/8</td>
<td>64/32</td>
<td>67/35</td>
</tr>
<tr>
<td>Thrombocytopenia (%)</td>
<td>12/4</td>
<td>38/12</td>
<td>35/11</td>
</tr>
<tr>
<td>Anemia (%)</td>
<td>14/1</td>
<td>26/3</td>
<td>24/3</td>
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MP indicates melphalan plus prednisone; MPR, melphalan, prednisone, lenalidomide; MPR-R, melphalan, prednisone, lenalidomide plus lenalidomide maintenance.

References