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Recent Phase III Trials in the Frontline Treatment of Multiple Myeloma: Evaluating Their Impact on Community Practice

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Abstract

Multiple myeloma (MM) is a significant malignancy that arises in the antibody-producing cells of the bone marrow. Generally regarded as incurable, patients who achieve optimal responses to treatment have the best prognosis. However, for many decades, standard chemotherapy induced complete responses in only a small number of patients. The recent addition of thalidomide, lenalidomide, and bortezomib has revolutionized the conventional chemotherapeutic regimens used for MM patients. Importantly, significant strides have been made in the treatment of elderly MM patients, for whom traditional treatment strategies such as autologous stem cell transplantation are not an option. Improvements in clinical response to therapy have concomitantly increased patients' survival and quality of life. Here, several key phase III trials which evaluated regimens containing these new agents are discussed. These trials were presented last December at the 49th Annual Meeting of the American Society of Hematology, in Atlanta, Georgia. Special focus here is on the patient cohorts treated in each study, as well as response rates and the impact these new agents will likely have on current patient care.

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Target Audience: This activity has been designed to meet the educational needs of oncologists, hematologist/oncologists, hematologists, and oncology nurses involved in the management of patients with multiple myeloma (MM).

Statement of Need/Program Overview: In order to maintain and further advances in emerging therapies for treating MM, it is essential that the latest developments be communicated as effectively and efficiently as possible in order to optimize patient care. This monograph will enable medical professionals to quickly and accurately synthesize the data and apply it appropriately to positively impact patient management strategies, prolong survival and perhaps achieve the truly elusive goal of curing patients with hematologic malignancies.

Educational Objectives

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

- Describe the importance of new study finding from phase III clinical trials in the treatment of multiple myeloma.
- Cite findings of current clinical trials evaluating treatment regimens and the effect on clinical remission in multiple myeloma.
- Indicate approaches for treating patients with multiple myeloma in order to improve outcomes.

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Discussions

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Many patients afflicted with multiple myeloma (MM) are elderly (≥65 years), and are therefore not candidates for high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). For these patients the standard treatment is melphalan-prednisone (MP); however, MP provides only minimal disease control, with a typical overall response rate (ORR) of 45–60% and complete responses (CRs) only rarely.[1] These patients have a median progression-free survival (PFS) of only 18 months; therefore, improvement to this regimen is an important goal. Here, the results of two phase III trials that examined novel MP-based combinations in the elderly population are discussed.

The proteasome inhibitor bortezomib is currently approved for relapsed MM, but its efficacy as frontline therapy for elderly patients is still under investigation. One phase I/II study in 60 patients age 65 years or older tested the safety of bortezomib added to MP.[2] That trial defined an optimal bortezomib dose of 1.3 mg/m^2 in this combination and reported a high ORR of 89%, including 32% CR. Remarkably, a recently updated time-to-events analysis showed that 85% of these patients will be alive at 3 years.[3] Based on these encouraging results, further exploration of this combination has ensued. MMY-3002 was an international phase III trial with the goal of evaluating the addition of bortezomib to a standard MP regimen.[4] This interventional trial enrolled 682 treatment-naive patients with newly diagnosed MM. All patients had symptomatic, measurable disease and were not eligible for either high-dose chemotherapy regimens or ASCT. Baseline characteristics were relatively similar between the two treatment groups and the median patient age was 71 years. Both disease progression and response to treatment were assessed every 3 weeks using a centralized laboratory, and clinical data were independently reviewed by a data-monitoring committee.

Individuals were randomized to receive nine 6-week cycles of either conventional MP (n=338) or MP plus bortezomib (BMP; n=344). In both groups, melphalan (9 mg/m^2) and prednisone (60 mg/m^2) were administered on the first 4 days of each treatment cycle, while those patients in the BMP group additionally received bortezomib (1.3 mg/m^2). Bortezomib was administered a total of 8 days during each of the first 4 treatment cycles, and 4 days during each of the subsequent 5 cycles.

The primary study endpoint, time to progression (TTP), was significantly increased with the addition of bortezomib. Compared with the MP arm, patients on the BMP arm had a significantly longer median TTP, with a 52% reduction in the risk of progression in the BMP group compared to the MP group (hazard ratio [HR], 0.483; P<.000001; Table 1).

Superior ORRs (CR + partial response [PR]) were observed on the BMP arm compared to the MP arm (82% vs 50%, respectively; P<.000001). Similarly, CR was also significantly increased in patients receiving BMP (35% vs 5%; P<.000001). The responses were somewhat lower but still significantly different when analyzed using the more stringent EBMT criteria (30% vs 4%).[5] At a median follow-up of 16.3 months, neither treatment arm had reached a median overall survival (OS); however, OS was significantly improved in the BMP versus MP group (HR, 0.607; P<.0078). The increases in both TTP and clinical response conferred by the addition of bortezomib corresponded to a significantly longer median time to next therapy for the BMP arm (HR, 0.522; P=.000009), allowing patients to enjoy prolonged treatment-free periods.

The marked efficacy of BMP was observed across all patient subgroups. Neither age nor renal function (assessed by creatinine clearance) significantly affected patient response. Additionally, high BMP response rates were seen among all cytogenetic subgroups, including t(4;14), t(14;16) and del(17p). These results indicate that BMP is effective regardless of risk or prognosis, allowing a large number of patients to benefit from the regimen.

There was a higher incidence of serious adverse events reported with BMP (46% vs 36% with MP). This difference was due to an increase in nonhematologic toxicities including gastrointestinal symptoms (20%) and peripheral sensory neuropathy (13%). Importantly, 75% of the peripheral neuropathy cases were fully resolved by a median of 64 days. An equal proportion of patients (14%) in each arm discontinued therapy due to adverse events.

Because of the superior responses produced by BMP over MP in all efficacy endpoints, the data-monitoring committee recommended that the study be terminated early. As the addition of bortezomib to the standard MP regimen prolonged both survival and progression, the BMP combination may become a new standard therapeutic option for MM patients unable to receive high-dose therapy.

Table 1. Results of BMP Versus MP

Efficacy endpoint	HR	95% CI	*P*
TTP	0.540	0.417–0.699	.000002
PFS	0.609	0.486–0.763	.00001
OS	0.607	0.419–0.880	.00782
CR	11.2	6.1–20.6	<.000001

BMP=bortezomib-melphalan-prednisone; CI=confidence interval; CR=complete response; HR=hazard ratio; MP=melphalan-prednisone; OS=overall survival; PFS=progression-free survival; TTP=time to progression.

A second agent, thalidomide, has also been investigated for its ability to improve the efficacy of the standard MP regimen. Thalidomide is a glutamic acid derivative that was shown in a key 1999 study to induce objective responses in 30% of patients with advanced refractory MM.[6] Thalidomide has multiple mechanisms, including immunomodulatory, anti-inflammatory, and antiangiogenic properties, all of which have been attributed to its antineoplastic effect.[7] Two randomized trials, one from Italy and the other from France, previously evaluated the efficacy of thalidomide added to MP (MPT) in elderly MM patients.[8,9] This combination was shown to be beneficial, producing a PR or better in 76–81% of patients tested. Recently, a phase III trial conducted by the Nordic Study Group further evaluated MPT in the elderly MM population.[10] In this study, 362 patients with a median age of 75 years were randomized to receive either standard MP or MPT. Thalidomide was initiated at a dose of 200 mg daily and then escalated up to 400 mg.

Unlike the dramatic effects produced by MPT in the Italian and French studies, the addition of thalidomide only minimally extended TTP over MP, although this difference was statistically significant. Neither PFS nor OS were significantly different between the two treatment arms, another key difference compared with the previous two studies. An elevated rate of early mortality was also observed in the MPT arm, with an increased mortality rate occurring in patients with poor performance status.

A notable difference in the Nordic study compared to the French and Italian studies was the relatively high dose of thalidomide used. In the Italian study, a 100 mg daily dose was administered, while patients in the French trial were initiated at 200 mg and allowed to increase up to 400 mg after 2–4 weeks in the absence of severe adverse effects.[8,9] Only a few patients from the French study dose-escalated up to 400 mg daily. Conversely, the protocol for the Nordic study called for all patients to increase to the 400 mg thalidomide dose. This higher dose could account for the increased incidence of toxicity observed in the Nordic study population, as well as the lack of benefit in OS between the two arms.

An important point to keep in mind is that the Nordic results were from a preliminary interim analysis, and a longer follow-up is needed to truly evaluate the MPT regimen in this cohort of patients. However, the key concept that can be concluded from the Nordic study is that thalidomide should not be administered at high doses in the elderly population, as the ensuing toxicity will result in poor compliance and treatment discontinuation. Instead, the maximally tolerated dose should be considered to be 200 mg daily.

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The MPT combination was further tested in the IFM 01-01 study, a phase III multicenter, double-blind trial.[1] Importantly, this study was distinct from the previously published IFM 99-06 trial, which evaluated the combination in MM patients between the ages of 65 and 75 years.[2] The IFM 01-01 study only included patients age 75 years or older, an age group often not included in clinical trials.

A total of 229 patients were randomized to receive either standard MP or MPT. Unlike the previously discussed Nordic study,[3] this trial used low doses of both melphalan (0.2 mg/kg) and thalidomide (100 mg daily) to reduce toxicity in these elderly patients. MP was administered on days 1–4 of each cycle, while thalidomide was taken continuously. Treatment was continued over 12 cycles of 6 weeks each, and patients in both arms received standard clodronate therapy. There was a greater proportion of males in the MP arm versus the MPT arm (52% vs 38%, respectively), but other baseline characteristics were equally distributed between treatment groups. Patients were followed for a median of 20 months (range, 0.5–60.0 months).

At 1 year, a significantly greater response rate was noted in patients in the MPT arm compared with the MP arm (P=.0001). A greater proportion of patients in the MPT arm had a CR (7% vs 1%, respectively), at least a PR (61% vs 31%, respectively), and at least a very good PR (VGPR; 23% vs 8%, respectively). Additionally, patients in the MPT arm experienced longer median PFS (24.1 vs 19.0 months, respectively; P=.001), median TTP (27.0 vs 20.9 months, respectively; P=.0009), and median OS (45.3 vs 27.7 months, respectively; P=.033). The efficacy results with MPT observed in this study were concordant in terms of PFS and OS with those of the IFM 99-06 trial, with its slightly younger patient population.[2]

Although significantly fewer deaths occurred in the MPT group (41 vs 59 in the MP group; P=.01), toxicity was more common, with more MPT patients experiencing grade 3–4 neutropenia (23% vs 9%; P=.003) and all grades of peripheral neuropathy (39% vs 22%; P=.003). Other grades 2–4 adverse events were similarly reported between the two treatment groups, including depression, edema, nausea/vomiting, constipation, somnolence, and thrombosis. Although the number of treatment withdrawals was similar for each arm, toxicities accounted for a greater percentage of the withdrawals in the MPT group (53% vs 15% in the MP arm; P<.001). Conversely, a lesser percentage of the withdrawals in the MPT group were due to progressive disease (PD; 31% vs 60% in the MP arm; P<.001). The median duration of treatment in the MPT and MP arms was 13.5 and 18 months, respectively.

When comparing the IFM trials with the Nordic study, one should keep in mind that lower doses of both melphalan and thalidomide may have contributed to a reduced number of early deaths in the IFM studies.[3] However, another important consideration is that IFM 01-01 enrolled a smaller proportion of patients with poor performance status compared to the Nordic study (approximately 10% and 30%, respectively), which may also further explain the lower mortality rate.

The clear benefit in CR, as well as the increase in OS by 18 months, suggests that MPT be considered a new standard regimen in elderly MM patients. The evidence from both IFM 99-06 and IFM 01-01 indicates that patients 75 years and older will benefit from this new combination.

For many years the standard frontline induction therapy for MM patients prior to ASCT has been a triple combination of vincristine, doxorubicin, and dexamethasone (VAD).[4] Recently, however, this strategy has been challenged by the introduction of novel therapeutic agents and combinations, including bortezomib, lenalidomide, and thalidomide.[4,5] One new induction regimen, evaluated in the IFM 2005-01 study, includes bortezomib combined with dexamethasone (BD) (Figure 1).[6] This phase III trial in 482 patients (<65 years) with newly diagnosed MM compared BD with standard VAD as induction therapy prior to ASCT, plus or minus consolidation therapy with dexamethasone, cyclophosphamide, etoposide, and platinum (DCEP). After G-CSF priming, stem cells were collected between cycles 3 and 4.

The primary study endpoint was response after induction. Compared with VAD, BD produced significantly improved response rates after induction therapy, including superior CR + near CR (nCR) (8% vs 21%, respectively; P<.0001). Additionally, when patients with a VGPR or better were considered, the response rates increased to 19% and 47% (P<.0001), respectively.

Importantly, the increased response rates following induction therapy produced by BD translated to significantly improved response rates after ASCT. In the intent-to-treat analysis, the CR + nCR rate following ASCT for patients in the BD arms was 35%, compared to only 24% for patients in the VAD arms, a statistically significant difference. DCEP consolidation therapy did not significantly improve patient outcomes in an intent-to-treat analysis. The BD regimen was well tolerated, with only a 6% incidence of grade 3 peripheral neuropathy and an 18% incidence of grade 2/3 neuropathy. The bortezomib combination did not affect stem-cell collection.

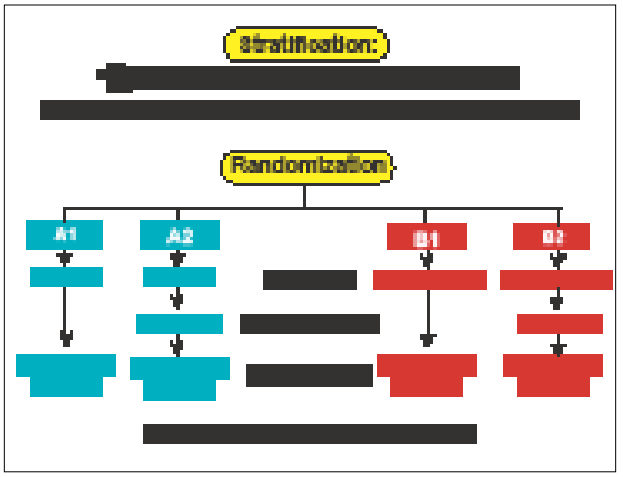

Figure 1. IFM 2005/01: study design.

ASCT=autologous stem cell transplantation; Bor-Dex=bortezomib + dexmethasone; DCEP=dexamethasone, cyclophosphamide, etoposide, prednisone; RIC allo=reduced-intensity conditioning allogeneic stem cell transplantation; VAD=vincristine, doxorubicin, dexamethasone; VGPR=very good partial response.

Based on the results of this trial, it is apparent that the BD combination should be considered a new standard therapeutic alternative for frontline induction therapy prior to ASCT. Even if BD does not immediately directly translate into prolonged PFS, its use should still be considered with optimization of the consolidation regimen to achieve improved PFS. With the availability of this and other new induction regimens that offer superior benefit and ease of administration, the traditional VAD regimen should no longer be considered as the standard frontline therapy prior to ASCT.

The Central European Myeloma Study Group evaluated thalidomide-dexamethasone (TD) versus MP as first-line treatment and thalidomide-interferon versus interferon maintenance therapy in elderly patients with multiple myeloma.[7] A total of 289 patients with previously untreated disease were randomized to receive either thalidomide (200–400 mg/day) and dexamethasone (40 mg on days 1–4 and 15–18 of odd cycles and days 1–4 of even cycles; n=145) or standard MP (n=143). The thalidomide dose was increased to 400 mg daily, if feasible. Induction therapy was continued for either a 4- or 6-week cycle. Patients with stable disease or better were then rerandomized to maintenance therapy with either thalidomide (100 mg/day) plus interferon α-2b (3 MIU 2 times/week) (n=56) or interferon α-2b alone (n=55).

The median patient age was 72 (range, 54–86 years). Baseline characteristics were evenly distributed between the two induction treatment groups with the exception of Eastern Cooperative Oncology Group (ECOG) performance status, which was >2 for a larger proportion of patients on the TD arm (30% vs 21% of the MP arm; *P*<.05).

Patients on the TD arm exhibited superior CR rates compared to the MP arm: the rate of CR + nCR was 30% versus 14%, respectively (*P*=.0014). Additionally, the median time to best response was significantly shortened in the TD arm versus the MP arm (16 vs 23 weeks, respectively; *P*<.0002). However, ORRs (69% vs 50%, respectively) and PFS (16.7 vs 20.7 months, respectively) were not significantly different between the two treatment arms.

Overall survival was significantly superior for the patients receiving MP versus those in the TD group (median OS: 49.4 vs 41.5 months; *P*=.024). This was partly due to a higher death rate observed during the first year of therapy in the TD group (31 vs 17 deaths, respectively), of which 20 were not due to PD. Additionally, multivariate analysis showed that an ECOG performance status of 2 or 3 was associated with death during the first year (overall risk: 7.90; 95% confidence interval, 1.39–44.8; *P*<.019).

Hematologic adverse events such as leukopenia and thrombocytopenia were more prevalent in the MP arm, while nonhematologic toxicities, including neuropathy, constipation, and psychological events, were more common in the TD arm. From this study it is clear that when choosing TD as induction therapy, the benefit of improved rates of response should be carefully weighed against increased toxicity and risk of early death.

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Thalidomide, an old drug with an infamous past, has redeemed itself as a new treatment paradigm for relapsed/refractory MM and also represents a standard of care for patients with newly diagnosed disease. As frontline therapy in preparation for autologous transplantation, TD provided superior response rates over VAD in a case-matched retrospective study[1] and was reported to be superior to dexamethasone alone in a phase III clinical trial.[2] More recently the addition of bortezomib to the TD regimen was shown to induce a rapid onset of remission in patients with both refractory and newly diagnosed MM.[3] Based on these encouraging results, an open-label, multicenter study was designed by the GIMEMA Italian Myeloma Network.[4] The aim of this trial was to prospectively evaluate the efficacy and safety of TD compared with this combination plus bortezomib (VTD) as induction therapy in preparation for double ASCT. Both regimens were also used as consolidation therapy following ASCT(s).

A preplanned interim analysis of 256 evaluable patients was performed. All patients were less than 65 years of age and had confirmed symptomatic, newly diagnosed MM. Randomization to either TD or VTD was based on patient stratification according to the International Staging System. Induction therapy consisted of three 21-day cycles. In the TD regimen (n=127), dexamethasone (40 mg/day) was administered on days 1–4 and 8–12 every cycle, while thalidomide was given daily. Patients on the VTD arm (n=129) received daily thalidomide and bortezomib (1.3 mg/m^2) twice weekly for 2 weeks, with a 10 day rest period, and dexamethasone (40 mg/day) on the days of and after each bortezomib dose. Thalidomide was initiated at 100 mg/day, and was subsequently increased to 200 mg daily after 2 weeks. Although administered on a slightly different schedule, the dexamethasone doses were adjusted so that an equal amount (320 mg) was administered over each treatment cycle. To reduce the risk of thalidomide-related thrombosis, patients in both arms were further randomized to receive prophylactic anticoagulation therapy with either low molecular–weight heparin (enoxaparin), low-dose aspirin, or fixed low-dose warfarin. After induction therapy, peripheral blood stem cells (PBSCs) were harvested, followed by double ASCT with concurrent melphalan (200 mg/m^2). Efficacy was assessed based on EBMT criteria with additional categories of nCR and VGPR. The primary study endpoint was the rate of CR + nCR after induction therapy.

In an intent-to-treat analysis, the VTD regimen produced a significantly superior response rate as primary therapy compared with the TD regimen, with a CR + nCR of 36% compared with 9% (P<.001). When those patients with at least a VGPR were considered, the response rates increased to 60% and 27%, respectively (P<.001).

A subset of 153 patients was also evaluated on an intent-to-treat basis for their response to first ASCT with melphalan. In comparison with the control group, patients in the VTD arm experienced superior response rates, including CR (P<.001), CR + nCR (P<.001), and at least a VGPR (P=.003).

Grade 3 or 4 nonhematologic adverse events were similar among the VTD and TD arms (38% and 30%, respectively). Peripheral neuropathy (7%) and skin rash (6.5%) were significantly more common with VTD, while deep-vein thrombosis (6.5%) was more frequent with TD. Prophylactic use of acyclovir prevented herpes zoster infections. A lesser number of patients discontinued treatment in the VTD group than the TD group (3% vs 6%, respectively). No toxicity-related deaths occurred on the VTD arm, while 1 was reported on the TD arm. No differences were noted in the PBSC harvest of either treatment arm.

Lenalidomide was investigated in combination with both low- and high-dose dexamethasone in an analysis of the E4A03 trial, conducted by ECOG.[5] High-dose dexamethasone combined with lenalidomide was previously found to be highly active as frontline MM therapy, but a large proportion of patients experienced grade 3 or higher nonhematologic adverse effects.[6] In the E4A03 trial, 445 treatment-naive patients with symptomatic MM were randomly assigned to one of two treatment arms. In each group, standard lenalidomide (25 mg/day) was administered for the first 21 days of a 28-day cycle. The first group (n=223; 196 evaluable) also received dexamethasone 40 mg on days 1–4, 9–12, and 17–20, for a total of 480 mg per cycle (high-dose arm), while the second group (n=222; 190 evaluable) received dexamethasone 40 mg on days 1, 8, 15, and 22, for a total of 160 mg per cycle (low-dose arm). The 28-day treatment cycle was repeated 4 times, after which patients in the high-dose arm could exit the study and receive an ASCT. Patients in the low-dose arm who did not achieve at least a PR after 4 cycles received an additional 4 cycles of thalidomide combined with dexamethasone, after which they could exit the study. The primary study endpoint was the rate of response at 4 months.

The response rate in the low-dose treatment arm was lower compared with the high-dose arm, but remained within the 15% limit of clinical equivalence. Within the first 4 cycles, the PR rate or better response was higher for patients in the high-dose dexamethasone group (80% vs 67% for low-dose group; P=.004), as was the VGPR rate (44.5% vs 26%, respectively; P<.001). Although the rate of CR was very low in both groups (2% vs 1%), this value was likely underestimated due to the lack of bone marrow samples for confirmation of CR available from many

patients. Additionally, the duration of response, median PFS (19 vs 22 months, respectively), and median TTP (22 vs 23 months, respectively) were similar for both arms.

OS was significantly superior in the low-dose arm. The estimated 1-year probability of OS was 0.88 versus 0.96, respectively (*P*=.003), while the estimated 2-year probability was 0.75 versus 0.87, respectively (*P*=.009). Interestingly, a subgroup analysis revealed that increased probability of OS in the low-dose group was significantly higher in patients age 65 years or older (*P*=.01) and in patients who were off study treatment at less than 6 months (*P*=.02).

The lower OS observed in the high-dose arm was most likely due to a higher incidence of adverse events. Patients in the high-dose dexamethasone group experienced significantly greater incidences of grade 3 or 4 nonhematologic toxicities (65% vs 45%, respectively; *P*<.001), including thromboembolic events (25%), infection (14%), fatigue (13%), hyperglycemia (11%) and nonneuropathic weakness (10%). Additionally, more early deaths (<4 months) were reported in the high-dose group versus the low-dose group (5% vs 0.5%; *P*=.01). Both toxicity and disease progression contributed to the higher death rate in the high-dose dexamethasone arm.

These results indicate that low-dose dexamethasone should be preferred to high-dose when combined with lenalidomide as induction therapy. However, the benefit in OS was mainly observed in older patients, suggesting that the low-dose regimen would be preferred for this subgroup of patients. Younger patients who are eligible for ASCT may benefit more from the higher dexamethasone dose.

The primary therapy combination of lenalidomide and dexamethasone was further evaluated in a Southwest Oncology Group (SWOG) trial. The S0232 study was a double-blind, placebo-controlled trial which evaluated the addition of lenalidomide to high-dose dexamethasone versus high-dose dexamethasone alone.[7] Eligible patients had measurable disease and, unlike patients in the ECOG study, were unable to undergo immediate ASCT. The median patient age was 64.6 years and baseline characteristics were similar for both treatment groups. A total of 198 patients with previously untreated, newly diagnosed MM were randomized to either treatment group. In both groups, dexamethasone 40 mg was administered on days 1–4, 9–12, and 17–20 of a 35-day cycle. In the combination arm (n=100), lenalidomide 25 mg/day was concurrently administered on days 1–28 while placebo was given to patients in the second arm (n=98). After 3 cycles of induction therapy, patients continued on 28-day cycles of maintenance therapy until disease progression. Patients in the placebo group were allowed to cross over to the lenalidomide arm during either the induction or maintenance periods at the occurrence of PD. Based on the toxicity data from the ECOG study, this trial was closed prematurely because the data and safety monitoring board felt it was unethical to continue to randomize patients to high-dose dexamethasone plus lenalidomide.[3]

A total of 156 patients were evaluable for response. Of these, 61 received only the combination regimen, 72 were in the placebo group, and 23 crossed over. Patients who received lenalidomide had a significantly higher ORR compared with patients receiving high-dose dexamethasone alone (84% vs 53%, respectively; *P*<.001). Of these, CRs were noted in 22% versus 4% of patients and PRs were reported in 62% versus 49%. Significantly, the 1-year PFS was superior in the lenalidomide group compared to the dexamethasone-alone group (77% vs 55%, respectively; *P*=.002), while 1-year OS was similar between the two groups (93% vs 91%).

A greater proportion of patients in the lenalidomide arm experienced grade 3–4 neutropenia (13.8%) and any grade of infection (51.4%). One patient in the lenalidomide group had an infection that resulted in death. Despite prophylactic administration of aspirin, more thromboembolic events (25 out of a total 32) occurred among patients receiving lenalidomide, although the difference between the two groups did not reach statistical significance.

The superior effect of the combination of lenalidomide and dexamethasone, especially in increasing response rate and PFS, suggests that this combination will be very useful as frontline treatment of MM. However, patients will need to be carefully monitored for serious adverse events, including neutropenia and infections.

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Question and Answer Forum

The faculty answers further questions about recent phase III trials in the frontline treatment of multiple myeloma.

How do you see these trials impacting the incorporation of new agents like bortezomib, lenalidomide, and thalidomide into current clinical practice?

TF In young patients, the BD combination is an apparent new standard for induction therapy, as it provided superior benefit to the current standard, VAD. Regarding the treatment of elderly MM patients, the MMY-3002 study clearly has established that BMP should be considered a new standard of care over the traditional MP. Additionally, in spite of the discouraging results from the Nordic study, MPT can also be used as standard treatment based on reports from both the Italian and French trials, as well as the IFM 01-01 trial discussed here. However, thalidomide should only be used at lower doses to reduce the toxicity observed in the Nordic patient cohort.

JSM The future investigation of new combinations, such as the addition of lenalidomide to MP, may also further increase the chemotherapy options for this difficult-to-treat population. The results of these studies together provide a great deal of encouragement for many subpopulations of MM patients, including newly diagnosed younger and elderly populations, as well as those with different prognoses determined by cytogenetic abnormalities and performance status.

How have these trials affected the standard of care for patients who are eligible for ASCT?

MC The first clear implication is that now we are able to offer these individuals more effective induction regimens than in the past. Recent trials with novel agents have reported rates of CR comparable to those obtained so far with single or even double ASCT. Increasing the frequency of CR before transplantation is an important objective since in several studies an even higher rate of CR, or at least VGPR, up to values in the range between 60% and 80%, was reported after ASCT. The goal for upcoming clinical trials should be to identify the induction therapy that effects the highest response rate with the lowest associated toxicity, as well as to evaluate the durability of remissions induced by novel agents incorporated into ASCT. Whether these newer drug combinations can actually replace ASCT should also be examined, although my personal opinion is that ASCT combined with novel agents will continue to play a major role in the treatment of younger MM patients in the near future.

How have these newer agents affected consolidation therapy following ASCT?

MC We currently have preliminary data showing that using thalidomide as consolidation therapy after ASCT may improve patient response, particularly among those failing at least a VGPR. Additionally, several smaller studies have suggested that consolidation therapy with novel agents results in molecular remissions in a certain fraction of patients, although this needs to be evaluated in larger trials. CR is generally considered as a surrogate marker for extended PFS and OS, and therefore improving the response status in MM patients is a primary goal.

Recent Phase III Trials in Frontline Treatment of Multiple Myeloma: Evaluating Their Impact on Community Practice

CME Post-Test: *Circle the correct answer for each question below.*

1. The MMY-3002 study, discussed by Dr. San Miguel, showed that bortezomib added to conventional MP produced significantly superior OR rates of _____.

   a. 5%
   b. 35%
   c. 50%
   d. 82%

2. True or False? The dramatic efficacy produced by bortezomib combined with MP in the MMY-3002 trial was not significantly affected by cytogenetic abnormalities.

   a. True
   b. False

3. True or False? The elevated rate of early mortality observed in the MPT arm of the Nordic trial was most likely attributable to high doses of melphalan.

   a. True
   b. False

4. The IFM 01-01 trial showed that thalidomide combined with MP was superior to MP alone in a patient subpopulation of _____.

   a. <35 years of age
   b. 35–65 years of age
   c. 65–75 years of age
   d. ≥75 years of age

5. According to Dr. Facon, a key point from the IFM 2005-01 trial was that the combination of _____ with dexamethasone was superior to the conventional VAD regimen as induction therapy in newly diagnosed MM patients prior to ASCT.

   a. bortezomib
   b. lenalidomide
   c. melphalan
   d. thalidomide

6. In a multicenter study conducted by the Central European Myeloma Study Group, the addition of thalidomide to dexamethasone as induction therapy produced superior CR rates compared to _____.

   a. BMP
   b. MP
   c. VAD
   d. melphalan alone

7. The GIMEMA study discussed by Dr. Cavo found that the addition of bortezomib to thalidomide and dexamethasone resulted in a CR + nCR rate of _____, which was significantly superior to the CR + nCR rate produced by thalidomide and dexamethasone alone.

   a. 9%
   b. 27%
   c. 36%
   d. 60%

8. Despite minimal effect on PFS and TTP, low-dose dexamethasone combined with lenalidomide produced superior rates of OS in the E4A03 trial, with a 2-year probability of _____ compared with high-dose dexamethasone and lenalidomide.

   a. 0.75
   b. 0.87
   c. 0.88
   d. 0.96

9. The lower OS observed in the high-dose dexamethasone arm of the E4A03 study was most likely due to an increase in grade ≥3 nonhematologic toxicities, which was reported in _____ of this group of patients.

   a. 5%
   b. 14%
   c. 25%
   d. 65%

10. The SWOG S0232 trial found that the addition of _____ to high-dose dexamethasone was associated with significant increases in OR compared with high-dose dexamethasone alone.

    a. bortezomib
    b. thalidomide
    c. melphalan
    d. lenalidomide

Evaluation Form: Recent Phase III Trials in Frontline Treatment of Multiple Myeloma: Evaluating Their Impact on Community Practice

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:

1. Describe the importance of new study findings from phase III clinical trials in the treatment of multiple myeloma.	1	2	3	4	5
2. Cite findings of current clinical trials evaluating treatment regimens and the effect on clinical remission in multiple myeloma.	1	2	3	4	5
3. Indicate approaches for treating patients with multiple myeloma in order to improve outcomes.	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.

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 post-test 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 post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests/Evaluation by Course" and search by project ID 5449. Upon successfully completing the post-test and evaluation, your certificate will be made available immediately.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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