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Front-Line Treatment in Younger Patients With Multiple Myeloma

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Abstract

The treatment of newly diagnosed myeloma has evolved rapidly. The choice of initial therapy depends on eligibility for stem cell transplantation, as well as baseline risk factors. Eligibility for transplantation is important since the choice of initial therapy is primarily melphalan-based in patients who are not candidates for transplant, while melphalan-containing regimens are avoided as induction therapy in transplant candidates. An assessment of risk based on independent prognostic markers is important mainly for prognosis but may have some value in choice of initial therapy. For example, bortezomib-based regimens may have particular value in patients with certain high-risk features. This review discusses the current status of front-line therapy in younger patients with myeloma who are candidates for stem cell transplantation.

In the late 1960s, melphalan and prednisone (MP) emerged as the major option for front-line therapy of patients with newly diagnosed myeloma, and remained so for more than two decades.^{1,2} In the 1990s, randomized trials demonstrated that autologous stem cell transplantation (ASCT) prolongs survival compared to conventional chemotherapy, and ASCT was incorporated into the treatment strategy either early in the disease course or at the time of relapse in eligible patients.^{3,4} The use of MP decreased following the emergence of ASCT because of the concern that exposure to melphalan may affect stem cell harvests.

For many years, vincristine, doxorubicin, and dexamethasone (VAD) and pulsed high-dose dexamethasone were the main options for front-line therapy in patients who were candidates for ASCT. In the last 10 years, front-line regimens for such patients changed dramatically following the arrival of active new agents such as thalidomide,⁵ bortezomib,^{6,7} and lenalidomide.^{8,9} New induction regimens not only control the disease and its symptoms in preparation for ASCT but also offer high overall and very good partial response (VGPR) rates, approaching levels previously noted only with ASCT. This review will discuss the current options for initial therapy in newly diagnosed patients who are candidates for ASCT.

KEY FACTORS IN DECIDING INITIAL THERAPY

The two main factors to consider in patients with newly diagnosed myeloma are risk factors that are known to affect overall survival (risk stratification) and eligibility for ASCT. Risk stratification is important to consider given emerging data that bortezomib may overcome some of the known adverse prognostic factors, and that patients with high-risk factors often relapse rapidly following ASCT. Eligibility for ASCT is important since the choice of initial therapy is primarily melphalan-based in patients who are not candidates for ASCT, while

melphalan-containing regimens should be avoided as induction therapy in transplant candidates.

Risk Stratification

The median survival of patients with symptomatic myeloma is approximately 4 years. However, survival varies widely based on performance status, as well as baseline cytogenetic and proliferative characteristics. Various risk-stratification models have been proposed, and most rely on a combination of cytogenetic abnormalities and an estimate of tumor burden and/or proliferation. A model used at the Mayo Clinic (mSMART: Mayo Stratification for Myeloma and Risk-adapted Therapy) is provided on Table 1.¹⁰ This model stratifies patients into high-risk and standard-risk myeloma based on detection of deletion 13 or hypodiploidy on meta-phase cytogenetic studies, deletion 17p- or immunoglobulin heavy chain (IgH) translocations t(4;14) or t(14;16) on molecular genetic studies, or plasma cell labeling index of 3% or higher on bone marrow immunofluorescent studies. The presence of any one or more of these high-risk factors classifies a patient as having high-risk MM.¹⁰ The median survival of high-risk MM is only 2–3 years even with tandem stem cell transplantation, compared to over 6–7 years in patients with average-risk MM.¹¹

Eligibility for ASCT

Eligibility for ASCT is determined by age, performance status, and coexisting comorbidities. All patients should be evaluated at diagnosis for transplant eligibility.

The determination of eligibility for ASCT varies across countries and institutions. In Europe, ASCT for myeloma is offered primarily to patients less than 65 years of age. In the United States, a strict age limit is not used. Instead, decisions are made on an individualized basis and can vary across institutions. The decision on transplant eligibility and timing of ASCT should also take into account the needs and wishes of the patient.

In general, patients must fulfill at least the following minimum requirements to be considered candidates for ASCT: age less than 78 years (United States) or 65 years (Europe); direct bilirubin less than 2.0 mg/dL; serum creatinine less than 2.5 mg/dL unless on chronic stable dialysis; Eastern Cooperative Oncology Group (ECOG) performance status 1 or 2 unless due to bone pain; and New York Heart Association functional status class I or II. Patients in whom the eligibility for ASCT is unclear at the time of diagnosis are best considered potential candidates for ASCT until proven otherwise.

FRONTLINE REGIMENS

Table 2 lists the most common regimens used in the treatment of newly diagnosed myeloma in patients who are considered candidates for ASCT, including recommended doses and activity.

Vincristine, Doxorubicin, and Dexamethasone

VAD was used for many years as pretransplant induction therapy for patients considered candidates for ASCT. Moreover, the activity of VAD is primarily due to the high-dose dexamethasone component, with vincristine and doxorubicin having minimal roles.¹² Prior to the arrival of new agents, some investigators switched to dexamethasone alone as a safer and better tolerated induction therapy for multiple myeloma, particularly in patients who were proceeding to more definitive therapy with early ASCT.

Cavo and colleagues in a matched case-control study of 200 patients demonstrated that response rates with VAD were significantly lower compared to thalidomide/dexamethasone

(Thal/Dex): 52% versus 76%, respectively.¹³ Preliminary results from a randomized trial from France and a trial from the Netherlands comparing Thal/doxorubicin/Dex confirm these findings.^{14,15} More recently, trials using bortezomib-based combinations have also demonstrated significant superiority over VAD (see below).^{16,17} As a result, VAD is no longer recommended as initial therapy.

Pulsed Dexamethasone

High-dose pulsed dexamethasone alone has also been used as induction therapy, with the rationale that it is the major component of VAD chemotherapy and is more convenient to administer than VAD. It is typically used at a dose of 40 mg orally on days 1–4, 9–12, and 17–20 every 4 to 5 weeks. Objective response rates are approximately 45%,¹⁸ slightly lower than VAD but significantly lower compared to newer induction regimens. In randomized trials the early mortality rate associated with dexamethasone is greater than 10% in the first 4 months of therapy, reflecting the toxicity as well as the ineffectiveness of this regimen.^{18,19} Consequently, single-agent dexamethasone is also no longer recommended as initial therapy.

Thalidomide/Dexamethasone

In the last few years, Thal/Dex has emerged as one of the most commonly used induction regimens for the treatment of newly diagnosed myeloma. The use of Thal/Dex was initially based on three phase II clinical trials that showed significant activity.^{20–22} Response rates with Thal/Dex ranged from 64%–76% in those studies, comparable or better than those obtained with infusional VAD. Thal/Dex had the advantage over VAD of not requiring intravenous administration.

The ECOG recently reported the results of a randomized trial comparing Thal/Dex to dexamethasone.¹⁸ Two hundred seven patients were studied. The best response within four cycles of therapy was significantly higher with Thal/Dex compared with dexamethasone alone: 63% versus 41%, respectively, $P = .0017$. Adjusted response rates, allowing for the use of serum M-protein values alone in patients in whom a measurable urine protein at baseline was unavailable at follow-up, were 72% with Thal/Dex versus 50% with dexamethasone alone. Stem cell harvest was successful in 90% of patients in each arm. Deep vein thrombosis (DVT) was more frequent with Thal/Dex (17% v 3%). Overall, grade 3 or higher nonhematologic toxicities were seen in 67% of patients within four cycles with Thal/Dex and 43% with dexamethasone alone ($P < .001$). Early mortality (first 4 months) was 7% with Thal/Dex and 11% with dexamethasone alone. Based on this trial, the US Food and Drug Administration (FDA) granted accelerated approval for Thal/Dex for the treatment of newly diagnosed myeloma.

Confirmatory results are available from a separate randomized, double-blind, placebo-controlled study comparing Thal/Dex versus placebo/dexamethasone (placebo/Dex) as primary therapy in 470 patients with newly diagnosed myeloma.²³ Based on European Bone Marrow Transplant Group (EBMT) criteria, overall response (complete responses [CRs] plus partial responses [PRs]) to therapy was significantly higher with Thal/Dex compared with placebo/Dex: 63% v 46%, respectively, $P < .001$. Based on the International Myeloma Working Group criteria, the proportion of patients achieving CR or VGPR was 43.8% with Thal/Dex versus 15.8% with placebo/Dex ($P < .001$), and the proportion of patients achieving CR was 8.1% with Thal/Dex versus 3.0% with placebo/Dex ($P = .02$). Response to therapy with Thal/Dex was rapid, with a median time to best response (CR or PR) of 8.3 weeks compared to 20.1 weeks for placebo/Dex. As in the ECOG study, grade 4 adverse events were more frequent with Thal/Dex than with placebo/Dex (30.3% v 22.8%). From the two phase III trials discussed above, Thal/Dex emerged as a reasonable induction regimen

for front-line therapy in transplant candidates. Studies show that therapy with Thal/Dex does not significantly affect stem cell yield.^{5,11}

A Dutch study compared thalidomide, doxorubicin, and dexamethasone (TAD) with VAD as induction therapy.^{14,24} After induction, patients in both arms proceeded to stem cell transplantation. A total of 556 patients were randomized and progression-free survival was superior with TAD compared with VAD: median 25 months to 33 months ($P < .001$). However, no difference in overall survival was seen.

Patients receiving thalidomide in combination with high-dose corticosteroids or chemotherapy need routine thromboprophylaxis with coumarin (target International Normalized Ratio [INR] 2–3) or low-molecular-weight heparin (equivalent of enoxaparin 40 mg once daily). Aspirin can be used instead in patients receiving only low doses of dexamethasone (40 mg once per week or lower) or prednisone in combination with thalidomide, provided no concomitant erythropoietic agents are used.²⁵

Despite the high activity of Thal/Dex, the regimen has limitations because of the high rate of nonhematologic toxicity seen in approximately two thirds of patients. Thal/Dex is not superior to MP in elderly patients; results of a randomized trial show MP is preferable to Thal/Dex in such patients because of increased death rate from infections associated with Thal/Dex.^{26,27} In younger patients, the increased response rates, time to progression, and progression-free survival seen with Thal/Dex and other thalidomide-based regimens need to be considered in the context of other rapid advances occurring in the treatment of myeloma (see below). One option to reduce toxicity is to reduce the dose of dexamethasone to 40 mg once per week, based on findings with lenalidomide plus dexamethasone discussed below. However, there are no good data to support this approach.

Lenalidomide/Dexamethasone

Lenalidomide/dexamethasone (Len/Dex) was studied in newly diagnosed myeloma in an attempt to improve on the Thal/Dex regimen, based on the assumption that lenalidomide is more potent and less toxic than thalidomide. The first phase II trial conducted at the Mayo Clinic demonstrated remarkably high activity with the Len/Dex regimen, with lower toxicity than previously seen with Thal/Dex. Thirty-one of 34 patients (91%) achieved an objective response, including two (6%) achieving CR and 11 (32%) meeting the criteria for VGPR.⁸ Lacy et al subsequently updated the results of this study. With longer follow-up, 56% of patients achieved a VGPR or better. In the subset of 21 patients receiving Len/Dex as primary therapy without ASCT, 67% achieved VGPR or better.²⁸ Approximately 50% of patients experienced grade 3 or higher nonhematologic toxicity, similar to rates seen with dexamethasone alone.

In an attempt to further reduce dexamethasone-related adverse effects while preserving efficacy, the ECOG conducted a randomized trial testing Len/Dex as administered in the Mayo phase II trial (and in the regulatory relapsed refractory myeloma studies) versus Len/low-dose Dex (40 mg dexamethasone once weekly).²⁹ Preliminary results reported in abstract form showed that toxicity rates were significantly higher with Len/standard-dose Dex compared with Len/low-dose Dex. Early (first 4 months) mortality rates were also higher, 5% and 0.5%, respectively. The early mortality rate in the Len/low-dose Dex arm is probably the lowest reported in any large phase III newly diagnosed trial in which enrollment was not restricted by age or eligibility for stem cell transplantation; DVT rates were also low, making this one of the safest pretransplant induction regimens for myeloma. Based on this experience, Len/low-dose Dex is currently the regimen of choice in the mSMART protocol for the treatment of standard-risk myeloma in patients who are candidates for ASCT outside the setting of a clinical trial.¹⁰

Recommendations for thromboprophylaxis are similar to those discussed above with Thal/Dex; aspirin alone is probably sufficient for patients receiving Len/low-dose Dex.²⁵ There are reports suggesting that stem cell mobilization with growth factors alone may be affected in a subset of patients receiving Len/Dex as initial therapy.^{30,31} Mobilization is not affected in studies that routinely used growth factors plus cyclophosphamide.³² Prolonged therapy and age over 65 years appear to be factors that affect mobilization. Currently for patients less than 65 years of age who receive four or fewer cycles of induction, we initially use growth factors alone to mobilize stem cells. If there are problems with collection, then a second attempt with cyclophosphamide or plerixafor is needed, and this approach usually enables adequate collection.³³ For patients who are age 65 years and older or who have received more than four cycles of induction, we recommend routine use of cyclophosphamide with growth factors for initial mobilization.

Bortezomib/Dexamethasone

Bortezomib has been studied extensively in newly diagnosed myeloma, both in patients who are candidates for transplantation and in elderly patients. In newly diagnosed myeloma, bortezomib produces response rates of approximately 40% as a single agent.³⁴ Significantly higher response rates (approximately 70%–90%) have been observed with bortezomib plus dexamethasone (Vel/Dex) in phase II studies.^{35,36} The CR plus VGPR rate is approximately 30% with Vel/Dex. Harousseau et al reported preliminary results of a randomized trial comparing VAD versus Vel/Dex as pretransplant induction therapy.¹⁶ With 482 patients enrolled, preliminary results show superior response rates and progression-free survival with Vel/Dex compared to VAD. The incidence of grade 3–4 adverse events was comparable between the two regimens. No adverse effect on stem cell mobilization has been noted with Vel/Dex.

Bortezomib, Doxorubicin, and Dexamethasone

Bortezomib, doxorubicin, and dexamethasone (PAD) has shown high activity in newly diagnosed myeloma in a phase II study with an overall response rate of 95% and a CR rate of 24%.³⁷ Sonneveld and colleagues tested PAD versus VAD in a randomized, open-label, phase III trial.¹⁷ Patients with newly diagnosed myeloma ages 18–65 years were randomly assigned to three cycles of VAD or PAD. VAD was administered at a dose of vincristine 0.4 mg, doxorubicin 9 mg/m² days 1–4, dexamethasone 40 mg days 1–4, 9–12, and 17–20. PAD was administered at a dose of bortezomib 1.3 mg/m² days 1, 4, 8, and 11, doxorubicin 9 mg/m² days 1–4, and dexamethasone 40 mg days 1–4, 9–12, and 17–20. After induction therapy, all patients were to receive ASCT (one or two transplants) followed by maintenance with either thalidomide 50 mg daily in the VAD arm or bortezomib 1.3 mg/m² once every 2 weeks in the PAD arm for 2 years. A total of 833 patients were randomized, and preliminary results on the first 300 patients are available. The overall response rate prior to ASCT was superior with PAD compared with VAD: 83% versus 59%, $P < .001$. Corresponding CR rates were 5% versus 1%. Post-transplant CR rates were 23% versus 9%, respectively, $P < .001$. Eighty percent of patients achieved at least VGPR with this regimen of PAD followed by ASCT. Again, following PAD, stem cell harvest was adequate in all patients.

Bortezomib, Thalidomide, and Dexamethasone

Cavo et al compared Thal/Dex versus bortezomib, thalidomide, and dexamethasone (VTD) as pretransplant induction therapy in a randomized controlled trial.³⁸ A total of 399 patients (199 randomized to VTD and 200 to Thal/Dex) could be evaluated for primary study and secondary endpoints. On an intent-to-treat basis, VTD had significantly higher response rates compared with Thal/Dex (92% v 78.5%, respectively, $P < .001$) following the three cycles of induction. CR rates were also better (21% v 6%, respectively, $P < .001$). Serious

adverse events occurred in 14% of patients randomized to VTD versus 13% with Thal/Dex. There were no problems with stem cell mobilization, with median yields of 9.3 and 10.6 ($\times 10^6$ CD34⁺ cells/kg), respectively. On an intent-to-treat basis, post-transplant CR rate was higher with VTD compared with Thal/Dex: 41% versus 20%, respectively, $P < .001$. Progression-free survival was significantly superior with VTD as compared to Thal/Dex ($P = .04$), but overall survival is similar so far. VTD thus is a highly active induction regimen, and has the additional advantage of not requiring major dose modifications in renal failure.

Other Induction Regimens

There are no studies that have compared Len/Dex versus bortezomib-based regimens. Bortezomib-based regimens are of particular value in patients with renal failure and in patients with high-risk myeloma (see below). Bortezomib is not associated with an increased rate of thrombosis, and hence is a useful option for patients who are at high-risk of thrombosis or in whom anticoagulation or aspirin is contraindicated.

The role of other pretransplant induction regimens needs to be weighed in terms of the added side effects that can affect quality of life, and should be considered investigational until future studies show that the addition of these agents improves long-term outcome compared to the regimens discussed above. One exception is patients presenting with very aggressive disease including plasma cell leukemia features or rapidly progressive disease with or without extramedullary features. In these patients, two cycles of the combination chemotherapy regimen VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide) developed by Barlogie et al as part of total therapy III is highly effective in controlling the disease rapidly.³⁹ Bortezomib, lenalidomide, and dexamethasone (VRd),⁴⁰ cyclophosphamide, bortezomib, and dexamethasone (CyBorD),⁴¹ and bortezomib, cyclophosphamide, lenalidomide, and dexamethasone (VCRd)⁴² have shown high activity in phase II studies. Phase III studies with these regimens are awaited.

APPROACH TO FRONTLINE THERAPY

The overall approach to treatment of symptomatic newly diagnosed multiple myeloma is outlined in Figure 1A and B. As discussed earlier, it is important to avoid protracted melphalan-based therapy (more than one or two cycles of MP) in patients with newly diagnosed myeloma who are considered eligible for ASCT, since it can interfere with adequate stem cell mobilization. Typically patients who are candidates for ASCT are treated with approximately four cycles of induction therapy prior to stem cell harvest. This includes patients who are transplant candidates but who wish to reserve ASCT as a delayed option for relapsed refractory disease. Although this is not routinely recommended, such patients can resume induction therapy following stem cell collection until a plateau phase is reached, reserving ASCT for relapse.

All of the regimens discussed in detail earlier act rapidly and are associated with high response rates. Thal/Dex and Len/Dex have the particular advantage of being orally administered. However, both are associated with an increased risk of DVT, necessitating routine thromboprophylaxis. In contrast, Vel/Dex and PAD require frequent intravenous administration but do not increase the risk of DVT. In the absence of randomized data, it is hard to make any strong recommendations on choice of induction therapy. Importantly, we prefer enrollment of patients with newly diagnosed myeloma onto clinical trials. In the absence of an appropriate trial, the choice of front-line therapy is typically dependent on the experience of the treating physician, and varies by country based on the availability of the various new agents.

The ease of oral administration, low neurotoxicity, low (<10%) risk of DVT with aspirin alone as prophylaxis, and ability to administer as chronic, primary therapy over a period of years with dose adjustments are advantages of Len/low-dose Dex. The need to take chronic anticoagulation (with either aspirin or warfarin) and adverse effect on stem cell mobilization with growth factors alone are disadvantages. Thal/Dex appears to have no advantage over Len/low-dose Dex except in patients with renal failure, in whom Len/Dex is not recommended. Vel/Dex and PAD are highly active, do not carry an increased risk of DVT, and represent effective combinations for pretransplant induction therapy. They are particularly attractive for patients who have high-risk features. However, they are not options for long-term primary therapy because of the need for frequent intravenous administration and the risk of painful neurotoxicity. VTD is a major option for patients with acute renal failure. VDT-PACE is an important regimen to consider in patients with aggressive disease such as multiple extramedullary plasmacytomas or plasma cell leukemia, in whom a rapid response is needed.

TREATMENT OF HIGH-RISK MYELOMA

Patients with high-risk myeloma tend to do poorly, with a median overall survival of approximately 2 years even with tandem ASCT.¹⁰ The main option for these patients is novel therapeutic strategies.^{10,11} Bortezomib-containing regimens should be considered early in the disease course as primary therapy. In at least three separate studies, bortezomib appears to overcome the adverse effect of deletion 13.^{43–45} Due to the high risk of early relapse, some centers in the United States choose to defer ASCT, while some consider allogeneic transplant options. Routine maintenance therapy could be considered (for example, Len/low-dose Dex) given the high risk of early relapse. Clearly, clinical trials and new agents specifically designed for high-risk myeloma are needed.

CONCLUSION

Novel therapies have made a substantial contribution to survival in myeloma. Thalidomide, lenalidomide, and bortezomib have been incorporated in the treatment of newly diagnosed myeloma in two- and three-drug combinations, resulting in high response rates and improvement in long-term outcomes. At present, novel agents are used to complement other standard approaches such as autologous stem cell transplantation. Future trials will define the optimal induction regimen for patient with myeloma, as well as clarify the role of transplantation in an era of novel therapy.

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Figure 1.

Approach to the treatment of newly diagnosed myeloma in patients who are candidates for transplant in the United States (A) and Europe (B). Rd, lenalidomide plus low-dose dexamethasone; CR, complete response; ASCT, autologous stem cell transplantation; Vel/Dex, bortezomib plus dexamethasone; PAD, bortezomib, doxorubicin, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone; CVD, cyclophosphamide, bortezomib, dexamethasone; BD, bortezomib, dexamethasone; HDT, high-dose therapy; allo-SCT, allogeneic stem cell transplantation.

Table 1Mayo Risk Stratification for Myeloma⁴⁶

High-Risk Characteristic	Percentage of Newly Diagnosed Patients With the Abnormality ⁴⁷⁻⁴⁹
Conventional cytogenetics:	
Deletion of chromosome 13 (monosomy)	14%
Hypodiploidy	9%
Either hypodiploidy or deletion 13	17%
Fluorescent in-situ hybridization (FISH)	
t(4;14)	15%
t(14;16)	5%
17p-	10%
Plasma cell labeling index (PCLI) studies: PCLI	3%
Any one of the above high-risk abnormalities	25-30%

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Table 2

Dosing Schedule and Response Rates of Commonly used Chemotherapy Regimens in Myeloma

Regimen	Suggested Dosing Schedule *	Response Rate in Newly Diagnosed Myeloma	CR + VGPR Rate in Newly Diagnosed Myeloma
Transplant candidates			
Thalidomide/dexamethasone [†] (Thal/Dex) ^{18,23}	Thalidomide 100–200 mg oral days 1–28 Dexamethasone 40 mg oral days 1, 8, 15, 22 every 28 days Repeated every 4 weeks × 4 cycles as pretransplant induction therapy; or continued for up to 1 year or progression if used as primary therapy	63%	44%
Lenalidomide/dexamethasone (Len/low-dose Dex) ⁵⁰	Lenalidomide 25 mg oral days 1–21 every 28 days Dexamethasone 40 mg oral days 1, 8, 15, 22 every 28 days Repeated every 4 weeks × 2–4 cycles as pretransplant induction therapy; or continued till progression if used as primary therapy. If continued beyond 1 year, dexamethasone is usually stopped at that point.	71%	42%
Bortezomib/dexamethasone (Vel/Dex) ¹⁶	Bortezomib 1.3 mg/m ² intravenous days 1, 4, 8, 11 Dexamethasone 40 mg oral days 1–4, 9–12 Reduce dexamethasone to days 1–4 only after first 2 cycles Repeated every 3 weeks × 2–4 cycles as pretransplant induction therapy	80%	47%
Bortezomib-thalidomide-dexamethasone (VTD) ^{†38}	Bortezomib 1.3 mg/m ² intravenous days 1, 4, 8, 11 Thalidomide 200 mg oral days 1–21 Dexamethasone 20 mg day of and day after bortezomib Repeated every 3 weeks × 3 cycles as pretransplant induction therapy	92%	61%
Bortezomib-doxorubicin-dexamethasone (PAD) ^{17,51}	Bortezomib 1.3 mg/m ² intravenous days 1, 4, 8, 11 Doxorubicin 9 mg/m ² intravenous rapid infusion days 1–4 Dexamethasone 40 mg days 1–4, 9–12, and 17–20 Repeated every 4 weeks × 3 cycles as pretransplant induction therapy	83%	42%
VDT-PACE ³⁹	Dexamethasone 40 mg/d orally daily days 1–4 Thalidomide 100 mg/d days 1–28 [‡] Cisplatin 10 mg/m ² /d intravenous infusion over 24 hours days 1–4 Cyclophosphamide 400 mg/m ² /d intravenous infusion over 24 hours days 1–4 Etoposide 40 mg/m ² /d intravenous infusion over 24 hours days 1–4	Not reported	Not reported

Regimen	Suggested Dosing Schedule *	Response Rate in Newly Diagnosed Myeloma	CR + VGPR Rate in Newly Diagnosed Myeloma
	<p>Doxorubicin 10 mg/m²/d intravenous infusion over 24 hours days 1–4</p> <p>Bortezomib 1 mg/m²/d intravenous on days 1,4,8,11</p> <p>Repeated every 4 weeks × 2 cycles as pretransplant induction therapy</p> <p>Note:</p> <p>(1) For intravenous infusion, each 24-hour dose of cisplatin is mixed with cyclophosphamide and etoposide in 1,000 mL of normal saline. Doxorubicin is administered as a separate intravenous infusion via central line, with each 24-hour dose mixed in 250 mL of normal saline</p> <p>(2) For patients with weight greater than 60 kg, all doses will be based on calculated body weight (actual weight + ideal body weight and the sum is divided by 2) and not to exceed a body surface area of 2 m².</p> <p>(3) Prophylaxis for deep vein thrombosis with low-molecular-weight heparin is recommended. In addition, prophylaxis with levofloxacin, fluconazole, and acyclovir is recommended to prevent infection. Prophylaxis against gastric ulceration is needed. Growth factors (either filgrastim (starting day 5) or pegfilgrastim (one dose on day 5) are needed.</p>		

Abbreviations: CR, complete response; VGPR, very good partial response; VDT-PACE, bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide.

* Starting and subsequent doses need to be adjusted for performance status, renal function, blood counts, and other toxicities.

[†] Dexamethasone dose listed is lower than used in trial.

[‡] Thalidomide dose listed is lower than used in trial.