Multiple Myeloma

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MULTIPLE MYELOMA IS A PLASMA-CELL NEOPLASM THAT IS CHARACTERIZED BY SKELETAL DESTRUCTION, RENAL FAILURE, ANEMIA, AND HYPERCALCEMIA.1 Although myeloma remains incurable, recent advances in its treatment, including the use of thalidomide and new drugs such as bortezomib and CC-5013, are promising.2

DIAGNOSIS

The most common symptoms on presentation are fatigue, bone pain, and recurrent infections.3 New diagnostic criteria require the presence of at least 10 percent plasma cells on examination of the bone marrow (or biopsy of a tissue with monoclonal plasma cells), monoclonal protein in the serum or urine, and evidence of end-organ damage.4,5 The end-organ damage that meets the criterion for the diagnosis consists of hypercalcemia, renal insufficiency, anemia, or bone lesions (a group of findings referred to as CRAB).4 Occasional patients presenting without a detectable monoclonal protein but otherwise meeting these diagnostic criteria are considered to have nonsecretory myeloma. The serum free light-chain assay is useful for monitoring many patients with oligosecretory and nonsecretory myeloma. The differential diagnosis includes monoclonal gammopathy of undetermined significance (MGUS), smoldering (asymptomatic) multiple myeloma, primary amyloidosis, solitary plasmacytoma, low-grade lymphoma, chronic lymphocytic leukemia, and metastatic carcinoma.4

The median length of survival after diagnosis is approximately three years. Recent advances have identified new prognostic markers, such as the complete deletion of chromosome 13 or its long arm, as detected by karyotyping; the t(4;14) or t(14;16) translocation; and increased density of bone marrow microvessels. These complement established markers of adverse outcomes, such as an increase in the plasma-cell–labeling index, increased levels of serum beta2-microglobulin, low levels of serum albumin, plasmablastic features in the bone marrow, and circulating plasma cells.6

PATHOPHYSIOLOGY

EVOLUTION OF MGUS

The first pathogenetic step in the development of myeloma is the emergence of a limited number of clonal plasma cells, clinically known as MGUS.7 Patients with MGUS do not have symptoms or evidence of end-organ damage, but they do have an annual risk of 1 percent of progression to myeloma or a related malignant disease.7 Approximately 50 percent of patients have translocations that involve the immunoglobulin heavy-chain locus on chromosome 14q32 and one of five partner chromosomes, 11q13 (CCND1) (the most common), 4p16.3 (FGFR3 and MMSET), 6p21 (CCND3),
16q23 (c-maf), and 20q11 (mafB). These and other cytogenetic changes (Fig. 1) are thought to play an important role in the evolution of MGUS.

PROGRESSION TO MYELOMA
With progression of MGUS to myeloma, complex genetic events occur in the neoplastic plasma cell (Fig. 1). Changes also occur in the bone marrow microenvironment, including the induction of angiogenesis, the suppression of cell-mediated immunity, and the development of paracrine signaling loops involving cytokines such as interleukin-6 and vascular endothelial growth factor. The resultant interactions of myeloma cells, bone marrow stromal cells, and microvessels contribute to persistence of the tumor and its resistance to drugs. Understanding the cellular microenvironment in myeloma has had a role in the development of drugs such as thalidomide and bortezomib, which are able to overcome chemotherapy-resistant disease. The development of bone lesions in myeloma is thought to be related to an increase in the expression by osteoblasts of the receptor activator of nuclear factor-κB (NF-κB) ligand (RANKL) and a reduction in the level of its decoy receptor, osteoprotegerin. The increase in the ratio of RANKL to osteoprotegerin results in the activation of osteoclasts and bone resorption. Overexpression of RANKL is probably mediated in part by the release of macrophage inflammatory protein 1α by neoplastic plasma cells. Improved understanding of myeloma-associated bone disease has led to the use of prophylactic bisphosphonate therapy.

There is no evidence that early treatment of asymptomatic (smoldering) multiple myeloma is beneficial. The median time from diagnosis to the progression to symptomatic disease is two to three years. Two recent studies suggest that thalidomide may delay the time to progression. However, because some patients may remain progression-free for several years, therapy for asymptomatic myeloma is not recommended, given the toxic effects of thalidomide. An approach to the treatment of newly diagnosed myeloma is illustrated in Figure 2.
When possible, patients should be encouraged to participate in clinical trials at the time of diagnosis and beyond.

**Induction Therapy in Patients Eligible for Autologous Stem-Cell Transplantation**

Patients who are eligible for autologous stem-cell transplantation are first treated with a regimen that is not toxic to hematopoietic stem cells. The use of alkylating agents is best avoided, because they can prevent an adequate mobilization of stem cells. Many physicians use vincristine, doxorubicin, and dexamethasone for three to four months as induction therapy. Despite an acceptable response rate, this therapy and similar intravenous regimens have disadvantages, including the need for an indwelling central venous line and the risk of catheter-related infections, thrombotic events, and alopecia. Furthermore, the role of doxorubicin and vincristine in the regimen consisting of vincristine, doxorubicin, and dexamethasone is limited, because dexamethasone alone contributes to most of the activity (Table 1).

An alternative choice for induction is the oral regimen of thalidomide plus dexamethasone. In a recent trial, 50 patients with newly diagnosed myeloma were treated with this combination. Thalidomide (at a dose of 200 mg per day) was given with dexamethasone (at a dose of 40 mg per day) on days 1 through 4, 9 through 12, and 17 through 20 (odd cycles) and on days 1 through 4 (even cycles). Each cycle was 28 days long, and there was typically no gap between the cycles unless time was needed for the resolution of toxic effects. The response rate in the patients in this trial was 64 percent, which is similar to that in previous trials with the regimen of vincristine, doxorubicin, and dexamethasone. No important problems were found in the collection or engraftment of stem cells in the patients after receiving this induction therapy. Deep-vein thrombosis was an unexpected adverse event in 12 percent of the patients in this trial. In a separate trial, the response rate with this regimen was 72 percent, and the use of prophylactic anticoagulation with warfarin or low-molecular-weight heparin prevented the occurrence of deep-vein thrombosis.

In a randomized trial comparing thalidomide plus dexamethasone with dexamethasone alone, the response rate with thalidomide plus dexamethasone was significantly better (P=0.01).

**Induction Therapy in Patients Not Eligible for Transplantation**

Patients who are not eligible for transplantation because of age, poor physical condition, or coexisting conditions receive standard therapy with alkylating agents. Although vincristine, doxorubicin, and dexamethasone, dexamethasone alone, or thalidomide plus dexamethasone can also be used as initial therapy for these patients, the oral regimen of melphalan plus prednisone is preferable in this setting to minimize toxic effects, unless there is a need for a rapid response, such as in patients with large, painful lytic lesions or with worsening renal...
### Table 1. Major Classes of Drugs Used in the Treatment of Myeloma.†

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regimen and Usual Starting Dose</th>
<th>Response Rate</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Newly Diagnosed Disease</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melphalan and prednisone‡</td>
<td>Repeated every 6 wk Melphalan, 8–10 mg PO on days 1–7 Prednisone, 60 mg per day PO on days 1–7</td>
<td>50–55</td>
<td>Myeloma Trialists' Collaborative Group</td>
</tr>
<tr>
<td>Combinations, e.g., VBMCP§</td>
<td>Repeated every 5 wk Vincristine, 0.03 mg/kg (maximum 2 mg) IV on day 1 Carmustine, 0.5 mg/kg IV on day 1 Melphalan, 0.25 mg/kg PO on days 1–7 Cyclophosphamide, 10 mg/kg IV on day 1 Prednisone, 1 mg/kg PO on days 1–7</td>
<td>60</td>
<td>Myeloma Trialists' Collaborative Group, Cavo et al.</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pulsed dexamethasone</td>
<td>Repeated every 4–5 wk Dexamethasone, 40 mg PO on days 1–4, 9–12, and 17–20</td>
<td>45</td>
<td>Alexanian et al., Alexanian et al.</td>
</tr>
<tr>
<td>VAD</td>
<td>Repeated every 4 wk Vincristine, 0.4 mg per day IV continuous infusion on days 1–4 Doxorubicin, 9 mg/m² IV continuous infusion on days 1–4 Dexamethasone, 40 mg PO on days 1–4</td>
<td>55–65</td>
<td>Alexanian et al., Alexanian et al., Alexanian et al.</td>
</tr>
<tr>
<td>Thalidomide and its analogues</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Thalidomide</td>
<td>Repeated every 4 wk 200–400 mg PO on days 1–28</td>
<td>35</td>
<td>Rajkumar et al., Weber et al., Singhal et al., Kumar et al., Juliussen et al.</td>
</tr>
<tr>
<td>Thalidomide–dexamethasone</td>
<td>Repeated every 4 wk Thalidomide, 200 mg PO on days 1–28 Dexamethasone, 40 mg PO on days 1–4, 9–12, and 17–20</td>
<td>65–70</td>
<td>Weber et al., Rajkumar et al., Dimopoulos et al.</td>
</tr>
<tr>
<td>Melphalan–prednisone–thalidomide</td>
<td>Repeated every 4 wk Melphalan, 4 mg/m² PO on days 1–7 Prednisone, 40 mg/m² PO on days 1–7 Thalidomide, 100 mg PO on days 1–28</td>
<td>80</td>
<td>Palumbo et al.</td>
</tr>
<tr>
<td>Cyclophosphamide–thalidomide–dexamethasone</td>
<td>Repeated every 3 wk Cyclophosphamide, 50 mg PO on days 1–21 Thalidomide, 200–800 mg PO on days 1–21 Dexamethasone, 40 mg PO on days 1–4</td>
<td>—</td>
<td>Garcia-Sanz et al.</td>
</tr>
<tr>
<td>CC-S013**</td>
<td>25–30 mg PO on days 1–21 every 28 days</td>
<td>—</td>
<td>Richardson et al.</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² on days 1, 4, 8, and 11 every 21 days</td>
<td>—</td>
<td>Richardson et al.</td>
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</tbody>
</table>

* PO denotes orally; VBMCP vincristine, carmustine, melphalan, cyclophosphamide, and prednisone; VAD vincristine, doxorubicin, and dexamethasone; IV intravenous; mg/kg milligrams per kilogram of body weight; and mg/m² milligrams per square meter of body-surface area.
† Percentages are estimates based on the results of all studies in which the given regimen was used.
‡ Several drug combinations have been studied; VBMCP is the combination most commonly studied and used.
§ Appropriate trials of melphalan–prednisone in patients with relapsed or refractory disease who have not received alkylator therapy have not been conducted.
¶ The response rate reflects effectiveness in patients with relapsed or refractory disease and previous alkylator therapy.
† In one study, dexamethasone was administered on days 1–4, 9–12, and 17–20 in odd cycles and on days 1–4 in even cycles.
** CC-S013 is not commercially available.
function. Despite better response rates with any of the more aggressive combination regimens than with melphalan plus prednisone (Table 1), no survival benefit has been shown. Melphalan is generally administered at a dose of 8 to 10 mg per day for 7 days (although lower doses may be needed in patients with advanced renal failure) with prednisone at a dose of 60 mg per day orally during the same 7 days, and both drugs are repeated every 6 weeks for a period of 12 to 18 months. The dosage of melphalan is adjusted to produce mild cytopenia at midcycle.

**AUTOLOGOUS STEM-CELL TRANSPLANTATION**

Although not curative, autologous stem-cell transplantation improves the likelihood of a complete response, prolongs disease-free survival and overall survival, and is a major advance in myeloma therapy (Table 2). The mortality rate is 1 to 2 percent, and approximately 50 percent of patients can be treated entirely as outpatients. Whether or not a complete response is achieved is an important predictor of the eventual outcome. Melphalan (at a dose of 200 mg per square meter of body-surface area) is the most widely used preparative regimen for autologous stem-cell transplantation and is superior to the older regimen of melphalan (140 mg per square meter) combined with 8 Gy of total-body irradiation. The data are limited on the effectiveness of autologous stem-cell transplantation in patients 65 years of age or older and those with end-stage renal disease. However, the procedure is feasible in these patients and can be undertaken after careful consideration of the possible risks and benefits, perhaps with the use of an intermediate dose of melphalan (100 mg per square meter).

The role of autologous stem-cell transplantation in the treatment of patients responding to induction therapy has been questioned. In a Spanish trial, patients responding to initial therapy had a similar overall survival and progression-free survival with either autologous stem-cell transplantation or eight additional courses of chemotherapy — suggesting that patients who benefit most from autologous stem-cell transplantation are those with disease refractory to induction therapy. The value of autologous stem-cell transplantation as initial therapy has also been challenged by the results of three randomized trials that showed that transplantation can be safely delayed and used as salvage therapy at the time of relapse (Table 2).

Generally, issues such as the inconvenience and the adverse effects of prolonged chemotherapy and difficulties in gaining the approval of health insurance plans for cryopreservation of stem cells still favor early autologous stem-cell transplantation. This is especially the case for patients younger than 65 years of age with adequate renal function.

**TANDEM TRANSPLANTATION**

In tandem (double) autologous stem-cell transplantation, patients undergo a second planned autologous stem-cell transplantation after they have recovered from the first. Tandem transplantation was developed by Barlogie and colleagues, to improve complete-response rates. In a recent randomized trial conducted in France, event-free survival and overall survival were significantly better among recipients of tandem transplantation than among those who underwent a single autologous stem-cell transplantation (P=0.01) (Table 2). Conversely, preliminary data from three other randomized trials showed no convincing improvement in overall survival among patients receiving tandem transplantation, although the follow-up was too short for definite conclusions to be drawn (Table 2). On the basis of the results of the French trial, it is reasonable to consider tandem transplantation for patients who do not have at least a very good partial response (defined as a reduction of 90 percent or more in monoclonal protein levels) with the first transplantation. However, until this issue is resolved, it may be advantageous to collect enough stem cells to allow a patient to undergo two transplantations, reserving a second autologous stem-cell transplantation for relapse.

Two challenges persist. First, the current conditioning regimens are inadequate. In an effort to improve them, the use of bone-seeking radioactive holmium and samarium is being tested. Second, reinfused hematopoietic stem cells are inevitably contaminated with tumor cells. Such contamination can be reduced with the use of CD34 selection or the delivery of in vitro chemotherapy to the collected stem cells. However, no effect on overall survival has been observed to date, reflecting the fact that residual drug-resistant cells in the marrow are the principal cause of the recurrence of disease.

**ALLOGENEIC TRANSPLANTATION**

The advantages of allogeneic transplantation are a graft that is not contaminated with tumor cells...
**Table 2. Results of Major Randomized Trials with Autologous Stem-Cell Transplantation in Myeloma.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparison</th>
<th>No. of Patients</th>
<th>Outcome</th>
<th>Comments</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intergroupe Francophone du Myélome 90</td>
<td>Conventional-dose chemotherapy vs. autologous bone marrow transplantation</td>
<td>200</td>
<td>Superior event-free survival and overall survival with transplantation; 5-yr survival, 52 percent with transplantation vs. 12 percent with chemotherapy (P=0.03)</td>
<td>All patients &lt;65 yr of age, all received interferon maintenance therapy, and survival with chemotherapy was shorter than expected</td>
<td>Attal et al.37</td>
</tr>
<tr>
<td>Medical Research Council Myeloma VII</td>
<td>Conventional-dose chemotherapy vs. autologous stem-cell transplantation</td>
<td>401</td>
<td>Superior progression-free survival and overall survival with transplantation; median survival, 54 mo with transplantation vs. 42 mo with chemotherapy (P=0.04)</td>
<td>All patients &lt;65 yr of age</td>
<td>Child et al.38</td>
</tr>
<tr>
<td>PETHEMA*</td>
<td>Conventional-dose chemotherapy vs. autologous stem-cell transplantation</td>
<td>216</td>
<td>No difference in progression-free survival or overall survival; median survival, 65 mo with transplantation vs. 67 mo with chemotherapy</td>
<td>Median age, 56 yr; only 164 patients responding to induction chemotherapy underwent randomization</td>
<td>Bladé et al.39</td>
</tr>
<tr>
<td>Myélome Autogreffe 91</td>
<td>Conventional-dose chemotherapy vs. autologous stem-cell transplantation</td>
<td>190</td>
<td>No significant difference in event-free survival or overall survival; median survival, 55 mo with transplantation vs. 50 mo with chemotherapy</td>
<td>All patients 55–65 yr of age</td>
<td>Fermand et al.40</td>
</tr>
<tr>
<td>Intergroup S9321</td>
<td>Conventional-dose chemotherapy vs. autologous stem-cell transplantation vs. allogeneic transplantation</td>
<td>549</td>
<td>Median progression-free survival, 25 mo with autologous transplantation vs. 21 mo with chemotherapy (P=0.05); no significant difference in overall survival</td>
<td>After 39 patients were enrolled, allogeneic transplantation group closed; 52 percent of patients assigned to chemotherapy received salvage transplantation at relapse</td>
<td>Barlogie et al.41</td>
</tr>
<tr>
<td>Myélome Autogreffe</td>
<td>Early vs. delayed autologous stem-cell transplantation</td>
<td>185</td>
<td>Median event-free survival, 39 mo with autologous transplantation vs. 13 mo with chemotherapy; no significant difference in overall survival</td>
<td>All patients &lt;56 yr of age; early transplantation associated with shorter duration of chemotherapy and symptoms</td>
<td>Fermand et al.42</td>
</tr>
<tr>
<td>Intergroupe Francophone du Myélome 94</td>
<td>Single vs. double autologous stem-cell transplantation</td>
<td>399</td>
<td>Superior event-free survival and overall survival with double transplantation; 7 yr survival, 42 percent with double transplantation vs. 21 percent with single transplantation (P=0.01)</td>
<td>All patients &lt;60 yr of age; benefit of second transplantation restricted to those with less than very good partial response to first</td>
<td>Attal et al.43</td>
</tr>
<tr>
<td>Bologna 96</td>
<td>Single vs. double autologous stem-cell transplantation</td>
<td>220</td>
<td>Superior event-free survival with double transplantation; no significant difference in overall survival; median survival, 60 mo with double transplantation vs. 56 mo with single transplantation</td>
<td>Interim analysis of first 220 patients</td>
<td>Cavo et al.44</td>
</tr>
<tr>
<td>Myélome Autogreffe 95</td>
<td>Single vs. double autologous stem-cell transplantation</td>
<td>230</td>
<td>No difference in progression-free or overall survival</td>
<td>All patients &lt;56 yr of age</td>
<td>Fermand et al.45</td>
</tr>
</tbody>
</table>

*PETHEMA denotes Programa para el Estudio y Tratamiento de las Hemopatías Malignas.*
and a graft-versus-myeloma effect. However, only 5 to 10 percent of patients are candidates for allogeneic transplantation when age, the availability of an HLA-matched sibling donor, and adequate organ function are taken into consideration. Furthermore, the high rate of treatment-related death has made conventional allogeneic transplantation unacceptable for most patients with myeloma. T-cell–depleted transplants appear to be ineffective.

Several recent trials have used nonmyeloablative conditioning regimens (also referred to as “mini” allogeneic transplantation). The greatest benefit has been reported in patients with newly diagnosed disease who have first undergone autologous stem-cell transplantation to reduce the tumor burden and afterward undergone mini–allogeneic (nonmyeloablative) transplantation of stem cells from an HLA-identical sibling donor. The rate of treatment-related deaths was 15 to 20 percent with this strategy. There is also a high risk of both acute and chronic graft-versus-host disease, although the emergence of these toxic effects appears to be necessary for disease control. Preliminary results from a French trial indicated that in patients with high-risk myeloma (those with a deletion of chromosome 13 plus high levels of beta2-microglobulin), the overall survival with this approach may not be superior to that with tandem autologous stem-cell transplantation.

Currently, the use of autologous stem-cell transplantation followed by mini–allogeneic transplantation remains investigational and is best performed as part of a clinical trial. Outside that setting, we consider this option only for selected high-risk patients with newly diagnosed disease who are younger than 60 years of age and have HLA-identical siblings as potential donors, and for whom the current approaches appear to be futile (i.e., patients with karyotypic deletion of chromosome 13 or hypodiploidy, the t(4;14) or t(14;16) translocation, or a plasma cell–labeling index of 3 percent or more).

**MAINTENANCE THERAPY**

Initial trials of the usefulness of maintenance therapy with interferon alfa produced conflicting results, and the results of a meta-analysis showed only a modest improvement in overall survival. Recent results from an intergroup trial showed no apparent benefit from the use of interferon as maintenance therapy.

A study by Berenson and colleagues indicated that maintenance with prednisone may be useful after conventional chemotherapy. The progression-free survival was significantly longer with 50 mg of oral, alternate-day prednisone (for a period of 14 months) than with 10 mg (for a period of 5 months; P=0.003). The overall survival was better with the use of the higher dose of prednisone, as compared with the lower dose (37 months and 26 months, respectively; P=0.05). It is unclear whether these results can be generalized, because this comparison study included only patients whose myeloma was responsive to corticosteroids and who had not previously undergone autologous stem-cell transplantation. Clinical trials are under way to evaluate novel approaches, such as the use of thalidomide and dendritic-cell vaccination as maintenance therapy.

**THERAPY FOR RELAPSED AND REFRACTORY MULTIPLE MYELOMA**

Almost all patients with multiple myeloma have a risk of eventual relapse. If relapse occurs more than six months after conventional therapy is stopped, the initial chemotherapy regimen should be re-instituted. Patients who have had stem cells cryopreserved early in the course of the disease can benefit from the use of autologous stem-cell transplantation as salvage therapy.

The highest response rates in relapsed myeloma have been with the use of intravenous vincristine, doxorubicin, and dexamethasone (Table 1). Intravenous doxorubicin hydrochloride liposome is a less cardiotoxic alternative to doxorubicin and is being tested in patients with newly diagnosed disease. Dexamethasone alone is also effective. Intravenous pulsed methylprednisolone (at a dose of 2 g three times per week) is an alternative to dexamethasone and may have fewer adverse effects.

In the past five years, major advances have been made with the use of thalidomide and the arrival of novel approaches such as bortezomib. Depending on the clinical situation, these and other agents (Table 1) are generally used sequentially, because disease refractory to one regimen or agent may respond to another.

**THALIDOMIDE**

Thalidomide was used as a sedative in the 1950s and was withdrawn from the market after initial reports of teratogenicity in 1961. Subsequently, the efficacy of thalidomide in erythema nodosum lep-
Rossum, Behçet’s syndrome, the wasting and oral ulcers associated with the human immunodeficiency virus syndrome, and graft-versus-host disease permitted its use in clinical trials and for compassionate use.74 In 1998, the Food and Drug Administration (FDA) approved the use of thalidomide in the treatment of erythema nodosum leprosum.

**Clinical Trials**

Trials with thalidomide as an anticancer agent were unsuccessful in the 1960s.75,76 However, the finding of increased angiogenesis in myeloma coupled with the recognition of the antiangiogenic properties of thalidomide led to the first clinical trial of this drug for the treatment of multiple myeloma, at the University of Arkansas. In that trial, the rate of response was 25 percent in patients with relapsed and refractory disease.25 Since then, several studies have confirmed the activity of thalidomide in relapsed myeloma, with response rates ranging from 25 percent to 35 percent.77-79 The responses are durable, with a median duration of approximately 12 months.26 Thalidomide had limited activity in extramedullary (soft-tissue) disease in one study.80

Given the activity of thalidomide as a single agent, subsequent trials explored its use in combination with other active agents in the treatment of relapsed myeloma. Response rates when thalidomide was used with corticosteroids, as compared with the rates with thalidomide alone, increased to approximately 50 percent29,81-83 and to more than 70 percent when used in a three-drug combination of thalidomide, dexamethasone, and an alkylating agent (either cyclophosphamide or melphalan).31,79,84 Thalidomide alone or in combination is now considered standard therapy for relapsed and refractory myeloma. As discussed earlier, this activity also has translated into the incorporation of thalidomide in the initial treatment of multiple myeloma.

**Adverse Effects**

Sedation, fatigue, constipation, and rash are common adverse effects but usually are responsive to dose reduction.85 Peripheral neuropathy occurs with long-term use and often necessitates the discontinuation of the therapy or a dose reduction. The incidence of deep-vein thrombosis is only 1 to 3 percent in patients receiving thalidomide alone but increases to 10 to 15 percent in patients receiving the drug in combination with dexamethasone and to about 25 percent in patients receiving the drug in combination with other cytotoxic chemotherapeutic agents, particularly doxorubicin.77,79,86-88 Other adverse effects include edema, bradycardia, neutropenia, impotence, and hypothyroidism. The use of thalidomide in pregnancy is absolutely contraindicated, and the System for Thalidomide Education and Prescribing Safety Program89 must be followed to prevent teratogenic effects.

**DOSAGE**

Thalidomide is usually administered in a dosage of 200 mg per day, which is increased to 400 mg per day after two to four weeks, if tolerated. Lower doses (50 to 100 mg) are being investigated, and to minimize long-term toxic effects, the dose should be adjusted to the lowest level that can achieve and maintain a response. Doses above 200 mg are generally not indicated when thalidomide is used in combination with corticosteroids or chemotherapy.

**Mechanism of Action**

Thalidomide undergoes rapid interconversion between the R-enantiomer and the S-enantiomer and spontaneous cleavage to more than 12 metabolites in solutions at physiologic pH.90 Furthermore, its activity in most in vitro assays is moderate or negligible, and its effects in animal models are dependent on the species and the route of administration. Thus, the study of its mechanism of action is difficult.91 Proposed mechanisms include the inhibition of tumor necrosis factor α, the prevention of free-radical–mediated DNA damage, the suppression of angiogenesis, an increase in cell-mediated cytotoxic effects, and the alteration of the expression of cellular adhesion molecules.74 Thalidomide may also inhibit the activity of NF-κB and the enzymes cyclooxygenase-1 and cyclooxygenase-2 (Fig. 3).

**Bortezomib**

Bortezomib (formerly known as PS-341) was the first proteasome inhibitor to enter clinical trials. It was granted accelerated approval by the FDA for the treatment of advanced myeloma in May 2003.

**Clinical Trials**

In preclinical models, bortezomib showed substantial activity against many cancers, including myeloma.92-96 Its promising efficacy against myeloma was noted in a phase 1 dose-finding study.
conducted by Orlowski and colleagues. On the basis of these observations, a phase 2 multicenter trial of intravenous bortezomib in myeloma was initiated (the drug was given at a dose of 1.3 mg per square meter over a period of three to five seconds on days 1, 4, 8, and 11 in a 21-day cycle for a maximum of eight cycles). Of 193 patients who could be evaluated, 92 percent had received three or more of the major classes of agents for myeloma, and in 91 percent the disease had been refractory to the most recent treatment. The partial-response rate with bortezomib was 27 percent, and 4 percent of patients achieved a complete response. The median duration of response was 12 months, and the responses were associated with improvement in cytopenia, renal function, and the quality of life. Older age (above 65 years) and extensive marrow involvement were associated with a lower rate of response.

A randomized, phase 2 trial of bortezomib in myeloma that had not responded to treatment or had relapsed after the initial induction therapy and consolidation therapy was also completed recently. In this trial, patients were randomly assigned to receive one of two doses of bortezomib (28 patients were assigned to receive a dose of 1.0 mg per square meter and 26 patients 1.3 mg per square meter) administered on days 1, 4, 8, and 11 in a 21-day cycle for a total of eight cycles. Responses occurred in 33 percent of those receiving 1.0 mg per square meter and in 50 percent of those receiving 1.3 mg per square meter. Although initial trials allowed a maximum of only eight cycles of bortezomib, recent data indicate that it is safe to administer at least an additional five or six cycles of therapy without undue toxic effects. A recent phase 3 trial involving 670 patients and comparing bortezomib with pulsed dexamethasone therapy was closed early because of a longer time to disease progression in patients receiving bortezomib. In trials to date, the response to bortezomib has been shown to be rapid, usually occurring within one or two cycles of the therapy.

Studies are under way of bortezomib in combination with other effective agents. In the initial phase 2 trial, dexamethasone was added to therapy for 106 patients whose condition had not responded or those in whom the disease had progressed while they were receiving bortezomib. In 19 of these patients (18 percent), there was a response to the addition of dexamethasone with a reduction of at least 25 percent in monoclonal protein levels, suggesting an additive effect that can be exploited in future trials. Other investigators are studying bortezomib in combination with thalidomide, pegylated doxorubicin, and alkylating agents.

**ADVERSE EFFECTS**

The most common adverse effects of bortezomib are gastrointestinal symptoms, cytopenia, fatigue, and peripheral neuropathy. A decrease in the platelet count to less than 50,000 per cubic millimeter occurs in almost 30 percent of patients. Peripheral neuropathy, often painful, develops in approximately 30 percent of patients and is more frequent in those who have previously received neurotoxic therapy and those with a preexisting neuropathy.

**DOSSING**

The recommended starting dose is 1.3 mg per square meter administered on days 1, 4, 8, and 11 of a 21-day cycle. Reductions to 1.0 mg per square
mechanism of action

Bortezomib is a specific inhibitor of the 26S proteasome, a large intracellular adenine triphosphate-dependent protease responsible for protein catabolism in all eukaryotic cells. Normally, cellular proteins destined for catabolism are first ubiquitinated—a pathway in which C-terminal glycine residues of ubiquitin molecules attach covalently to specific lysine moieties on the protein.107 Ubiquitinated proteins are identified and degraded in the central portion of the proteasome, a pathway critical for normal cellular events to occur, including cell cycling, signal transduction, and transcriptional regulation. Inhibition of this pathway creates major imbalances in the levels of various regulatory proteins, leading to arrest of the cell cycle and apoptosis.

The therapeutic effect of bortezomib-induced inhibition of the proteasome in myeloma is probably a result of direct cytotoxicity and of effects on the bone marrow microenvironment (Fig. 3).94,108 One of the consequences of proteasome inhibition is the accumulation of IkB, an inhibitor of the major transcription factor NF-κB.109 At the cellular level, inhibition of NF-κB leads to a decrease in the expression of adhesion molecules and various growth, survival, and angiogenic factors. It also causes a decrease in the levels of the proteins that promote apoptosis, Bcl-2 and A1/Bfl-1, triggering the release of cytochrome-c, activation of caspase 9, and apoptosis of myeloma cells.94 However, inhibition of NF-κB is unlikely to be the sole mechanism of the observed antmyeloma effects.92,94,110

CC-5013

As a means to overcoming the nonhematologic toxic effects of thalidomide, including teratogenicity, several active analogues of thalidomide have been developed. CC-5013 (lenalidomide) is an amino-substituted variant of thalidomide that belongs to a class of analogues known as immunomodulatory drugs. Its preclinical activity is more potent and more promising than the activity of thalidomide. The drug induces apoptosis and decreases the binding of myeloma cells to stromal cells in bone marrow.111 It also inhibits angiogenesis and promotes cytotoxicity mediated by natural killer cells.112,113

In two phase 2 trials of CC-5013, there was a reduction of at least 50 percent in monoclonal protein levels in approximately 30 percent of patients with relapsed myeloma, and myelosuppression was the major dose-limiting toxic effect.114,115 A multicenter, randomized phase 2 study in which the subjects had relapsed refractory myeloma was recently completed,32 in which CC-5013 was administered at a dose of 15 mg twice per day or a dose of 30 mg once per day for a period of 3 weeks and was followed by a 1-week rest (in a 28-day cycle). The cycle was repeated until disease progression or toxic effects occurred. In 24 percent of 83 patients who could be evaluated, there was a reduction of at least 50 percent in monoclonal protein levels. The most common adverse effects were grade 3 or higher thrombocytopenia (i.e., a platelet count of less than 50,000 per cubic millimeter), which occurred in 18 percent of patients, and neutropenia (i.e., a neutrophil count of less than 1000 per cubic millimeter), which occurred in 28 percent of patients. Adverse events were more frequent among those receiving 15 mg twice per day. Common adverse effects observed with thalidomide, however, such as sedation, constipation, and neuropathy, were not observed. CC-5013 appears to be a promising agent for the treatment of myeloma, and trials conducted for approval by the FDA are under way.

Other Novel Agents

Several other agents, including 2-methoxyestradiol, neovastat, oblimersen, farnesyltransferase, and histone deacetylase inhibitors, are being actively investigated.10,112 Preliminary evidence suggests that arsenic trioxide has clinical activity against myeloma,116 and trials are under way to confirm this possibility and to determine optimal dosing. Another thalidomide analogue, CC-4047, also has shown activity.117

Treatment of Complications

Table 3 summarizes current management strategies for complications observed in patients with myeloma. Important advances include the prevention and treatment of hypercalcemia and bony lesions with the monthly administration of bisphosphonates in patients with myeloma bone disease.118,119 Such treatment may be complicated by albuminuria, renal dysfunction, and osteonecrosis of the jaw. Another recent advance is the use of vertebroplasty or kyphoplasty to reduce pain and help re-
store vertebral height in patients with compression fractures.

**FUTURE DIRECTIONS**

Ongoing randomized trials promise to define further the roles of new agents, mini–allogeneic transplantation, and maintenance therapy. There is a continuing search for active agents based on advances in understanding the biology of myeloma. Microarray-based pharmacogenomic analysis may usher in an era of therapy tailored to the individual patient.

Finally, two paths are being explored simultaneously, one to improve rates of complete response with the intense use of available methods, which is aimed at finding a cure, and the other to exploit conventional and novel agents in an effort to control myeloma and convert it into a chronic indolent disease. Success in either direction would be momentous.

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CORRECTION

Multiple Myeloma

Multiple Myeloma. On page 1869, in the second full paragraph in the left-hand column, lines 11 through 12 should have read, “a decrease in the levels of the proteins that inhibit apoptosis,” rather than “the levels of the proteins that promote apoptosis,” as printed.