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In Focus: Multiple Myeloma

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8505 Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantation in previously untreated multiple myeloma: updated data from IFM 2005/01 trial

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Autologous stem cell transplantation (ASCT) is currently the standard of care for multiple myeloma (MM) patients who are 65 years or younger and who have a high rate of complete remission (CR) plus very good partial remission (VGPR). Previous phase II studies have demonstrated that the combination of bortezomib (Velcade, Millennium) and dexamethasone (Vel/Dex) is an effective induction therapy. Following these studies, French researchers conducted a phase III trial that compared Vel/Dex (4 cycles) to vincristine/doxorubicin/dexamethasone (VAD; 4 cycles) as induction therapy prior to ASCT. Consolidation with two cycles of dexamethasone, cyclophosphamide, etoposide, and platinum (DCEP) was analyzed as well. The study randomized 482 patients with MM (≤ 65 years) to one of four treatment arms: VAD (n=121), VAD plus DCEP (n=121), Vel/Dex (n=121), or Vel/Dex plus DCEP (n=119). The primary objective of the study was to identify the CR plus near-CR (nCR) rate. The rate of nCR plus the increase in VGPR in the intent-to-treat (ITT) population was significantly higher in those treated with Vel/Dex compared to VAD postinduction (21.3%, 46.7% vs 8.3%, 18.6%; $P=.0023$ vs $P<.0001$). The higher nCR/VGPR rates observed in the patients treated with Vel/Dex continued post-ASCT in patients who received ASCT as well as the ITT population. DCEP did not increase response rates in either treatment arm. During induction, grade 3 or worse adverse events were similar in the Vel/Dex and VAD groups (38.2% vs 40.6%); however, serious adverse events and adverse events resulting in death were lower in patients treated with Vel/Dex compared to patients treated with VAD (25.2% vs 31.0% and 0.8% vs 2.9%, respectively). Conversely, neuropathic symptoms of all grades occurred more frequently in patients treated with Vel/Dex (35.3%

vs 22.6%). The study results demonstrated the efficacy of Vel/Dex in improving postinduction response rates compared to VAD, which in turn led to a higher increase in VGPR rates after ASCT. The study findings suggest that Vel/Dex should be deemed the standard induction treatment prior to ASCT.

8518 Bortezomib, pegylated-liposomal-doxorubicin and dexamethasone as induction therapy prior to reduced intensity autologous stem cell transplant followed by lenalidomide and prednisone as consolidation and lenalidomide alone as maintenance

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As mentioned, several new regimens, such as Vel/Dex, have been introduced as induction treatment prior to ASCT and as subsequent consolidation maintenance to improve CR rates. Italian researchers initiated a study in elderly myeloma patients, which evaluated bortezomib as induction therapy prior to ASCT followed by consolidation/maintenance with lenalidomide (Revlimid, Celgene). The study enrolled patients with newly diagnosed MM who were between 65 and 75 years of age. Patients underwent four 21-day cycles of pegylated liposomal doxorubicin (Doxil, Ortho Biotech) and dexamethasone (PAD; bortezomib 1.3 mg/m² on days 1, 4, 8, and 11; pegylated liposomal doxorubicin 30 mg/m² on day 4; and dexamethasone 40 mg on days 1–4, 8–11, 15–18 for cycle 1 and days 1–4 for cycles 2–4). Stem cell harvesting used cyclophosphamide (3 g/m²) plus granulocyte colony-stimulating factor. Following the cycles of PAD, patients were conditioned with tandem melphalan 100 mg/m² and stem cell support (MEL100). After patients underwent ASCT, they received four 28-day cycles of lenalidomide plus prednisone (LP; lenalidomide 25 mg/day on days 1–21 plus prednisone 50 mg every other day) followed by lenalidomide alone (10 mg/day on days 1–21 every 28 days) as maintenance. Primary objectives were safety and efficacy; safety con-

stituted any grade 3 nonhematologic toxicity present in less than 30% of patients and efficacy referred to a nCR rate higher than 35%. The study found that after 4 PAD cycles, 95% of the 94 enrolled patients experienced at least partial remission (PR), 60% experienced at least VGPR, 23% experienced at least nCR, and 13% had CR. Following MEL100, 95% of patients achieved PR, 80% achieved at least VGPR, 60% at least nCR, and 33% CR. After LP consolidation, all patients demonstrated PR, 89% had at least VGPR, 78% at least nCR, and 56% CR. The primary endpoint of safety was achieved, with 25% of patients experiencing grade 3/4 hematologic toxicity, 17% having grade 3/4 peripheral neuropathy, and 11% with grade 3/4 infections during PAD cycles. During LP consolidation one adverse event of deep vein thrombosis and one discontinuation due to prolonged anemia and thrombocytopenia were reported. The study findings demonstrated a successful response rate after the administration of PAD as induction prior to ASCT followed by LP as consolidation in the elderly patient population.

8520 Safety and efficacy of lenalidomide, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma: a phase I/II study

PG Richardson, S Lonial, A Jakubowiak, S Jagannath, N Raje, D Avigan, IM Ghobrial, R Knight, D Esseltine, KC Anderson

Bortezomib alone and a combination of lenalidomide and dexamethasone (Len/Dex) are two therapies that are approved for patients with relapsed MM following one or more prior therapies. Whereas lenalidomide plus bortezomib with or without dexamethasone is used in relapsed or refractory MM, Len/Dex and Vel/Dex are active in frontline MM. Dr. Richardson and colleagues initiated a study to define the maximum tolerated dose and response rate with a combination of these three agents in previously untreated patients with MM. The study enrolled 66 patients who received lenalidomide 15–25 mg on days 1–14; bortezomib 1.0–1.3 mg/m² on days 1, 4, 8, and 11; and dexamethasone 40 mg/20 mg (cycles 1–4 and 5–8) on the day of and after bortezomib for up to eight 21-day cycles, initially at four planned dose levels. Depending on whether patients experienced dose-limiting toxicities (DLTs), dose escalation was performed. Response rates were evaluated by Uniform criteria and modified criteria from The European Group for Blood & Marrow Transplantation (EBMT). To date, study results are available for 53 of 66 patients. Of these patients, 33 are in phase I at the starting dose and 17 patients at the maximum planned dose, and 20 are in phase II (at the maximum planned dose). Patients received a median of six cycles, with 16 (32%) patients completing all eight cycles and 14 discontinuing. DLTs due to high-dose

dexamethasone were seen in patients who were at dose level 4 (2 events of G3 hyperglycemia); two toxicities (deep vein thrombosis) unrelated to dose level were also reported. Dose reductions during cycle 2, mostly in dose levels 1–4, occurred in patients receiving lenalidomide (n=12), bortezomib (n=11), and dexamethasone (n=18). The current response rate was found to be 98% in 42 patients; 52% of patients experienced CR/nCR/VGPR. After a median follow-up of 4 months, median time to progression, progression-free survival (PFS), and overall survival (OS) were not reached. The study results confirm that the combination of lenalidomide, bortezomib, and dexamethasone is very active and well-tolerated in newly diagnosed MM patients. Enrollment for the phase II study is close to completion.

8521 A randomized Southwest Oncology Group study comparing dexamethasone to lenalidomide plus dexamethasone as treatment of newly-diagnosed multiple myeloma: impact of cytogenetic abnormalities on efficacy of lenalidomide plus dexamethasone, and updated overall study results

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Recently, results of superior 1-year PFS were reported for patients with newly diagnosed MM treated with Len/Dex versus dexamethasone alone. High-risk cytogenetic abnormalities (HRCAs) confer poor prognosis with standard therapies, such as high-dose melphalan; therefore, it is unknown whether patients with these abnormalities who are on Len/Dex will also have inferior results. In order to evaluate this phenomenon, Dr. Zonder and colleagues prospectively investigated the effect of abnormal karyotype (AK) and HRCAs (defined as deletion of chromosomes 13 and/or 17 by fluorescence in situ hybridization [FISH]) on 1-year PFS and OS. In this study, 198 patients were assigned to lenalidomide (25 mg/day; 28 of 35 days × 3 cycles, then 21 of 28 days as maintenance) plus dexamethasone (40 mg/day on days 1–4, 9–12, 17–20 for induction and days 1–4 and 15–18 for maintenance) or dexamethasone (same induction and maintenance schedule) plus placebo on a randomized basis. If patients experienced progressive disease on dexamethasone alone, crossover to Len/Dex therapy was permitted. Baseline karyotypes and FISH results were presented for 103 and 80 patients, respectively. The presence of AK was seen in 10 of 52 samples from patients on dexamethasone and in 11 of 51 samples from patients on Len/Dex. HRCAs were present in 12 of 45 samples from patients on dexamethasone and in 8 of 35 samples from patients on Len/Dex. Patients receiving Len/Dex without the presence of AK had higher 1-year PFS and OS compared to patients with

AK (86% and 97%, respectively, vs 55% and 82%). For those patients with AK who were administered dexamethasone alone, 1-year PFS and OS (33% and 77%, respectively) were considerably lower than in patients who were receiving Len/Dex. Unlike AK, patients with HRCAs on Len/Dex had higher 1-year PFS and OS compared to patients without HRCAs (100% and 100% vs 73% and 92%, respectively). Study results concluded that patients with newly diagnosed MM on Len/Dex with AK had lower PFS and OS compared to those without AK, which was not the case for HRCAs. Additionally, patients with AK who were administered Len/Dex had higher PFS and OS compared to those patients on dexamethasone alone. Follow-up is ongoing.

8523 Complete remission and survival in multiple myeloma

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Although length of survival has been the major index of better treatment in MM, other endpoints, such as frequency and duration of PR and CR have also been evaluated. A retrospective review with multivariate analysis of outcomes among newly diagnosed patients who received primary chemotherapy followed by intensive therapy during the first year was performed to evaluate the importance of such endpoints. Clinical outcomes, such as response to treatment, were analyzed in 759 MM patients treated between 1987 and 2007; 406 of those patients were also administered intensive therapy in conjunction with ASCT within the first year. Patient response to treatment was evaluated according to the EBMT criteria, and CR was defined as the disappearance of serum myeloma protein by immunofixation on two consecutive studies. In order to determine features that are related to prolonged survival, multiple prognostic variables were evaluated. To avoid potential bias from the definite survival of patients who were responsive to therapy, landmark analyses were used to compare survival times for patients alive after 1 year. The study found that the response rate for all patients was 66%, including 8% of patients who had CR after primary chemotherapy. The response rate after high-dose therapy was 75%, including 20% of patients who had CR. The median survival was 56 months. When survival was compared 12 months after start of treatment in patients with CR versus patients with PR or no remission (NR), it was found that patients with CR (n=144) lived significantly longer than patients with PR or NR (9.6 years vs 4.0 and 2.2 years, respectively). Furthermore, the review found that median survival times (10–15 years) from the onset of CR were similar for groups of patients who achieved

CR after just chemotherapy or after intensive therapy for NR or PR or as consolidation of CR. Cox regression analysis was used to evaluate patients at 12 months; the analysis determined that the presence of CR and of International Staging System stage I disease, and the provision of intensive therapy, were independently related to long survival. This retrospective review concluded that prospective trials are necessary for a definitive analysis of CR as a substitute endpoint for long-term survival.

8524 Final analysis of MM-014: single-agent lenalidomide in patients with relapsed and refractory multiple myeloma

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Len/Dex has been approved for patients with MM that has been previously treated. An open-label multi-institution study investigated the efficacy and safety of lenalidomide monotherapy (30 mg once daily) in patients with relapsed or refractory MM. The study, which enrolled 222 patients, was a single-arm design, administering lenalidomide daily on days 1–21 of 28 days. Concomitant treatment with dexamethasone was prohibited and anticoagulation prophylaxis was not recommended. Response to therapy was evaluated every month by modified criteria from EBMT and toxicity was measured by the National Cancer Institute Common Toxicity Criteria version 3. All enrolled patients had received more than two prior anti-MM treatments (43% of patients received bortezomib, 80% received thalidomide [Thalomid, Celgene], and 45% received stem cell transplantation), and 46% of all patients received more than four prior therapies with mean time from diagnosis of 4 years. Treatment was given as tolerated until disease progression and of all patients, 64 (29%) received treatment for more than 9 months. The overall response for the ITT population (n=222) was considerably lower compared to the efficacy-evaluable population (n=184; 26% vs 32%). However, the number of patients who experienced stable disease was similar in the ITT and efficacy-evaluable populations (66% vs 68%). At the end of the study, 151 patients (69%) had disease progression with median time-to-progression of 5.4 months. Additionally, median PFS was 4.7 months and median OS was 1.9 years; 41% of patients were alive after 3 years. The median length of response was 13 months. Grade 3/4 toxicities, including neutropenia (60%), thrombocytopenia (39%), anemia (20%), febrile neutropenia (4%), and DVT (4%), were reported during the study. The positive results of this study suggest that lenalidomide monotherapy is effective, durable, and well-tolerated for pretreated patients with relapsed or refractory MM.