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# Recent Advances in the Treatment of Multiple Myeloma

A Review of Selected Presentations From
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With expert commentary by
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This activity has been designed to meet the educational needs of hematologists, oncologists, and other healthcare professionals involved in the management of patients with multiple myeloma (MM).

## Statement of Need/Program Overview

MM remains the second most common hematologic malignancy in the United States, after non-Hodgkin lymphoma. Historically, MM has been a difficult and frustrating disease for patients and their healthcare providers. Despite the availability of numerous therapeutic options, MM remains essentially incurable. Nearly all patients relapse and eventually become refractory to existing treatments. It has recently been suggested that survival time could double with newer therapies. Clinical trials in relapsed/refractory MM are currently testing many different combination regimens with novel agents, such as bortezomib, lenalidomide, and thalidomide. Patients with comorbidities, including renal failure, extramedullary disease, hyposecretory myeloma, and advanced bone disease, require specialized care.

## Educational Objectives

After completing this activity, the participant should be better able to:

1. Determine the best treatment options for newly diagnosed patients with MM based on recent research data.
2. Recognize the most appropriate treatment options for patients with relapsed and refractory MM based on recent research data.
3. Assess the need for maintenance therapy in MM and propose appropriate options for maintenance therapy.
4. Describe the most appropriate techniques for monitoring MM.

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# Recent Advances in the Treatment of Multiple Myeloma

A Review of Selected Presentations From the 52nd American Society of Hematology Annual Meeting and Exposition

## 37 Phase III Intergroup Study of Lenalidomide Versus Placebo Maintenance Therapy Following Single Autologous Hematopoietic Stem Cell Transplantation (AHSCT) for Multiple Myeloma: CALGB 100104[1]

PL McCarthy, K Owzar, KC Anderson, CC Hofmeister, DD Hurd, H Hassoun, S Giralt, EA Stadtmauer, PG Richardson, DJ Weisdorf, R Vij, JS Moreb, NS Callander, K van Besien, T Gentile, L Isola, RT Maziarz, DA Gabriel, A Bashey, H Landau, T Martin, MH Qazilbash, D Levitan, B McClune, V Hars, J Postiglione, C Jiang, E Bennett, SS Barry, L Bressler, M Kelly, M Sexton, C Rosenbaum, H Parameswaran, MC Pasquini, MM Horowitz, TC Shea, SM Devine, C Linker

McCarthy and colleagues presented the results of a study aimed at evaluating the role of lenalidomide, a synthetic derivative of the immunomodulatory agent thalidomide, as maintenance therapy following autologous stem cell transplant (ASCT).[1] Here, data from the third intent-to-treat analysis were reported from the Cancer and Leukemia Group B (CALGB) 100104 study; the second analysis has previously been reported.[2]

A total of 568 patients with Durie-Salmon stage I–III multiple myeloma (MM) who were less than 70 years of age were enrolled in this double-blind, placebo-controlled, phase III clinical trial. All patients had achieved stable disease or better after 2 or more cycles of induction therapy, and were within 1 year of having initiated MM treatment; all patients also had adequate stem cell count ($\geq 2 \times 10^6$ CD34+ cells/kg). Patients underwent a single ASCT with 200 mg/m$^2$ melphalan and were restaged on days 90–100. Patients in a complete remission (CR), partial remission (PR), or with stable disease were randomized to receive either 10-mg/day lenalidomide (n=231) or placebo (n=229), which were administered until disease progression. Prior to randomization, patients were stratified according to β2-microglobulin baseline levels and the use of thalidomide or lenalidomide during induction therapy. Baseline characteristics were well balanced between the 2 treatment arms, and three-quarters (74%) of individuals had received lenalidomide or thalidomide as induction therapy prior to study enrollment.

Lenalidomide maintenance therapy was associated with a 60% reduction in the risk of disease progression, with significantly fewer patients experiencing an event compared with placebo (19.9% vs 41.5%; *P*<.0001). The median time to disease progression (TTP), the primary endpoint of the study, was also significantly improved with lenalidomide compared to placebo (42.3 vs 21.8 months; *P*<.0001). The TTP benefit associated with lenalidomide was observed across the characteristics used to stratify patients. There was no significant difference in the median OS between the 2 groups; however, the investigators noted this could be due to study unblinding and patient crossover (78.2% of eligible patients in the placebo arm crossed over to receive lenalidomide).

Significantly more patients treated with lenalidomide experienced grade 3 or higher adverse events (AEs) compared with patients treated with placebo, including both hematologic toxicities (45% vs 11%; *P*<.0001) and nonhematologic toxicities (33% vs 25%; *P*=.0350). Grade 3 or higher hematologic toxicities included neutropenia, thrombocytopenia, febrile neutropenia, and anemia. Grade 3 or higher nonhematologic toxicities included infections, fatigue, rash, and diarrhea. This led to a higher proportion of patients in the lenalidomide arm discontinuing study treatment due to AEs (12% vs 1%), although discontinuation due to reasons other than AEs was also more common (20% vs 7%). A total of 5 new cases of acute myelogenous leukemia or myelodysplastic syndrome were reported; of these, 2 patients were not treated with lenalidomide, and 1 patient treated with lenalidomide had also received prior breast cancer therapy.

## 40 HOVON-65/GMMG-HD4 Randomized Phase III Trial Comparing Bortezomib, Doxorubicin, Dexamethasone (PAD) vs VAD Followed by High-dose Melphalan (HDM) and Maintenance with Bortezomib or Thalidomide in Patients with Newly Diagnosed Multiple Myeloma (MM)[3]

P Sonneveld, I Schmidt-Wolf, B van der Holt, L el Jarari, U Bertsch, H Salwender, S Zweegman, E Vellenga, J Schubert, IW Blau, A Jie, B Beverloo, D Hose, A Jauch, H van de Velde, M Schaafsma, W Lindemann, MJ Kersten, U Duehrsen, M Delforge, K Weisel, S Croockewit, H Martin, S Wittebol, C Scheid, G Bos, M van Marwijk-Kooy, P Wijermans, H Lokhorst, H Goldschmidt

The reversible proteasome inhibitor bortezomib is currently approved for the treatment of MM in both the

frontline and relapsed/refractory setting. Although it has been extensively evaluated in MM, the efficacy of bortezomib as maintenance therapy following ASCT remains unclear.[4] In this abstract, Sonneveld and colleagues addressed this question and focused on the role of bortezomib therapy across prognostic subgroups of MM patients.[3]

The Dutch-Belgian Hemato-Oncology Cooperative Group and German Multiple Myeloma Group (HOVON-65/GMMG-HD4) study was a randomized phase III trial, which was conducted in the Netherlands and Germany. A total of 744 patients with Durie-Salmon stage II or III (International Staging System [ISS] stages I–III) newly diagnosed symptomatic MM were enrolled and randomized to receive either 3 cycles of PAD (n=371; 1.3 mg/m$^2$ bortezomib on days 1, 4, 8, 11; 9 mg/m$^2$ doxorubicin on days 1–4; and 40 mg dexamethasone on days 1–4, 9–12, and 17–20) followed by stem cell collection and transplantation and subsequent bortezomib maintenance therapy (1.3 mg/m$^2$ every 2 weeks), or 3 cycles of VAD (n=373; 0.4 mg vincristine on days 1–4; 9 mg/m$^2$ doxorubicin on days 1–4; and 40 mg dexamethasone on days 1–4, 9–12, and 17–20) followed by stem cell collection and transplantation and subsequent thalidomide maintenance therapy (50 mg/day). Maintenance therapy was continued for 2 years. When possible, patients were offered allogeneic stem cell transplant with no maintenance therapy. German patients underwent 2 ASCTs, whereas patients from the Netherlands underwent only one. Patients with a World Health Organization (WHO) performance score of 0–3 were allowed in the study, as were patients with renal failure. However, patients with amyloidosis, nonsecretory/nonmeasurable MM, severe concurrent disease, or baseline grade 2–4 neuropathy were excluded from the study. Baseline characteristics were well distributed between the 2 treatment arms. A total of 45%, 17–25%, and 20–27% of patients in each arm had ISS stage I, stage II, or stage III disease, respectively. Elevated creatinine levels (>2 mg/L) were present in 9–12% of patients.

The primary outcome, progression-free survival (PFS), was found to be significantly prolonged among patients treated with the PAD/bortezomib regimen compared with the VAD/thalidomide regimen (hazard ratio [HR], 0.79; 95% CI, 0.66–0.95; *P*=.01). Overall survival (OS) was also significantly improved in the PAD/bortezomib-treated patients (HR, 0.73; 95% CI, 0.56–0.96; *P*=.02). Importantly, both the PFS and OS benefit associated with PAD/bortezomib remained significant (*P*<.01) across all patient subgroups, including those with poor prognosis. For example, the 36-month PFS was 37% versus 29%, and the 36-month OS was 68% versus 50% for PAD/bortezomib- versus VAD/thalidomide-treated ISS stage III patients. For patients with elevated creatinine levels, the 36-month PFS (49% vs 12%) and 36-month OS (72% vs 32%) rates were also improved for PAD/bortezomib versus VAD/thalidomide treatments. Patients with the 13 or 13q chromosomal deletion achieved a 36-month PFS of 40% versus 29% for PAD/bortezomib versus VAD/thalidomide treatments. In a multivariate analysis, several factors were identified as significantly prognostic for PFS and OS, including study group, WHO performance score, ISS disease stage, presence of the 13q chromosomal deletion, and immunoglobulin (Ig) G and IgA clonal cell characteristics. OR (≥PR) was also significantly improved among patients treated with PAD/bortezomib versus VAD/thalidomide, following both induction therapy (78% vs 55%; *P*=.001) and high-dose melphalan (88% vs 77%; *P*<.001).

Compared with thalidomide, maintenance treatment with bortezomib was well tolerated over the 2-year treatment period. Rates of grade 3/4 infection were higher with PAD/bortezomib versus VAD/thalidomide (24% vs 18%), but rates of grade 3/4 gastrointestinal toxicity (4% vs 7%), peripheral neuropathy (9% vs 15%), and constitutional symptoms (2% vs 2%) were all decreased with PAD/bortezomib compared to VAD/thalidomide. A total of 56% and 64% of patients in the PAD/bortezomib and VAD/thalidomide groups, respectively, initiated maintenance therapy; 28% and 19% in each group completed 2 years of maintenance therapy. Three times as many patients in the VAD/thalidomide arm as in the PAD/bortezomib arm discontinued maintenance treatment due to toxicity (29% vs 9%), whereas a similar proportion discontinued due to disease progression (34% vs 35%).

## **310** Maintenance Treatment with Lenalidomide After Transplantation for Myeloma: Final Analysis of the IFM 2005-02[5]

M Attal, VC Lauwers, G Marit, D Caillot, T Facon, C Hulin, P Moreau, C Mathiot, M Roussel, C Payen, H Avet-Loiseau, J Luc Harousseau

Lenalidomide is an important agent for the treatment of MM in younger, transplant-eligible patients. In these patients, standard treatment includes high-dose therapy followed by ASCT.[6] However, many of these patients often experience disease relapse, likely due to residual disease following transplant. Thus, maintenance therapy has been explored as a strategy to reduce or eliminate this residual disease. Based on encouraging results with thalidomide in this setting,[7-9] attention has now turned to lenalidomide due to its lower incidence of neurologic complications and hematologic toxicity. In this abstract, Attal and colleagues reported the final analysis of the IFM 2005-02 study, which aimed to evaluate the safety and

efficacy of lenalidomide as maintenance therapy following ASCT in younger MM patients.[5] As a result of significant PFS benefit with lenalidomide demonstrated in the first interim analysis,[10] this study was unblinded in June 2010 following recommendation by the Data Safety and Monitoring Board.

This was a prospective, placebo-controlled, phase III trial, which enrolled 614 MM patients (<65 years of age) with nonprogressive disease within 6 months of first-line ASCT. All patients received 2 cycles of consolidation therapy with 25-mg/day lenalidomide on days 1–21 of 28 days. Following stratification for β2-microglobulin level at baseline, presence of chromosome 13 deletion, and very good partial response (VGPR) or better following ASCT, patients were randomized to receive either 10–15 mg/day lenalidomide (n=307) or placebo (n=307) maintenance therapy until evidence of disease relapse. Baseline characteristics were well balanced between the 2 treatment arms, with a median patient age of 55 years and nearly half of patients (43–48%) having ISS stage I disease. The majority of patients (79% in each arm) had only 1 ASCT, and the remaining 21% had 2 ASCT treatments. The median time from diagnosis to randomization was 10 months (range: 8–12) in each arm, and the median time from ASCT to consolidation was 4 months (range: 3–5) in each arm.

As was shown in the initial interim analysis, results in this final analysis confirmed that patients treated with lenalidomide maintenance experienced significantly longer PFS compared with patients receiving placebo (HR, 0.5; *P*<.00000001). This benefit in PFS associated with lenalidomide was observed across all patient subgroups, regardless of baseline β2-microglobulin levels, presence of the chromosome 13 deletion, and type of induction regimen used. PFS was significantly associated with the degree of response both prior to and after consolidation therapy. HRs more heavily favored lenalidomide among patients reaching PR or stable disease prior to consolidation (HR, 0.46; 95% CI, 0.32–0.66; *P*<.00001) and a CR after consolidation therapy (HR, 0.31; 95% CI, 0.14–0.68; *P*=.021). In fact, the response achieved following consolidation therapy was found to be highly prognostic for PFS (VGPR vs no response; *P*=.001). There was no difference in OS between patients who received lenalidomide versus placebo maintenance therapy.

Overall, lenalidomide maintenance therapy was well tolerated, although these patients had a higher rate of treatment discontinuation due to AEs compared with those treated with placebo (21% vs 15%). Some of the grade 3/4 AEs that occurred more frequently with lenalidomide maintenance therapy included neutropenia, thrombocytopenia, anemia, and skin disorders. Secondary hematologic malignancies (10 vs 2) and nonhematologic malignancies (6 vs 1) were also more frequent in the lenalidomide maintenance arm compared with placebo.

## 619 Phase 3b UPFRONT Study: Safety and Efficacy of Weekly Bortezomib Maintenance Therapy After Bortezomib-based Induction Regimens in Elderly, Newly Diagnosed Multiple Myeloma Patients[11]

R Niesvizky, IW Flinn, RM Rifkin, NY Gabrail, V Charu, B Clowney, J Essell, YA Gaffar, TA Warr, R Neuwirth, D Corzo, JA Reeves

In another abstract that investigated the efficacy and safety of bortezomib for transplant-ineligible elderly MM patients, Niesvizky and colleagues reported the results of the UPFRONT (Safety and Efficacy of Weekly Bortezomib Maintenance Therapy After Bortezomib-Based Induction Regimens in Elderly, Newly Diagnosed Multiple Myeloma Patients) study, a randomized, open-label, multicenter, phase IIIb clinical trial.[11]

In this study, 3 different bortezomib-based regimens were evaluated in eight 21-day cycles—VcD (1.3 mg/m$^2$ bortezomib on days 1, 4, 8, and 11; 20 mg dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12 for cycles 1–4 and days 1, 2, 4, and 5 for cycles 5–8), VcTD (1.3 mg/m$^2$ bortezomib on days 1, 4, 8, and 11; 100 mg thalidomide on days 1–21; and 20 mg dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12 for cycles 1–4 and days 1, 2, 4, and 5 for cycles 5–8), and VcMP (1.3 mg/m$^2$ bortezomib on days 1, 4, 8, and 11; 9 mg/m$^2$ melphalan on days 1–4 of every other cycle; and 60 mg/m$^2$ prednisolone on days 1–4 of every other cycle). Unless contraindicated, patients in the VcTD arm also received aspirin, warfarin, or low-molecular-weight heparin unless it was contraindicated. After induction therapy, all patients (regardless of treatment arm) received five 35-day cycles of bortezomib maintenance therapy (1.6 mg/m$^2$ on days 1, 8, 15, and 22). A total of 300 patients were randomized 1:1:1 (n=100 in each arm). All patients had newly diagnosed symptomatic MM, and they were found to be transplant-ineligible due to age, comorbidities, or preference. Patients having grade 2 or higher peripheral neuropathy in the 21 days prior to study enrollment were ineligible for participation. The baseline patient characteristics were well balanced among the 3 treatment arms, and 47% (VcD), 46% (VcTD), and 39% (VcMP) of patients in each arm had 1 or more comorbidities at baseline.

After a median follow-up of 13.4 months, PFS—the primary study endpoint—did not significantly differ between the 3 treatment arms (median PFS: 13.8, 18.4, and 17.3 months, for VcD, VcTD, and VcMP, respectively). Additionally, the OR was similarly high across the 3 treatment arms both after induction alone (68%, 78%, and 71% for VcD, VcTD, and VcMP, respectively) and

after induction and maintenance (71%, 79%, and 73% for VcD, VcTD, and VcMP, respectively). Most patients reported an improved quality of life over the study.

During induction therapy, high rates of grade 3 or higher toxicity were reported, including fatigue, neutropenia, diarrhea, and pneumonia. These were considered to be due to dexamethasone or melphalan and were reduced during the maintenance period. However, during induction, more patients in the VcTD arm than either the VcD or VcMP arms experienced grade 3 or higher peripheral neuropathy (26% vs 15% and 20%). The majority of patients received their planned dosage of induction (76%, 63%, and 69% for VcD, VcTD, and VcMP) and maintenance (73%, 77%, and 85% for VcD, VcTD, and VcMP) treatments.

## 620 Bortezomib, Melphalan, Prednisone and Thalidomide Followed by Maintenance with Bortezomib and Thalidomide (VMPT-VT) for Initial Treatment of Elderly Multiple Myeloma Patients: Updated Follow-up and Impact of Prognostic Factors[12]

A Palumbo, S Bringhen, M Cavalli, R Ria, M Offidani, F Patriarca, C Nozzoli, T Guglielmelli, G Benevolo, V Callea, R Zambello, G Pietrantuono, L De Rosa, AM Liberati, C Crippa, G Perrone, F Ciambelli, AM Carella, S Palmieri, M Gilestro, V Magarotto, MT Petrucci, P Musto, G Gaidano, M Boccadoro

Unfortunately, only limited treatment options are available for MM patients who are not candidates for stem cell transplantation.[13] Additionally, many transplant-ineligible patients are elderly; thus, the outcomes and treatment options are often further limited by age and comorbidities. Bortezomib, which has been shown to be active in both the frontline and relapsed/refractory MM settings, has potential for treatment of this patient population. Here, Palumbo and colleagues report an updated follow-up of a multicenter, randomized, Italian study, which evaluated 2 bortezomib-based regimens as frontline therapy for elderly and/or transplant-ineligible MM patients.[12] Bortezomib was investigated as both induction and maintenance therapy.

A total of 511 patients with symptomatic MM were enrolled; patients were either greater than or equal to 65 years of age, or less than 65 years of age but were otherwise transplant-ineligible. Individuals with elevated creatinine levels (>2.5 mg/L) were not allowed. Patients were randomized to receive nine 5-week cycles of induction therapy with either bortezomib, melphalan, prednisone, and thalidomide (VMPT; n=254; 1.3 mg/m$^2$ bortezomib on days 1, 8, 15, and 22; 9 mg/m$^2$ melphalan on days 1–4; 60 mg/m$^2$ prednisone on days 1–4; and 50 mg/day thalidomide) or VMP (n=257; 1.3 mg/m$^2$ bortezomib on days 1, 8, 15, and 22; 9 mg/m$^2$ melphalan on days 1–4; and 60 mg/m$^2$ prednisone on days 1–4). Patients treated with VMP then received maintenance therapy with VT (1.3 mg/m$^2$ bortezomib on days 1 and 15, and 50 mg/day thalidomide) until disease progression; patients treated in the VMPT arm received no maintenance therapy. During induction therapy, 73 and 66 patients in the VMPT and VMP groups, respectively, were treated with twice-weekly bortezomib instead. Baseline characteristics were well distributed among the 2 treatment arms, with a median age of 71 years and 27% of patients 75 years of age or older in each arm.

Compared with the VMP arm, patients in the VMPT/VT arm achieved significantly higher rates of VGPR or better (50% vs 64%; $P$=.001) and PR or better (81% vs 90%; $P$=.007). Further, 42% of patients treated with VMPT/VT achieved a CR as a best response, compared with 24% in the VMP arm ($P$<.0001). PFS (HR, 0.59; $P$<.0001) and time to next therapy (HR, 0.52; $P$<.0001) were also significantly prolonged in the VMPT/VT arm compared with the VMP arm. However, a slight improvement in OS was not significant (HR, 0.81; $P$=.35). A number of factors were identified as significantly prognostic for superior PFS with VMPT/VT, including age of less than 75 years ($P$<.0001), ISS disease stage I/II ($P$<.0001), and absence of cytogenetic abnormalities ($P$=.003).

Overall, the VMP/VT arm was well tolerated, although slightly more patients discontinued treatment compared with the VMP arm (21% vs 16%, respectively). Neutropenia ($P$=.02), cardiologic toxicity ($P$=.04), and deep vein thrombosis or pulmonary embolism ($P$=.05) all occurred at a significantly higher frequency in the VMP/VT arm. During maintenance therapy, several grade 3/4 AEs were found to be newly occurring or worsening, including sensory neuropathy, hematologic toxicities, deep vein thrombosis, infection, and cardiologic events.

## 622 A Phase 3 Study Evaluating the Efficacy and Safety of Lenalidomide Combined with Melphalan and Prednisone in Patients ≥ 65 Years with Newly Diagnosed Multiple Myeloma (NDMM): Continuous Use of Lenalidomide Vs Fixed-duration Regimens[14]

A Palumbo, M Delforge, J Catalano, R Hajek, M Kropff, MT Petrucci, Z Yu, L Herbein, JM Mei, CJ Jacques, MA Dimopoulos

Another potential option for transplant-ineligible patients is lenalidomide. Here, Palumbo and colleagues report an updated interim analysis of the MM-015 study, a randomized, double-blind, multicenter phase III trial.[14] In this study, the safety and efficacy of lenalidomide was investigated in both the induction and maintenance settings.

A total of 459 elderly (≥65 years of age) patients with newly diagnosed MM were randomized in this study. After stratification by age and disease stage,

patients were randomized into 3 treatment arms, in which they first received nine 28-day cycles of induction therapy followed by maintenance treatment. Patients were randomized to receive either MPR-R (n=152; 0.18 mg/kg melphalan on days 1–4; 2 mg/kg prednisone on days 1–4; and 10 mg/day lenalidomide on days 1–21 induction therapy followed by 10 mg/day lenalidomide on days 1–21 maintenance therapy), MPR (n=153; 0.18 mg/kg melphalan on days 1–4; 2 mg/kg prednisone on days 1–4; and 10 mg/day lenalidomide on days 1–21 induction therapy followed by placebo on days 1–21 maintenance therapy), or MP (n=154; 0.18 mg/kg melphalan on days 1–4; 2 mg/kg prednisone on days 1–4; and placebo on days 1–21 induction therapy followed by placebo on days 1–21 maintenance therapy). Baseline patient characteristics were well balanced between the 3 treatment arms, and approximately half of patients (48–51%) had ISS stage III disease. The median Karnofsky performance score was 80–90%. This second interim analysis was conducted with 70% of events reported, after a median follow-up of 21 months. The investigators noted that this study was unblinded in May 2010 as a result of a recommendation of the Data Safety and Monitoring Board; therapy was continued in the current treatment arms.

Patients in the MPR-R arm experienced a prolonged median PFS compared with the MPR arm and a significantly prolonged median PFS compared with the MP arm (31 months vs 14 months and 13 months, respectively; HR, 0.398; $P$<.0000001 for MPR-R vs MP). Importantly, this improvement was also observed in patients 65–75 years of age (not reached vs 14.7 and 12.4 months, respectively; HR, 0.315; $P$<.001 for MPR-R vs MP). PFS was also found to favor MPR-R versus MP across several other patient groups, including patients with ISS stage I/II disease, with creatinine clearance of 60 mL/min or higher, with β2-microglobulin levels less than or equal to 5.5 mg/L, and with a Karnofsky performance score of 90 or higher. In contrast, there was no significant difference in OS between the 3 treatment arms, either in the overall patient group or in a patient subgroup analysis. At the beginning of maintenance therapy, a comparison of patients in the MPR-R and MPR arms showed that the continuation of lenalidomide maintenance therapy versus placebo was associated with a significantly reduced risk of disease progression (HR, 0.314; $P$<.001). More patients in the MP and MPR arms, compared with MPR-R, required salvage therapy (most commonly lenalidomide or bortezomib).

Compared with the MP arm, patients who received lenalidomide in either the MPR-R or MPR arms had a higher frequency of grade 3/4 AEs. Grade 4 hematologic AEs, which were more common with lenalidomide therapy, included anemia, febrile neutropenia, neutropenia, and thrombocytopenia. Grade 3/4 nonhematologic AEs more common with lenalidomide included infections, pulmonary embolism, deep vein thrombosis, fatigue, and rash. Overall, these occurred more often during the induction phase compared with the maintenance phase. As a result, patients in the MPR-R and MPR arms exhibited higher rates of treatment discontinuation due to toxicity during induction therapy.

## **862** Carfilzomib, Lenalidomide, and Dexamethasone in Newly Diagnosed Multiple Myeloma: Initial Results of Phase I/II MMRC Trial[15]

AJ Jakubowiak, D Dytfeld, S Jagannath, DH Vesole, TB Anderson, BK Nordgren, D Lebovic, KE Stockerl-Goldstein, KA Griffith, MA Hill, CK Harvey, AM Dollard, R Ott, SL Kelley, J Barrickman, M Kauffman, R Vij

In addition to single-agent activity in MM, carfilzomib was also previously shown to be active in combination with lenalidomide and low-dose dexamethasone in a phase Ib clinical study of patients with relapsed/refractory MM.[16] Here, Jakubowiak and colleagues reported the results of a phase I/II study designed to determine the maximum tolerated dose (MTD) of this combination and to evaluate its safety and efficacy in patients with newly diagnosed MM.[15] This is the first published study to evaluate carfilzomib in the frontline MM setting.

The combination of carfilzomib, lenalidomide, and dexamethasone was administered in 28-day cycles. During the phase I portion of this trial, only carfilzomib was dose escalated, whereas both lenalidomide (25 mg on days 1–21) and dexamethasone (40 mg weekly during cycles 1–4 and 20 mg weekly during cycles 5–8) were kept at constant doses. Carfilzomib was initiated at 20 mg/m$^2$, with a maximal planned dose of 27 mg/m$^2$ and a decrease to 15 mg/m$^2$ as needed; it was administered on days 1, 2, 8, 9, 15, and 16 of each cycle. After a toxicity assessment, the study protocol was amended with the addition of a higher carfilzomib dose (36 mg/m$^2$), and the total phase I trial enrollment was increased to 35 patients. Overall, 36 patients are expected to be treated at the MTD during the phase I/II study. Patients who achieved a PR or better after 4 or more cycles could proceed to stem cell collection and ASCT; these patients were offered to continue treatment with the carfilzomib-based combination. Following the completion of 8 cycles, patients continued to receive maintenance doses of the combination (carfilzomib on days 1, 2, 15, and 16; lenalidomide on days 1–21; and dexamethasone weekly), administered at the dosage tolerated.

This analysis includes data from 24 enrolled patients (4, 14, and 6 patients at carfilzomib doses of 20, 27, and 36 mg/m$^2$); of these, toxicity data were available for 21 patients. The MTD had not yet been reached at the time

of this analysis. One dose-limiting toxicity was observed; this patient experienced nonfebrile neutropenia at the 27-mg/m$^2$ carfilzomib dose, which required lenalidomide dose reduction. Of the 23 patients who continued on therapy, the majority (n=20) had no need for dose modifications. Reversible hematologic toxicities were noted, including grade 3/4 neutropenia (n=3), grade 3/4 thrombocytopenia (n=3), and grade 3 anemia (n=2). Grade 3 nonhematologic AEs included glucose elevations related to dexamethasone (n=5), deep vein thrombosis (n=1), fatigue (n=1), and mood alteration (n=1). Even after prolonged therapy, only 2 cases of peripheral neuropathy were reported, both of which were grade 1 in severity.

After a median of 4 months of treatment (range: 1–8), 19 patients who completed 1 or more treatment cycles were found to be evaluable for response. All of these patients had a PR or greater; 63% had VGPR or better and 37% had a CR or near CR (nCR). This response was rapid, with the majority of patients (n=17) achieving a PR after the first treatment cycle. None of the evaluable patients had experienced disease progression in the follow-up period. After a median of 4 treatment cycles, a total of 7 patients proceeded to stem cell collection (median 6.3 × 10$^6$ CD34+ cells/kg collected).

## 985 Results of PX-171-003-A1, an Open-label, Single-arm, Phase 2 (Ph2) Study of Carfilzomib (CFZ) in Patients (pts) with Relapsed and Refractory Multiple Myeloma (MM)[17]

DS diCapua Siegel, T Martin, M Wang, R Vij, AJ Jakubowiak, S Jagannath, S Lonial, V Kukreti, NJ Bahlis, M Alsina, AA Chanan-Khan, G Somlo, F Buadi, FJ Reu, JA Zonder, K Song, E Stadtmauer, AF Wong, M Vallone, Y-L Chang, M Kauffman, RZ Orlowski, AK Stewart, SB Singhal

Despite the availability of several agents for frontline therapy, the majority of patients with MM eventually experience disease relapse. Current results with bortezomib and lenalidomide in relapsed/refractory MM show that patients experience a median survival of 8 months with treatment.[18] Thus, there is a need for new agents to treat relapsed/refractory disease. In a previous phase II study, the novel proteasome inhibitor carfilzomib was demonstrated to have single-agent activity in the relapsed/refractory MM setting, achieving a 21% overall response (OR) rate in patients previously treated with bortezomib and a 45–55% OR rate in bortezomib-naïve patients.[19] In this current abstract, diCapua Siegel and colleagues presented data from another phase II trial, which evaluated single-agent carfilzomib specifically in MM patients who had experienced multiple relapses and who had been refractory to their last prior treatment.[17]

PX-171-003-A1 was an open-label, single-arm, phase II trial, which enrolled 266 patients with MM. All patients had evidence of relapsed and progressive disease when they entered the study, and two-thirds (65%) had proven refractory to bortezomib at some point. Further, all patients had relapsed after at least 2 previous lines of treatment; these must have included bortezomib and an immunomodulatory agent (either thalidomide or lenalidomide). Carfilzomib was administered for 12 cycles, on days 1, 2, 8, 9, 15, and 16; during cycle 1, the dose was 20 mg/m$^2$; it was 27 mg/m$^2$ for the remaining cycles. The median patient age was 63 years (range: 37–87), patients had a median duration of MM of 5.4 years (range: 0.5–22.3), and 69% of patients had an ISS disease stage of II/III. Most patients (83%) had experienced disease progression at 60 days or less from their last therapy. A total of 257 patients were considered evaluable for this analysis.

Overall, carfilzomib was associated with a 24% OR rate, the primary endpoint of the study. However, slightly more patients (34%) achieved clinical benefit (OR or minimal response). The median duration of OR was 8.3 months. The majority of responses were PR or VGPR, although a small proportion achieved a CR (18.7%, 5.1%, and 0.4%, respectively). Although carfilzomib was active even among bortezomib-refractory patients, both the proportion of responding patients (17%) and the median duration of OR (7.8 months) were decreased. Importantly, the OR to carfilzomib was observed regardless of whether patients were considered to be low or high risk. For example, similar proportions of patients achieved an OR regardless of bone marrow involvement (<50% vs ≥50% involvement: 24% vs 26%), number of previous chemotherapy lines (<5 vs ≥ 5 lines: 25% vs 24%), cytogenetics (good vs poor: 24% vs 28%), and baseline peripheral neuropathy (absent or present: 26% vs 24%). The median PFS was 3.7 months (95% CI, 2.8–4.6) and the median OS was 15.5 months (95% CI, 12.7–19.0).

Grade 3/4 hematologic toxicities—including thrombocytopenia (27%), anemia (22%), lymphopenia (18%), and neutropenia (10%)—were the most frequent treatment-emergent AEs. The incidence of new onset grade 3/4 peripheral neuropathy was low (<1%). The majority of patients (82%) discontinued treatment, either due to disease progression (57%) or AEs (12%). A minority of patients (16%) completed all 12 intended cycles of carfilzomib.

## 1938 Carfilzomib: High Single Agent Response Rate with Minimal Neuropathy Even in High-risk Patients[20]

R Vij, JL Kaufman, AJ Jakubowiak, AK Stewart, S Jagannath, V Kukreti, KT McDonagh, M Alsina, NJ Bahlis, A Belch, FJ Reu, NY Gabrail, J Matous, DH Vesole, RZ Orlowski, MH Le, P Lee, M Wang

In another abstract, Vij and colleagues reported the results of a phase II trial, which evaluated single-agent carfilzomib

in patients with relapsed or refractory MM after 1–3 prior lines of chemotherapy.[20] Specifically, this abstract focused on an analysis of bortezomib-naïve patients with high-risk disease, defined as having either significant comorbidities or poor-risk cytogenetics.

A total of 110 bortezomib-naïve MM patients were included from PX-171-004, an ongoing phase II clinical trial. Single-agent carfilzomib was administered for up to 12 cycles on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle; patients received either 20 mg/m$^2$ carfilzomib for all cycles, or 20 mg/m$^2$ during cycle 1 and 27 mg/m$^2$ for all subsequent cycles. Patients received 4 mg dexamethasone prior to carfilzomib administration in cycle 1 only. A total of 60% of patients had an Eastern Cooperative Oncology Group (ECOG) performance score of 1 or higher, and half (53%) had grade 1/2 neuropathy at baseline. Nearly one-third (30%) had moderately impaired kidney function, defined as a creatinine clearance of less than 60 mL/min, and diabetes was present in 17% of patients. A total of 13% of patients had poor-risk cytogenetics.

The primary endpoint, OR rate among all 110 bortezomib-naïve patients, was 48%. However, patients who had received the dose-escalating carfilzomib regimen achieved a higher OR than patients who had received only 20-mg/m$^2$ carfilzomib continuously (54% vs 43%). The OR among patients who had an ECOG performance score of 1 or higher was slightly lower than among patients with an ECOG performance score of 0 (42% vs 50%). Similarly, the OR was slightly lower but similar between patients with stage I/II/unknown or stage III ISS disease (46% vs 41%). Patients with elevated (≥2.5 mg/L) serum β2-microglobulin achieved a lower OR than patients with normal (<2.5 mg/L) levels (41% vs 54%). The OR was similar between patients with normal or favorable cytogenetics compared with poor-risk cytogenetics (46% vs 40%).

The most frequently observed treatment-emergent AEs were fatigue (61%), nausea (43%), anemia (39%), dyspnea (36%), cough (34%), headache (31%), thrombocytopenia (30%), and upper respiratory infections (30%). Most of these were grade 2 or higher in severity. Hematologic toxicities, including lymphopenia, neutropenia, thrombocytopenia, and anemia, were among the most common grade 3/4 AEs, as well as pneumonia and fatigue. Nearly one-quarter (23%) of patients completed all 12 cycles of carfilzomib; notably, no patients discontinued treatment due to the development of peripheral neuropathy. Only one patient with renal impairment discontinued treatment due to an increase in creatinine levels.

## **1953** Long-term Treatment and Tolerability of the Novel Proteasome Inhibitor Carfilzomib (CFZ) in Patients with Relapsed and/or Refractory Multiple Myeloma (R/R MM)[21]

S Jagannath, R Vij, JL Kaufman, T Martin, R Niesvizky, NY Gabrail, M Alsina, AF Wong, MH Le, L McCulloch, AL Hannah, M Kauffman, DS diCapua Siegel

Bortezomib and carfilzomib are both proteasome inhibitors with activity in MM. Unlike bortezomib, carfilzomib has demonstrated a lower incidence of off-target effects and, importantly, is not associated with the development of neurotoxicity over long-term administration in animals. Further, carfilzomib is active even in bortezomib-resistant MM cells.[22] Based on these promising preclinical data, Jagannath and colleagues conducted an assessment of the long-term safety of carfilzomib in patients with relapsed/refractory MM.[21]

This assessment included patients enrolled in multiple clinical trials evaluating carfilzomib, including a phase I study in patients with hematologic malignancies (PX-171-002), a phase II study in relapsed/refractory MM (PX-171-003), a phase II trial in MM patients who relapsed following 1–3 therapies (PX-171-004), and a phase II trial in patients with relapsed/refractory MM and varying degrees of renal dysfunction (PX-171-005). All patients were treated with carfilzomib; most received 20 mg/m$^2$ on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle for all cycles, although some patients were treated with 27-mg/m$^2$ carfilzomib for cycles 2–12. A small number of patients were treated with higher doses (36 mg/m$^2$ or 45 mg/m$^2$). Patients who had completed their full planned course of carfilzomib therapy were offered enrollment into the PX-171-010 extension trial, in which patients continued to receive carfilzomib at the same dose level and frequency as in their last treatment cycle. A reduction in carfilzomib frequency to twice weekly every other week was allowed at the investigator's discretion. Patients in the extension study continued to receive carfilzomib until disease progression or unacceptable toxicity.

Of the patients who completed 12 cycles of carfilzomib therapy in their initial study, 42 continued to receive carfilzomib (38 were enrolled in PX-171-010 and 4 were treated on single-patient investigational new drug applications prior to the initiation of the extension trial). Of these patients, the majority (n=38) received single-agent carfilzomib, with several (n=4) patients from PX-171-005 receiving carfilzomib in combination with low-dose dexamethasone. At the time of this analysis, 60% (n=25) of the 42 patients remained on treat-

ment (median carfilzomib dose 27 mg/m$^2$; range: 15–45 mg/m$^2$). Among these patients, the median duration of carfilzomib therapy was 14 months, with the longest period reaching over 27 months; carfilzomib therapy was continued for more than 18 months in 12 patients. Of the remaining 40% of the 42 patients (n=17) who discontinued carfilzomib, all but one did so due to progressive disease; the remaining patient had pneumonia and decided to not restart therapy.

Over the course of long-term carfilzomib administration in this analysis, no cumulative toxicities were observed. The AEs reported were similar in severity and frequency as those reported in the previous single-agent carfilzomib trials. During the extension study, serious AEs were reported in 7 patients, 4 of whom had events that were possibly related to treatment (infection, dyspnea, bronchitis, and asthenia). In the 7 cases, carfilzomib was either interrupted and subsequently restarted or maintained. No cases of peripheral neuropathy or significant renal dysfunction were reported in the extension trial.

## **3065** Vorinostat Overcomes Lenalidomide-Dexamethasone and Lenalidomide-Bortezomib-Dexamethasone Resistance in Relapsed/Refractory Multiple Myeloma[23]

DS diCapua Siegel, L McBride, E Bilotti, L Schmidt, Z Gao, M Tufail, N Lendvai, A McNeill, K Donadio, K Olivo, U Bednarz, T Graef, DH Vesole

The oral histone deacetylase (HDAC) inhibitor vorinostat, currently approved for the treatment of cutaneous T-cell lymphoma, is a novel agent that has been investigated for MM. Previous studies have suggested it has efficacy both as a single agent and in combination with bortezomib in patients with relapsed/refractory MM; it has also been investigated in combination with immunomodulatory agent therapy.[24-26] Encouraging results have also been observed in a phase I trial of vorinostat combined with lenalidomide and dexamethasone in patients with heavily pretreated relapsed/refractory MM.[27] Here, diCapua Siegel and colleagues report their experience in a single institution with vorinostat-based combinations.[23]

In this retrospective chart review of 28 consecutive patients, all cases received 28-day cycles of either 300-mg or 400-mg vorinostat once daily on days 1–7 and 15–21 plus 10–25 mg lenalidomide on days 1–21. Of these, 10 patients additionally received 1.3-mg/m$^2$ bortezomib on days 1, 4, 8, and 11. All patients had been shown to be refractory to prior treatment with lenalidomide plus dexamethasone, and 20 patients were refractory to previous bortezomib, lenalidomide, and dexamethasone. The median number of prior lines of therapy was 4 (range: 2–10) and the median number of prior regimens was 5 (range: 2–11). ASCT was performed in 23 patients.

An OR rate of 43% was reported, which included 8 patients with a PR and 4 patients with a VGPR or better. Minimal responses were noted in 5 additional patients, and 8 patients achieved stable disease. Thus, the overall clinical benefit rate in response to vorinostat-based treatment was 89%. The duration of response ranged widely from 2 to over 23 months. The most frequently reported AEs were related to gastrointestinal toxicity, mainly diarrhea and cramping. Although cytopenias were also observed, the investigators reported that their incidence was not higher than what would be expected from these patients with lenalidomide treatment alone.

## **4038** The Ratio of Monoclonal to Polyclonal Immunoglobulins Assessed with the Hevylite Test Predicts Prognosis, is Superior for Monitoring the Course of the Disease and Allows Detection of Monoclonal Immunoglobulin in Patients with Normal or Subnormal Involved Immunoglobulin Isotype[28]

H Ludwig, L Mirbahai, N Zojer, A Bradwell, S Harding

Determining patient prognosis is an essential component of the overall management strategy for MM. Properly defining a patient's prognosis can help both the clinician and the patient to choose a course of therapy. Additionally, it is also essential to monitor a patient's response to treatment in order to determine if a change in therapy is needed and to help guide the patient in future clinical decisions. A number of tools are currently used in the clinic to both determine a patient's prognosis and measure treatment response. Most commonly, patient prognosis is scored using the ISS in combination with cytogenetics, and treatment response is assessed using response criteria developed by the European Group for Blood and Marrow Transplantation or the International Myeloma Working Group. Response to treatment is also evaluated by measuring the residual MM paraprotein, using serum free light chain, serum protein electrophoresis, or immunofixation. In this abstract, Ludwig and colleagues investigated the potential of a new biomarker, the ratio of monoclonal to isotype matched polyclonal immunoglobulins, to help determine patient prognosis at time of treatment initiation as well as evaluation of response during long-term follow-up.[28]

A total of 103 treatment-naïve MM patients (median age, 67 years; range: 32–86 years) were included in this study. All patients were enrolled in clinical studies between 1994 and 2007, either in a trial comparing thalidomide plus dexamethasone with melphalan plus prednisone or a trial comparing 2 versus 3 ASCTs after induction therapy with vincristine plus doxorubicin and dexamethasone. Patients expressed a variety of MM immunoglobulin subtypes, including IgGκ (n=35), IgGλ (n=17), IgAκ

(n=29), and IgAλ (n=22). ISS stage was assigned in all but 2 cases (38%, 41%, and 21% for ISS stage I, II, and III, respectively). The heavy/light chain (HLC) immunoglobulin ratios were determined using commercially available kits.

After a median follow-up of 13 months (range: 85 days–58 months), the overall median OS was 37.9 months. The 4-year OS rate was 37%. In a multivariate analysis, only β2-microglobulin levels (HR, 1.9; 95% CI, 1.105–3.93; *P*=.028) and the HLC ratio (HR, 1.89; 95% CI, 1.092–3.362; *P*=.039) were found to be significantly associated with OS; lactate dehydrogenase levels, serum albumin levels, age, and creatinine levels were not significantly correlated. The β2-microglobulin levels and HLC ratios were combined to form a 3-tiered risk stratification model. Patients were categorized as having 0 risk factors (β2-microglobulin level <3.5 mg/L and HLC ratio < median), 1 risk factor (either β2-microglobulin level >3.5 mg/L or HLC ratio > median), or 2 risk factors, (both β2-microglobulin level >3.5 mg/L and HLC ratio > median); these were associated with a median OS of 118, 53, and 29 months, respectively. Importantly, when the β2-microglobulin levels and HLC ratio were combined, they were found to have a greater prognostic value than ISS stage alone (*P*=.001 vs *P*=.09).

Over the follow-up period, nearly half of patients (n=46; 45%) achieved normal or subnormal levels of immunoglobulin. The majority of these cases (n=35) exhibited abnormal HLC ratios; 7 of these had been reported to be negative by immunofixation, demonstrating the improved sensitivity of the commercial assay to detect residual disease.

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# Commentary

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Multiple myeloma is a disease of the elderly; 75% of diagnosed patients are over the age of 55, and the median age of onset is 70 years.[1] The benefit of high-dose therapy and stem cell transplantation has therefore been limited to younger patients without comorbidities.[2,3] However, the introduction of novel agents, such as the immunomodulatory molecules thalidomide and lenalidomide and the proteasome inhibitor bortezomib, have had a great effect on the overall outcome of patients young and old, as well as those with comorbidities. As these drugs were introduced over the past decade, the improvement in survival was mainly noted in patients with relapsed or refractory myeloma. When these drugs were moved upfront in the treatment of newly diagnosed myeloma, a higher response rate and greater depth of response, along with improvement in progression-free survival (PFS) and overall survival (OS), were observed.[4] Although major benefits have been seen in a majority of patients with good-risk myeloma, new strategies and treatment options are needed to improve the outcome in a smaller subset of patients presenting with high-risk features.[5]

Current clinical research is focused on developing treatment for all phases of multiple myeloma. New drug combinations are being explored for induction therapy to improve the depth of response, maintenance therapy is being investigated both in younger patients after stem cell transplantation and in elderly patients after initial therapy, and new drugs are being explored in the relapsed setting. For the first time, monoclonal antibodies are making some headway in the management of myeloma.

Doublets of novel agents and dexamethasone have been explored as initial therapy in randomized trials compared to standard therapies. Thalidomide/dexamethasone is equivalent to melphalan/prednisone (MP) or vincristine/doxorubicin/dexamethasone (VAD) induction,[6] bortezomib/dexamethasone is superior to VAD induction before transplant,[7] and lenalidomide/dexamethasone results are comparable to those achieved with bortezomib.[8] The addition of a novel agent to the backbone of MP has improved the outcome of elderly patients, both in the 65–75 year age group as well as the 75–85 year age group.[9,10] Thalidomide is unable to overcome the high-risk features of this population, and failed to show consistent improvement in survival among several large, randomized trials.[11-13] The proteasome inhibitor bortezomib, when combined with MP, shows improvement in OS across the age spectrum and across renal impairment and high-risk genetic features.[14] The toxicities seen with bortezomib—especially peripheral neuropathy—can be substantially mitigated, and its tolerance can be improved in elderly patients without losing clinical benefit by administering bortezomib once weekly.[15] In all these trials, improvement in OS was associated with a higher complete response (CR) and very good partial response (VGPR) rate and improved PFS.[7-15]

Investigators have started exploring more intensive combinations of drugs from different classes. Combining a proteasome inhibitor with an immunomodulatory drug, or an alkylating agent, and dexamethasone (bortezomib/thalidomide/dexamethasone [VTD], bortezomib/lenalidomide/dexamethasone [VRD], bortezomib/cyclophosphamide/dexamethasone [VCD]) resulted in a doubling of the CR rate to 40% and overall response rate (ORR) to over 90%.[16-19] The addition of a fourth drug to these combinations has not resulted in further improvement in the CR rate or ORR, as evidenced by the efficacy findings of bortezomib/melphalan/prednisone/thalidomide (VMPT) from the EVOLUTION trial and the Italian Multiple Myeloma Network (GIMEMA) trial.[15,18] However, addition of high-dose therapy and stem cell transplantation does increase the CR rate to approximately 60%. This has resulted in less utilization of second stem cell transplantation.[7]

The total therapy approach incorporates intensive induction followed by consolidation with tandem transplantation and subsequent maintenance therapy.[20-22] This approach has shown a very high CR rate, PFS, and OS. There has been a progressive increase in the CR rate and in OS with the addition of thalidomide, as seen in the findings from the Total Therapy II trial, and with the addition of bortezomib, as seen in the Total Therapy III trial.[21,22] The total therapy approach was tested in a recent trial by the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and German Multiple Myeloma Group (GMMG). In the HOVON-65/GMMG-HD4 trial, 744 patients were randomized to bortezomib, doxorubicin, and dexamethasone (PAD) versus VAD induction followed by transplantation.[23] Patients on the bortezomib arm received bortezomib maintenance therapy and patients on the VAD arm received thalido-

mide maintenance. The response rates were superior in the bortezomib arm, with improvement in PFS and OS. Maintenance therapy with bortezomib improved the outcome of patients with high-risk genetic abnormalities such as t(4;14), +1q21, and del(13q), but not del(17p). This study confirms that the use of best possible induction therapy followed by transplantation and maintenance therapy improves the overall life expectancy of patients with multiple myeloma. The UPFRONT (Safety and Efficacy of Weekly Bortezomib Maintenance Therapy After Bortezomib-Based Induction Regimens in Elderly, Newly Diagnosed Multiple Myeloma Patients) trial has shown that bortezomib maintenance is equally well-tolerated by elderly patients ineligible for stem cell transplantation.[24]

The purpose of maintenance therapy is to eliminate or suppress the minimum residual tumor clone over a prolonged period of time to improve the remission duration and life expectancy. Immunomodulatory molecules are well suited for maintenance therapy, as they can be administered orally at low doses for a prolonged period of time. Maintenance therapy with thalidomide post-transplantation was shown to improve PFS and OS in 2 large, randomized trials, though thalidomide maintenance trials have had a high discontinuation rate.[25,26] Recent trials have shown a mixed benefit with thalidomide and prednisone maintenance.[27,28] Therefore, new studies are looking at lenalidomide and bortezomib for maintenance therapy.

The GIMEMA investigators have attempted to improve the results of the VMP regimen by adding thalidomide and maintaining remission with bortezomib and thalidomide (VMPT-VT).[15,29] Transplant-ineligible patients over the age of 65 were randomized to either the standard VMP regimen or VMPT induction followed by VT maintenance. This study was initiated with standard twice-weekly bortezomib administration. After the first 66 and 73 patients in the VMP and VMPT groups, respectively, were treated with a twice-weekly infusion of bortezomib, the study was modified to reduce the dose intensity of bortezomib to once weekly for 4 weeks. The addition of thalidomide and the incorporation of maintenance therapy in the VMPT-VT arm increased the CR rate to 38% and the ORR to 90%, with improvement in PFS at 3 years to 54% compared to 40% with VMP. Administering once-weekly bortezomib reduced the incidence of neuropathy by 50% (21% vs 43%), and grade 3/4 neuropathy declined to 2%. Discontinuation due to painful neuropathy was substantially lower, at 4%, with weekly bortezomib as compared to 16% with twice-weekly bortezomib administration. The total delivered dose of bortezomib was the same 40 mg/m$^2$ whether given once or twice weekly because the discontinuation rate was higher in twice weekly dosing (16% vs 4%).

Another series of large randomized trials have evaluated the efficacy of lenalidomide as maintenance therapy. There were 2 large phase III posttransplant trials comparing low-dose lenalidomide 10 mg versus placebo.[30,31] Both the IFM 2005-02 trial and the CALGB 100104 trial had virtually identical improvement in PFS; the median PFS was 2 years in the placebo arm and 42 months in the lenalidomide arm—an 18-month improvement over placebo. However, a survival advantage was not observed in the IFM 2005-02 trial.[30] During the CALGB 100104 trial, the Data Safety Monitoring Board recommended unblinding the trial after the interim analysis, as the primary objective of improved PFS was met, and allowed patients from the placebo arm to cross over to receive lenalidomide. Consequently, over 80% of patients originally on the placebo arm have received lenalidomide.[31] In a pivotal, large, international, randomized trial, lenalidomide maintenance following melphalan, prednisone, and lenalidomide (MPR-R) was compared to MP and MPR for 9 cycles without maintenance.[32] The median PFS was 31 months for MPR-R compared with 14 months for the other 2 arms (MP, MPR), a 17-month improvement in PFS. Although maintenance therapy with lenalidomide prolonged PFS, there was no difference in OS between the 3 arms. This was accounted for by improved response to salvage therapy with lenalidomide and/or bortezomib following relapse.

Results from the MM-015 trial indicate that patients who relapse early without maintenance therapy can be salvaged effectively with novel agents. Patients with high-risk disease may be in need of maintenance therapy to prolong their remission because, generally, salvage therapies are less effective upon relapse. Thalidomide maintenance has been hampered by early discontinuation due to side effects of peripheral neuropathy, and cytopenia is common with lenalidomide maintenance. Therefore, factors such as side effects, quality of life, and long-term risk-benefit ratio have to be carefully weighed before recommending maintenance therapy to a patient.

Somewhat disconcerting is the increased incidence of second malignancy among the patients who receive lenalidomide maintenance. This was more pronounced in the French trial, where incidence of a second malignancy was 5.5% in the lenalidomide arm compared to 1% in the placebo arm.[30] The analysis of the intent-to-treat population in the CALGB 100104 trial, which was performed until the study was unblinded, also showed an increased incidence of second malignancy in patients receiving lenalidomide compared to those receiving placebo (6.5% vs 2.6%).[31] In the MM-015 trial, the incidence of second malignancy was 3.1% in the lenalidomide maintenance arm and 1.3% in the MP followed by no maintenance arm.[32]

National registries from Finland, Sweden, and the United States have reported a higher incidence of myeloid leukemia in patients with multiple myeloma.[33-35] This was largely attributed to the use of a chronic alkylating

agent such as melphalan. A slightly higher incidence of non-Hodgkin lymphoma was noted in the Swedish and Finnish registries, but not in the Surveillance, Epidemiology, and End Results data. Further follow-up and detailed analysis of the emerging data are being performed; caution should be exercised in prescribing lenalidomide maintenance therapy following melphalan-based therapy beyond 2 years. Patients who have recurrent myeloma after failing both immunomodulatory molecules and bortezomib have no real treatment options, and their life expectancy is limited to less than a year. This is an area of intensive research for new drug development, and the next generation of proteasome inhibitors and immunomodulatory drugs are showing some promise.

Proteasome inhibition induces apoptosis in myeloma tumor cells. Carfilzomib is an irreversible inhibitor of the proteasome that can be given on consecutive days for sustained proteasome inhibition resulting in a greater antitumor effect. It does not have neurotoxicity in animal models. When tested in relapsed and refractory patients, the ORR was 24%, and stable disease or better was noted in 69% of the patients.[36] Among the 257 evaluable patients, the median remission duration was 8.3 months and the median OS was 15.5 months, which is a substantial improvement compared to the expected median survival of 9 months, as reported by the International Myeloma Working Group for this patient population.[37] In bortezomib-naïve patients with relapsed myeloma, single-agent carfilzomib had a very high response rate of 52%, with 29% of patients achieving VGPR or better; the median time to progression has not been reached.[38] Carfilzomib can be combined safely with other drugs. When combined with lenalidomide and dexamethasone, preliminary reports indicate an unprecedented CR rate of over 60% and a VGPR rate of over 80%.[39] Carfilzomib is generally well tolerated, with minimum neuropathy, and would be an excellent addition to the treatment armamentarium.[40]

A wide variety of histone and nonhistone proteins are regulated by acetylation. The acetylation/deacetylation balance resulting from the activity of histone acetyltransferases and histone deacetylases (HDACs) is responsible for modulating normal cellular processes, including cell cycle arrest and apoptosis.[41] HDAC inhibition increases histone and nonhistone acetylation. Histone acetylation causes epigenetic effect by the uncoiling of DNA within chromatin and open chromatin structure for transcriptional activation of genes, including tumor suppressors. Nonhistone acetylation regulates activities of transcription factors including p53.[42] Inhibition of HDAC6, a class II HDAC, blocks aggresome formation in multiple myeloma cells.[43] When myeloma cells are treated with bortezomib, the aggresomal pathway provides an alternative route (compensatory mechanism) for degradation of polyubiquitinated proteins in cells and it avoids apoptosis. Therefore, HDAC inhibitors have been explored in the treatment of multiple myeloma. This class of drug has been ineffective when given as single agents. However, when combined with bortezomib, they have been able to synergize and help overcome drug resistance to bortezomib.[44] Currently, 2 large international phase III trials studying HDAC inhibitors plus bortezomib have been completed, and their results are awaited.[45]

Our ability to induce CRs has increased with the development of novel agents. Achievement of CR has been shown to correlate with PFS and in some cases with OS. CR has been defined as the absence of monoclonal spike in serum protein electrophoresis, no monoclonal band on immunofixation electrophoresis, and bone marrow less than 5% plasma cells. More recently, 5-color flow cytometry to denote absence of clonal plasma cells in the bone marrow and normalization of kappa:lambda ratio by serum free light chain assay, and a new methodology to detect the ratio of monoclonal to isotype matched polyclonal immunoglobulins have established a more stringent criteria for definition of CR and prediction of early relapse.[46]

In summary, the review of the select abstracts that were presented at the 2010 meeting of the American Society of Hematology highlights the progress in the treatment of multiple myeloma. Combinations of novel agents have increased the depth and durability of response, thereby increasing PFS. Maintenance therapy has consistently improved the PFS by 18 months. However, the possibility of emergence of myeloid malignancy after melphalan followed by long-term maintenance with lenalidomide warrants caution. Clinical activity reported to date with new drugs such as carfilzomib and pomalidomide, as well as HDAC inhibitors in combination with bortezomib, is a cause for optimism in the continued improvement in the management of multiple myeloma.

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