Chapter

79

Multiple Myeloma — Recent Advances and the Management of the Relapsed/Refractory Patient

HEMANT MALHOTRA

INTRODUCTION

Multiple myeloma is a plasma-cell neoplasm that is characterized by skeletal destruction, renal failure, anemia, and hypercalcemia[1,2] (Fig. 1). There has been unprecedented progress in the past decade or two in the understanding of the patho-physiology of the disease and the development and availability of new drugs and treatment paradigms in the management of this disorder. Understanding of the role of the bone marrow microenvironment and targeting this in addition to the myeloma cell has led to major success in the treatment of myeloma.

Current standard of care for the symptomatic patient of multiple myeloma includes controlling the disease with oral or IV chemotherapy, consolidation of the gains of chemotherapy with one or two autologous stem cell transplants followed by some form of maintenance treatment (interferon or thalidomide) to prolong remission and delay relapse. Although myeloma remains incurable today, recent advances in its treatment, including the use of thalidomide, other immuno-modulatory agents—IMiDs—such as Lenolidomide (CC-5013, Revelmid) and new, first-in-class, proteosome inhibitor drugs such as bortezomib are promising[3].

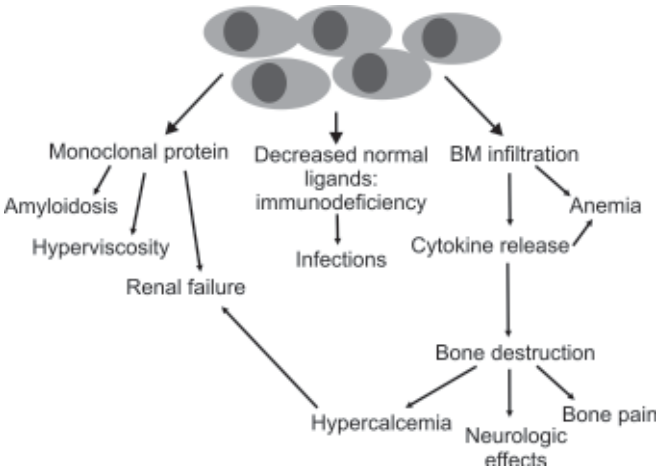

Fig. 1: Clinical manifestations of multiple myeloma

Almost all patients of myeloma will, over a period of time, relapse. Treatment options for the relapsed patient will depend on not only the duration of remission by the initial first-line treatment but also on what first-line treatment the patient has received, most importantly, whether the patient has received a autologous stem cell transplantation (SCT) in the past or not. For the patient who has not been transplanted and does not have a contraindication to transplantation, the best option is consideration of a SCT. In the Indian context, because of a variety of reasons, socio-economic concerns being one of the foremost, only a small minority of patients undergo SCT, either as first-line or after relapse. In these patients, prior therapy and the duration of remission become important considerations while choosing treatment options during relapse. For example, the choice of treatment for relapse in a patient who has received thalidomide as single agent or in combination with steroids as first-line treatment will be different from the patient who has received only alkylating agents (melphalan or cyclophosphamide) and steroids as first-line therapy.

In the present review, the first-line treatment options will be briefly outlined after which consideration to the choices of treatment of the relapsed patients with special emphasis on the newer drugs will be highlighted. In the past few years, with the availability of new and effective anti-myeloma drugs, there has been a paradigm shift in the first-line treatment of this disease and this will also be discussed.

Multiple myeloma is a systemic malignancy of plasma cells that is highly treatable but rarely curable. It is potentially curable when it presents as a solitary plasmacytoma of bone or as an extramedullary plasmacytoma. The median survival in the pre-chemotherapy era was about 7 months. After the introduction of chemotherapy, prognosis improved significantly with a median survival of 24 to 30 months and a 10-year survival of 3%. Even further improvements in prognosis have occurred because of the introduction of newer therapies such as pulse corticosteroids, thalidomide, bortezomib, and autologous and allogeneic stem cell transplantation. The disease is staged by estimating the myeloma tumor cell mass on the basis of the amount of monoclonal (or myeloma) protein (M protein) in the serum and/or urine, along with various clinical parameters, such as the hemoglobin and serum calcium concentrations, the number of lytic bone lesions, and the presence or absence of renal failure. The stage of the disease at presentation is a strong determinant of survival, but it has little influence on the choice of therapy since almost all patients, except for rare patients with solitary bone tumors or extramedullary plasmacytomas, have generalized disease. Treatment selection is influenced by the age and general health of the patient, prior therapy, and the presence of complications of the disease[4].

Monoclonal gammopathy of undetermined significance or smoldering myeloma must be distinguished from progressive myeloma. Asymptomatic patients with multiple myeloma who have no lytic bone lesions and normal renal function may be initially observed safely[5,6]. Treatment should be given to patients with symptomatic advanced disease. Treatment should be directed at reducing the tumor cell burden and reversing any complications of disease, such as renal failure, infection, hyperviscosity, or hypercalcemia with appropriate medical management.

TREATMENT OPTIONS FOR THE NEWLY DIAGNOSED MYELOMA PATIENT

Treatment options for patients with symptomatic myeloma range from pulse dexamethasone with or without thalidomide, conventional chemotherapy to high-dose chemotherapy, and autologous peripheral stem cell transplantation or allogeneic bone marrow transplantation. Treatment choice is determined largely by the age and general health of the patient and should be finely attuned to the preferences of patients and their families.

Conventional chemotherapy using alkylators prolongs the survival of patients with symptomatic myeloma to a median of 40 to 46 months for patients with stage I disease, 35 to 40 months for patients with stage II disease, and 24 to 30 months for patients with stage III disease. At this time, however, most patients begin with nonalkylator therapy to avoid exposing the tumor to these types of drugs prior to autologous or allogeneic stem cell transplantation therapy, which involves high doses of the drugs. The two most common induction regimens are high-dose pulse dexamethasone with or without thalidomide[7-9] or VAD (vincristine + doxorubicin + dexamethasone)[10,11]. At this time, there are 5 active strategies for multiple myeloma:

1. High-dose corticosteroids.
2. Anti-angiogenic agents such as thalidomide or Linolidomide with or without corticosteroids
3. Conventional chemotherapy – oral or IV
4. Autologous or allogeneic peripheral stem cell transplantation.
5. Proteasome inhibitors such as bortezomib.

Typical chemotherapy regimens include:

1. VAD[10-12]
2. Oral thalidomide alone or in combination with high-dose dexamethasone[8,9,13-16].
3. High-dose dexamethasone.[7]
4. Cyclophosphamide plus prednisone[17].
5. Autologous or allogeneic stem cell transplantation[18-26].
   Bortezomib (proteasome inhibitor)[25].
7. Melphalan and prednisone (MP)[26, 27].
8. VBMCP (the M2 protocol: vincristine + carmustine + melphalan + cyclophosphamide + prednisone)[26].
9. VMCP/VBAP (vincristine + melphalan + cyclophosphamide + prednisone alternating with vincristine + carmustine + doxorubicin + prednisone)[26,28].

TO TRANSPLANT OR NOT TO TRANSPLANT?

There is now level-1 evidence from four well conducted randomized trials that autologous stem cell transplantation prolongs both disease-free as well as overall survival in patients with myeloma. All eligible and affordable patients of myeloma should be offered a transplant after stabilization of their disease with appropriate induction treatment. Because of a variety of reasons, the most important being socio-economic concerns, the majority of Indian patients are not candidates for a transplant. The strategies of treatment of patients who are candidates for SCT versus the patient, who is definitely not, are different.

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[29]. Many physicians use vincristine, doxorubicin, and dexamethasone for three to four months as induction therapy[10]. 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[6]. Thalidomide (at a dose of 200 mg per day) was given with dexamethasone (at a dose of 40 mg per day) on day 1 through 4, 9 through 12, and 17 through 20 (odd cycles) and on day 1 through 4 (even cycles). Each cycle was 28 day 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%, 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[16,30]. Deep-vein thrombosis was an unexpected adverse event in 12% of the patients in this trial. In a separate trial, the response rate with this regimen was 72%, and the use of prophylactic anticoagulation with warfarin or low-molecular-weight heparin prevented the occurrence of deep-vein thrombosis[9]. In a randomized trial comparing thalidomide plus dexamethasone with dexamethasone alone, the response rate with thalidomide plus dexamethasone was significantly better ($P=0.01$)[31].

Induction Therapy in Patients Not Eligible for Transplantation

Patients who are not eligible for transplantation because of age, poor physical condition, socio-economic reasons or coexisting conditions (the vast majority in India) 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 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[32]. 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[33]. 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)[34,35]. The mortality rate in western data is only 1 to 2%, and approximately 50% of patients can be treated entirely as outpatients. Well established BMT units in India now also have a mortality rate of less than 5%. 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[33]. 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)[37].

Tandem (double) Transplantation

In tandem (double) autologous stem-cell transplantation, patients undergo 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[38,39]. In a recent randomized trial conducted in France, event-free survival and overall survival were significantly better among recipients of tandem transplantation than among

Table 1: Major classes of drugs used in the treatment of multiple myeloma

Drug	*Regimen and usual starting dose*	*Response rate*		*References*
		New	*Relapse*	
ALKYLATING AGENTS				
Melphlan + Pred	Repeated q 6wks Mel-8-10 mg PO on days 1-7 Pred 60 mg per day PO on days 1-7	50-55	–	Myeloma trialist group
Combinations, e.g. VBMCP	Repeated q 5 wks VCR 0.03 mg/kg IV D-1 CCNU 0.5 mg/kg PO D 1-7 Mel 0.25 mg/kg PO D 1-7 CTX 10 mg/kg IV D-1 Pred 1mg/kg PO D 1-7	60	15	Myeloma trialist group
CORTICOSTEROIDS				
Pulse Dexamethasone	Repeated q 4 wks 40 mg PO D 1-4, 9-12 and 17-20	45	25-35	Alexanian
VAD	Repeated q 4 wks VCR 0.4 mg/kg IV continuous infusion D 1-4 Doxorubicin 9 mg.m.sq. IV cont. infusion D 1-4 Dexa 40 mg PO D 1-4, 9-12 and 17-20	55-65	25-50	Alexanian
THALIDOMIDE AND ANALOGUES				
Thalidomide	Repeated q 4 wks 200-400 mg PO D 1-28	35	25-45	Rajkumar Singhal
Thal + Dex	Repeated q 4 weeks Thal 200 mg PO D 1-28 Dex 40 mg PO D 1-4, 9-12 and 17-20	65-70	50	Juliusson Weber
Mel + Pred + Thal	Repeated q 4 wkly Mel 4 mg.m.sq. PO D 1-7 Pred 40 mg/m.sg PO D 1-7 Thal 100 mg PO D 1-28	80	–	Palumbo
CTX + Thal + Dex	Repeated q 3 wks CTX 50 mg PO D 1-211 Thal 200-800 mg PO D 1-21 DEX 40 mg PO D 1-4	–	75	Garcia-Sanz
Lenalidomide (Revelmid)	25-30 mg PO D 1-21 q 28 days	–	25	Richardson
Bortezomib	1.3 mg on D 1,4,8 and 11 q 21 days	–	21	Richardson

those who underwent a single autologous stem-cell transplantation (P=0.01)[40]. (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[41,42] (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% or more in monoclonal protein levels) with the first transplantation[40]. 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[43].

ALLOGENEIC TRANSPLANTATION

The advantages of allogeneic transplantation are a graft that is not contaminated with tumor cells and a graft-versus-myeloma effect[44,45]. However, a very small minority of patients are candidates for allogeneic transplantation when age, the availability of an HLA-matched sibling donor, expense, and adequate organ

Table 2: Results of major trials of autologous stem-cell transplantation in myeloma

Trial	*Comparison*	*No. of pts.*	*Outcome*	*Comment*
Intergroupe Francophone Du Myelome 90	Conventional dose chemotherapy with autologous BMT	200	Superior EFS and OS with BMT; 5 year survival 52% v/s 12% (p=0.03)	All pts less than 65 yr of age, all received maintenance IFN
Medical Research Council Myeloma VII	Conventional dose chemotherapy versus autologous SCT	401	Superior PFS and OS with SCT, 54 v/s 42 months (p=0.04)	All pts less than 65 yr of age
PETHEMA	Conventional dose chemotherapy versus autologous SCT	216	No difference in PFS or OS, median survival 65 v/s 67 months	Median age 56 yr only 164 pts responding to induction Rx underwent SCT
Intergroup S 9321	Conventional dose chemotherapy versus autologous SCT versus allogenic BMT	549	Median PFS 25 v/s 21 months (p=0.05) ; no sig difference in OS	52% pts assigned to chemo group received SCT at relapse
Myelome Autograffe	Early v/s delayed SCT	185	Median EFS 39 v/s 13 months; no sig difference in OS	All pts < 56 yr of age
Intergroupe Francophone Du Myelome 94	Single v/s double SCT	399	Superior EFS and OS with double SCT; 7 yr survival 42 v/s 21% (p=0.01)	All pts < 60 yr benefit of second SCT limited to pts who have less than good partial response to first SCT
Bologna 96	Single v/s double SCT	220	Superior EFS with double SCT; no sig difference in OS, 60 v/s 56 months	Interim analysis of first 220 pts
Myelome Autograffe 95	Single v/s double SCT	230	No difference in PFS or OS	All pts < 56 yr of age

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[46].

Several recent trials have used nonmyeloablative conditioning regimens (also referred to as "mini" allogeneic transplantation)[47]. 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[48]. The rate of treatment-related deaths was 15 to 20% with this strategy[49]. 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 beta$_2$-microglobulin), the overall survival with this approach may not be superior to that with tandem autologous stem-cell transplantation[50].

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[51]. Recent results from an intergroup trial showed no apparent benefit from the use of interferon as maintenance therapy.

A study by Berenson and colleagues[52] 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 underway to evaluate novel approaches, such as the use of thalidomide and dendritic-cell vaccination as maintenance therapy.

Novel antimyeloma agents are also being evaluated as maintenance therapy. Thalidomide has shown promise as maintenance therapy post-HSCT. Preliminary results of the randomized IFM 99-02 trial demonstrated improved PFS in the thalidomide plus pamidronate arm compared to no maintenance or pamidronate alone (56 versus 37 and 34%, respectively; P=0.01; median follow-up 36 months). At the time of the interim analysis, there were no differences yet observed in OS[53]. Despite initial good results, the use of thalidomide is associated with significant side effects that are dependent upon dose and treatment duration.

CHANGING PARADIGM FOR NEWLY DIAGNOSED MYELOMA

Traditionally, for those patients preselected for autologous stem cell transplantation (ASCT), the degree of clinical response with induction therapy has not been as important as the fact that the patient has actually undergone transplantation. In fact, it was assumed that with induction therapy, most patients would, at best, achieve only a partial response (PR), and even patients who achieved only a minor response to induction therapy would still go on to receive transplantation. Transplant patients have had better outcomes than non-transplant patients, particularly those non-transplant patients who achieved only minor responses to induction therapy.

However, with the introduction of novel agents, the old paradigm is being replaced by an entirely new treatment paradigm. Patients, rather than undergoing an up-front discussion about transplantation, are now being started on treatment regimens with novel agents that can significantly increase the chance of CR irrespective of age and other factors. This allows for the deferral of decisions about transplantation until after induction therapy has been completed. Moreover, patients receiving ASCT after achieving a CR to induction therapy may ultimately have better outcomes than patients who achieved only PR or minor responses, although this has yet to be confirmed in clinical trials.

The paradigm shift involving use of newer up-front therapies stems directly from the introduction of new therapeutic agents that have generated considerable interest in the multiple myeloma treatment community: immunomodulatory agents, such as thalidomide[8,9,16,31] and lenalidomide[54,55], and the proteasome inhibitor bortezomib[56-58]. These agents have been labeled "novel" because they have mechanisms of action that are more specific than those of traditional cytotoxic chemo-therapy. Both thalidomide and lenalidomide function as immunomodulators, whereas bortezomib is the first drug in its class to block the activity of a subcellular. These newer agents have been combined with dexamethasone with additive effect. Three drug combinations (the PAD regimen–PS-341/bortezomib, doxorubicin, dexamethasone)[58] are also being used in first-line as well as the relapse setting with very impressive response rates.

SUPPORTIVE CARE IN MYELOMA

Skeletal Complications

Skeletal involvement often leads to pain, pathologic fractures, hypercalcemia, or cord compression. These complications result from increased osteoclastic bone resorption. The increase in osteoclastic activity in multiple myeloma is mediated by the release of osteoclastic stimulating factors including interleukin 1 (IL-1), IL-6, and tumor necrosis factor. Bisphosphonates are specific inhibitors of osteoclastic activity and have been evaluated as adjunctive therapy to chemotherapy for multiple myeloma. Multiple randomized trials have reported significant improvement in bone pains and skeletal events after use of pamidronate and zoledronic acid[59-61].

Patients should be encouraged to be as active as possible, but they must avoid undue trauma. Fixation of fractures or pending fractures with an intramedullary rod and methylmethacrylate has produced good results. Bone pain should be treated with analgesics or narcotics, as necessary.

Hypercalcemia

Hypercalcemia occurs in 15% of patients with multiple myeloma at diagnosis and should be suspected in the presence of anorexia, nausea, vomiting, polyuria, polydipsia, increased constipation, weakness, confusion, or stupor. If hypercalcemia is untreated, renal insufficiency develops. Hydration plus prednisone (25 mg qid) is effective in most cases. The prednisone should be reduced in dosage and then discontinued as soon as the serum calcium becomes normal. If hypercalcemia persists, the patient should be treated with pamidronate or zoledronic acid.

Renal Failure

Approximately 20% of patients with multiple myeloma have a creatinine level of 2.0 mg/dl or more at diagnosis. The two major causes of renal insufficiency are "myeloma kidney" and hypercalcemia.

Dehydration, infection, nonsteroidal anti-inflammatory agents, and roentgenographic contrast media may contribute to acute renal failure. The risk of renal failure with roentgenographic contrast media is minimal if dehydration is avoided. Hyperuricemia may contribute to renal insufficiency but can be treated easily with allopurinol.

Maintenance of a high urine output (3 l/day) is important for preventing renal failure in patients with Bence Jones proteinuria. Prompt treatment of hypercalcemia and correction of dehydration and electrolyte imbalance are crucial.

Acute renal failure should be treated with appropriate fluid and electrolyte replacement. Alkalinization of the urine is useful. A prospective randomized trial in which renal biopsies were performed found that by the time cast formation reached an advanced stage, irreversible renal damage had already occurred and few of the patients responded to vigorous plasmapheresis. Patients with acute or subacute renal failure should be treated with VAD—vincristine and doxorubicin by continuous infusion for 96 hours plus dexamethasone, 40 mg daily on days 1-4, 9-12, and 17-20. A trial of plasmapheresis in younger patients with acute renal failure is recommended because renal biopsy is impractical in most instances. Hemodialysis or peritoneal dialysis is necessary in the event of symptomatic azotemia.

Anemia

Anemia occurs in almost all patients during the course of multiple myeloma. Subcutaneous erythropoietin was found to be useful in significant improvement in the patients' quality of life and an improved sense of well-being in randomized trials[62-64].

Infection

Patients should receive pneumococcal and influenza vaccinations despite their suboptimal antibody response. Prompt and appropriate therapy of bacterial infections is essential. Patients who present with a high fever and chills should have blood and urine cultures and a chest X-ray. Antibiotics should be started immediately and changed as results of cultures indicate. Prophylactic daily oral penicillin often benefits patients with recurrent pneumococcal infections. Since many infections occur in the first 2 months after the start of chemotherapy, the use of daily oral trimethoprim-sulfamethoxazole is helpful[62]. Intravenously administered gamma globulin may be beneficial for patients with recurrent infections, but it is inconvenient and expensive.

Neurologic Disorders

Spinal cord compression should be suspected in patients with severe back pain who develop weakness or paresthesias of the lower extremities, or have bladder or bowel dysfunction. Magnetic resonance imaging (MRI) or computed tomography must be done immediately. MRI is particularly useful in demonstrating extramedullary plasmacytoma. Radiation therapy and dexamethasone are usually effective, and surgical decompression is rarely necessary.

Hyperviscosity

Hyperviscosity is characterized by oral or nasal bleeding, blurred vision, paresthesias, headache, or congestive heart failure. It may result from high concentrations of IgA or, rarely, IgG. Serum viscosity levels do not correlate well with symptoms or clinical findings. Consequently, a decision to perform plasmapheresis depends on the symptoms and changes in the ocular fundus. Plasmapheresis promptly relieves the symptoms and should be done regardless of the viscosity level if the patient has signs or symptoms of hyperviscosity[66].

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 reinstituted (Table 3). In patients relapsing within 6 months or having refractory disease, new drugs and combinations should be used (Table 4). 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[65]. 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[69].

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[70]. Subsequently, the efficacy of thalidomide in erythema nodosum leprosum, 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[71]. In 1998, the Food and Drug Administration (FDA) approved the use of thalidomide in the treatment of erythema nodosum leprosum. The drug is approved and available in India for use in relapse as well as for first-line treatment of patients with myeloma and is marketed by many Indian pharmaceutical companies.

Table 3: Treatment options for patients who have received one form of primary treatment

Disease status	*Treatment options*
Responsive	• Continuation of current therapy until plateau is reached • Autologous stem cell transplant • Allogeneic stem cell transplant if a HLA matched-donor is available
Stable	• Continuation of current therapy until plateau is reached • Autologous stem cell transplant • Allogeneic stem cell transplant
Plateau	• Observation, with supportive care as required • Maintenance therapy with steroids, interferon or thalodomide • Autologous stem cell transplant
Refractory disease	• Salvage chemotherapy, thalidomide, or thalidomide plus dexamethasone, bortezomib, or bortezomib plus steroids
Relapsed disease	• Repeat of primary therapy if relapse occurs after 6 months of discontinuing therapy • Salvage chemotherapy, thalidomide, or thalidomide plus dexamethasone, or Bortezomib, or bortezomib plus steroids depending on the speed of disease progression • Allogeneic stem cell transplant

Table 4: Treatment options for patients who myeloma have received more than one therapy for myeloma

Disease status	*Treatment options*
Responsive	• Observation, with supportive care as required • Maintenance therapy with steroids or interferon • Autologous stem cell transplant • Continuation current therapy until plateau • Stem cell transplant (autologous or allogeneic)
Stable	• Observation, with supportive care as required • Maintenance therapy with steroids or interferon
Plateau	• Observation, with supportive care as required • Maintenance therapy with steroids or interferon • Stem cell transplant (autologous or allogeneic)
Refractory disease	• Salvage chemotherapy, thalidomide, or thalidomide plus dexamethasone, Bortezomib, or bortezomib plus steroids • Salvage therapy • Allogeneic stem cell transplant
Relapsed disease	• Salvage chemotherapy, thalidomide, or thalidomide plus dexamethasone, Bortezomib, or bortezomib plus steroids • Salvage therapy • Allogeneic stem cell transplant

Clinical Trials

Trials with thalidomide as an anticancer agent were unsuccessful in the 1960s. 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% in patients with relapsed and refractory disease[13]. Since then, several studies have confirmed the activity of thalidomide in relapsed myeloma, with response rates ranging from 25 to 35%[72-74]. The responses are durable, with a median duration of approximately 12 months[72]. Thalidomide had limited activity in extramedullary (soft-tissue) disease in one study.

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%[75-77] and to more than 70% when used in a three-drug combination of thalidomide, dexamethasone, and an alkylating agent (either cyclophosphamide or melphalan)[74]. 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[78]. 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% in patients receiving thalidomide alone but increases to 10 to 15% in patients receiving the drug in combination with dexamethasone and to about 25% in patients receiving the drug in combination with other cytotoxic chemotherapeutic agents, particularly doxorubicin[72,74]. Other adverse effects include edema, bradycardia, neutropenia, impotence, and hypothyroidism. The use of thalidomide in pregnancy is absolutely contraindicated.

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[79]. 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[79]. Proposed mechanisms include the inhibition of tumor necrosis factor alpha, 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. Thalidomide may also inhibit the activity of NF-kappa-B and the enzymes cyclooxygenase-1 and cyclooxygenase-2 (Fig. 2).

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. The original multinational brand as well as one generic form of the drug is presently available in India.

Clinical Trials

In preclinical models, bortezomib showed substantial activity against many cancers, including myeloma. Its promising efficacy against myeloma was noted in a phase 1 dose-finding study conducted by Orlowski and colleagues[80]. On the basis of these observations, a phase 2 multicenter trial of intravenous bortezomib in myeloma was initiated[81]. Of 193 patients who could be evaluated, 92% had received three or more of the major classes of agents for myeloma, and in 91% the disease had been refractory to the most recent treatment. The partial-response rate with bortezomib was 27%, and 4% 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[81].

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 also was completed recently[82]. 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% of those receiving 1.0 mg per square meter and in 50% of those receiving 1.3 mg per square meter. 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[58]. 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[81]. In 19 of these patients (18%), there was a response to the addition of dexamethasone with a reduction of at least 25% 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[56,57].

Adverse Effects

The most common adverse effects of bortezomib are gastrointestinal symptoms, cytopenia, fatigue, and peripheral neuropathy[81]. A decrease in the platelet count to less than 50,000 per cubic millimeter occurs in almost 30% of patients. Peripheral neuropathy, often painful, develops in approximately 30% of patients and is more frequent in those who have previously received neurotoxic therapy and those with a preexisting neuropathy.

Dosing

The recommended starting dose is 1.3 mg per square meter administered on days 1, 4, 8 and 11 of a 21-day cycle[81]. Reductions to 1.0 mg per square meter or, if needed, to 0.7 mg per square meter may be necessary, depending on the toxic effects.

Mechanism of Action

Bortezomib is a specific inhibitor of the 26S proteasome, a large intracellular adenosine 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. 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. 2). One of the consequences of proteasome inhibition is the accumulation of I-kappa-B, an inhibitor of the major transcription factor NF-kappa-B.

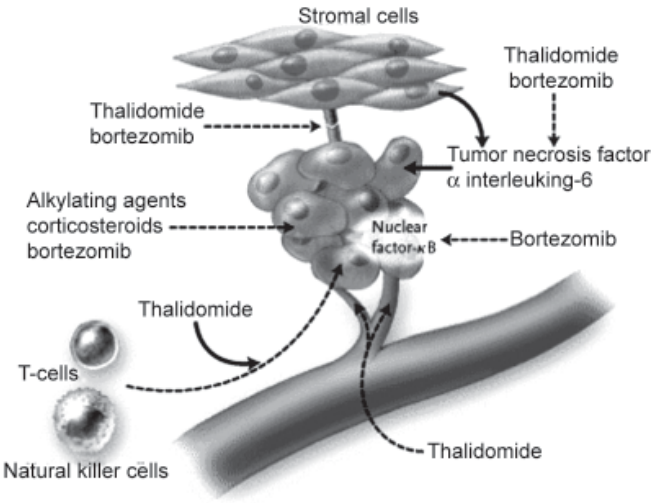

Fig. 2: Proposed mechanism of action of drugs to target the myeloma cell and components of the bone marrow microenvironment

LENALIDOMIDE (REVELMID)

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. It also inhibits angiogenesis and promotes cytotoxicity mediated by natural killer cells[83].

In two phase 2 trials of CC-5013, there was a reduction of at least 50% in monoclonal protein levels in approximately 30% of patients with relapsed myeloma, and myelosuppression was the major dose-limiting toxic effect[84,85]. A multicenter, randomized phase 2 study in which the subjects had relapsed refractory myeloma was recently completed[58]. In 24% of 83 patients who could be evaluated, there was a reduction of at least 50% 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% of patients, and neutropenia (i.e. a neutrophil count of less than 1000 per cubic millimeter), which occurred in 28% of patients. Common adverse effects observed with thalidomide, however, such as sedation, constipation, and neuropathy, were not observed.

OTHER NOVEL AGENTS

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

SUMMARY AND CONCLUSIONS

There have been major advancements in the treatment of multiple myeloma in the past one to two decades. In addition to the myeloma cell, the bone marrow microenvironment now is being targeted. With the availability in the market of several new classes of drugs, the complete remission rates and the response durations in the patient with myleoma has been progressive increasing. Even though most patients of myeloma cannot be cured today, prolonged survivals is possible in a substantial majority of patients.

One or two stem cell transplants should be offered to all patients of myeloma after disease stabilization with an appropriate regimen. Post-transplant maintenance with steroids or thalidomide is now standard of care. New agents and combinations with drugs like thalidomide, linalidomide, bortezomib are effective in the patient who relapsed after transplant. These newer agents are now being used up front in the newly diagnosed patient and new paradigms of treatment are emerging. Multiple clinical trials addressing various clinical questions and dilemmas are ongoing and results are expected in the new future.

REFERENCES

1. Rajkumar SV, Kyle RA. Multiple myeloma: diagnosis and treatment. Mayo Clin Proc 2005;80(10):1371-82.
2. He Y, Wheatley K, Clark O, et al. Early versus deferred treatment for early stage multiple myeloma. Cochrane Database Syst Rev 2003;(1):CD004023.
3. Riccardi A, Mora O, Tinelli C, et al. Long-term survival of stage I multiple myeloma given chemotherapy just after diagnosis or at progression of the disease: a multicentre randomized study. Cooperative Group of Study and Treatment of Multiple Myeloma. Br J Cancer 2000;82(7):1254-60.
4. Alexanian R, Dimopoulos MA, Delasalle K, et al. Primary dexamethasone treatment of multiple myeloma. Blood 1992;80(4):887-90.
5. Rajkumar SV, Gertz MA, Lacy MQ, et al. Thalidomide as initial therapy for early-stage myeloma. Leukemia 2003;17(4):775-9.
6. Weber D, Rankin K, Gavino M, et al. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. J Clin Oncol 2003;21(1):16-9.
7. Alexanian R, Barlogie B, Tucker S: VAD-based regimens as primary treatment for multiple myeloma. Am J Hematol 1990;33(2):86-9.
8. Segeren CM, Sonneveld P, van der Holt B, et al. Vincristine, doxorubicin and dexamethasone (VAD) administered as rapid intravenous infusion for first-line treatment in untreated multiple myeloma. Br J Haematol 1999;105(1):127-30.
9. Anderson H, Scarffe JH, Ranson M, et al. VAD chemotherapy as remission induction for multiple myeloma. Br J Cancer 1995;71(2):326-30.
10. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999;341(21):1565-71.
11. Richardson P, Schlossman R, Jagannath S, et al. Thalidomide for patients with relapsed multiple myeloma after high-dose chemotherapy and stem cell transplantation: Results of an open-label multicenter phase 2 study of efficacy, toxicity, and biological activity. Mayo Clin Proc 2004;79(7):875-82.
12. Juliusson G, Celsing F, Turesson I, et al. Frequent good partial remissions from thalidomide including best response ever in patients with advanced refractory and relapsed myeloma. Br J Haematol 2000;109(1):89-96.
13. Rajkumar SV, Hayman S, Gertz MA, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. J Clin Oncol 2002;20(21):4319-23.
14. Bergsagel DE, Stewart AK. Conventional-dose chemotherapy of myeloma. In: Malpas JS, Bergsagel DE, Kyle RA, et al: Myeloma: Biology and Management. 3rd ed. Philadelphia, Pa: WB Saunders Co, 2004;203-17.
15. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. N Engl J Med 1996;335(2):91-7.
16. Stewart AK, Vescio R, Schiller G, et al. Purging of autologous peripheral-blood stem cells using CD34 selection does not improve overall or progression-free survival after high-dose chemotherapy for multiple myeloma: Results of a multicenter randomized controlled trial. J Clin Oncol 2001;19(17):3771-9.
17. Lenhoff S, Hjorth M, Holmberg E, et al. Impact on survival of high-dose therapy with autologous stem cell support in patients younger than 60 years with newly diagnosed multiple myeloma: a population-based study. Nordic Myeloma Study Group. Blood 2000;95(1):7-11.
18. Desikan R, Barlogie B, Sawyer J, et al. Results of high-dose therapy for 1000 patients with multiple myeloma: durable complete remissions and superior survival in the absence of chromosome 13 abnormalities. Blood 2000;95(12):4008-10.
19. Reynolds C, Ratanatharathorn V, Adams P, et al. Allogeneic stem cell transplantation reduces disease progression compared to autologous transplantation in patients with multiple myeloma. Bone Marrow Transplant 2001;27(8):801-7.
20. Badros A, Barlogie B, Siegel E, et al. Improved outcome of allogeneic transplantation in high-risk multiple myeloma

patients after nonmyeloablative conditioning. J Clin Oncol 2002;20(5):1295-303.

21. Bladé J, Vesole DH, Gertz Morie. High-dose therapy in multiple myeloma. Blood 2003;102(10):3469-70.
22. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003;348(26):2609-17.
23. Gregory WM, Richards MA, Malpas JS. Combination chemotherapy versus melphalan and prednisolone in the treatment of multiple myeloma: an overview of published trials. J Clin Oncol 1992;10(2):334-42.
24. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. Myeloma Trialists' Collaborative Group. J Clin Oncol 1998;16(12):3832-42.
25. Durie BG, Dixon DO, Carter S, et al. Improved survival duration with combination chemotherapy induction for multiple myeloma: a Southwest Oncology Group Study. J Clin Oncol 1986;4(8):1227-37.
26. Goldschmidt H, Hegenbart U, Wallmeier M, Hohaus S, Haas R. Factors influencing collection of peripheral blood progenitor cells following high-dose cyclophosphamide and granulocyte colony-stimulating factor in patients with multiple myeloma. Br J Haematol 1997;98:736-44.
27. Ghobrial IM, Dispenzieri A, Bundy KL, et al. Effect of thalidomide on stem cell collection and engraftment in patients with multiple myeloma. Bone Marrow Transplant 2003;32:587-92.
28. Rajkumar SV, Blood E, Vesole D, et al. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2006;24(3):431-6.
29. Myeloma Trialists' Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. J Clin Oncol 1998;16:3832-42.
30. Rajkumar SV, Gertz MA, Kyle RA, Greipp PR. Current therapy for multiple myeloma. Mayo Clin Proc 2002;77:813-22.
31. Bladé J, Vesole DH, Gertz M. Transplantation for multiple myeloma: who, when, how often? Patient selection and goals. Blood 2003;102:3469-77.
32. Kumar A, Loughran T, Alsina M, Durie BG, Djulbegovic B. Management of multiple myeloma: a systematic review and critical appraisal of published studies. Lancet Oncol 2003;4:293-304.
33. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m2 melphalan and 8 Gy total body irradiation plus 140 mg/m2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. Blood 2002;99:731-35.
34. Palumbo A, Bringhen S, Petrucci MT, et al. A prospective randomized trial of intermediate dose melphalan (100 mg/m2) vs. oral melphalan/prednisone. Blood 2004;104(10):3052-7.
35. Barlogie B, Jagannath S, Vesole DH, et al. Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. Blood 1997;89:789-93.
36. Barlogie B, Jagannath S, Desikan KR, et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. Blood 1999;93:55-65.
37. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 2003;349:2495-2502.
38. Cavo M, Tosi P, Zamagni E, et al. The "Bologna 96" clinical trial of single vs. double autotransplants for previously untreated multiple myeloma patients. Blood 2002;100:179a-179a. abstract.
39. Fermand J-P, Alberti C, Marolleau J-P. Single versus tandem high dose therapy (HDT) supported with autologous blood stem cell (ABSC) transplantation using unselected or CD34-enriched ABSC: results of a two by two designed randomized trial in 230 young patients with multiple myeloma (MM). Hematol J 2003;4:Suppl 1:S59-S59. abstract.
40. Sirohi B, Powles R, Singhal S, et al. High-dose melphalan and second autografts for myeloma relapsing after one autograft: results equivalent to tandem autotransplantation. Blood 2001;98:402a-402a. abstract.
41. Mehta J, Singhal S. Graft-versus-myeloma. Bone Marrow Transplant 1998;22:835-43.
42. Gahrton G, Svensson H, Cavo M, et al. Progress in allogeneic bone marrow and peripheral blood stem cell transplantation for multiple myeloma: a comparison between transplants performed 1983-93 and 1994-98 at European Group for Blood and Marrow Transplantation centres. Br J Haematol 2001;113:209-16.
43. Lokhorst HM, Segeren CM, Verdonck LF, et al. Partially T-cell-depleted allogeneic stem-cell transplantation for first-line treatment of multiple myeloma: a prospective evaluation of patients treated in the phase III study HOVON 24 MM. J Clin Oncol 2003;21:1728-33.
44. Einsele H, Schafer HJ, Hebart H, et al. Follow-up of patients with progressive multiple myeloma undergoing allografts after reduced-intensity conditioning. Br J Haematol 2003;121:411-18.
45. Maloney DG, Sahebi F, Stockerl-Goldstein KE, et al. Combining an allogeneic graft-vs-myeloma effect with high-dose autologous stem cell rescue in the treatment of multiple myeloma. Blood 2001;98:434a-435a. abstract.
46. Maloney DG, Molina AJ, Sahebi F, et al. Allografting with nonmyeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. Blood 2003;102:3447-54.
47. Moreau P, Garban F, Facon T, et al. Preliminary results of the IFM9903 and IFM9904 protocols comparing autologous followed by miniallogeneic transplantation and double autologous transplant in high-risk de novo multiple myeloma. Blood 2003;102:43a-43a. abstract.
48. Myeloma Trialists' Collaborative Group. Interferon as therapy for multiple myeloma: an individual patient data overview of 24 randomized trials and 4012 patients. Br J Haematol 2001;113:1020-34.
49. Berenson JR, Crowley JJ, Grogan TM, et al. Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. Blood 2002;99:3163-68.
50. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, et al. Maintenance treatment with thalidomide

and pamidronate after autologous transplantation for myeloma: second analysis of a prospective randomized study of the Intergroupe Francophone du Myelome. Haematol/Hematol J 2005;90:19 PL 4.01.

51. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood 2005;106:4050-53.
52. Niesvizky R, Pekle K, Gelbshtein U, et al. BiRD (Biaxin, Revlamid, Dexamethasone) combination therapy results in high complete remissions and overall responses in multiple myeloma with poor prognostic features. Program and abstracts of the 47th Annual Meeting of the American Society of Hematology; December 10-13, 2005; Atlanta, Georgia. Abstract 642.
53. Adams J, Kauffman M. Development of the proteasome inhibitor Velcade (bortezomib). Cancer Invest 2004;22:304-11.
54. Oakervee HE, Popat R, Curry N, et al. PAD combination therapy (PS-341/bortezomib, doxorubicin and dexamethasone) for previously untreated patients with multiple myeloma. Br J Haematol 2005;129:755-62.
55. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352:2487-98.
56. Berenson J, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. N Eng J Med 1996;334:488-93.
57. Berenson J, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. J Clin Oncol 1998;16:593-602.
58. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of tumor-induced hypercalcemia: a pooled analysis. Proc Am Soc Clin Oncol 2000;19:605a .
59. Garton JP, Gertz MA, Witzig TE, et al. Epoetin alfa for the treatment of anemia of multiple myeloma. Arch Intern Med 1995;155:2069-74.
60. Österborg A, Boogaerts MA, Cimino R, et al. Recombinant human erythropoietin in transfusion-dependent anemic patients with multiple myeloma and non-Hodgkin's lymphoma-a randomized multicentre study. Blood 1996;87:2675-82.
61. Ludwig H, Leitgenb C, Pecherstorfer M, Fritz E. Quality of life during erythropoietin therapy in chronic anemia of cancer. (abstract). Proc Am Soc Clin Oncol 1993;12:401 .
62. Oken MM, Pomeroy C, Weisdorf D, et al. Prophylactic antibiotics for the prevention of early infection in multiple myeloma. Am J Med 1996;100:624 -28.
63. Gertz MA, Kyle RA. Hyperviscosity syndrome. J Intensive Care Med 1995;10:128-41.
64. Gertz MA, Lacy MQ, Inwards DJ, et al. Early harvest and late transplantation as an effective therapeutic strategy in multiple myeloma. Bone Marrow Transplant 1999;23:221-26.
65. Hussein MA, Wood L, Hsi E, et al. A phase II trial of pegylated liposomal doxorubicin, vincristine, and reduced-dose dexamethasone combination therapy in newly diagnosed multiple myeloma patients. Cancer 2002;95:2160-68.
66. Gertz MA, Garton JP, Greipp PR, Witzig TE, Kyle RA. A phase II study of high-dose methylprednisolone in refactory or relapsed multiple myeloma. Leukemia 1995;9:2115-18.
67. Lenz W. Thalidomide and congenital abnormalities. Lancet 1962;1:45-45.
68. Rajkumar SV, Mesa RA, Tefferi A. A review of angiogenesis and anti-angiogenic therapy in hematologic malignancies. J Hematother Stem Cell Res 2002;11:33-47.
69. Barlogie B, Desikan R, Eddlemon P, et al. Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a phase 2 study of 169 patients. Blood 2001;98:492-94.
70. Rajkumar SV, Fonseca R, Dispenzieri A, et al. Thalidomide in the treatment of relapsed multiple myeloma. Mayo Clin Proc 2000;75:897-901.
71. Dimopoulos MA, Anagnostopoulos A, Weber D. Treatment of plasma cell dyscrasias with thalidomide and its derivatives. J Clin Oncol 2003;21:4444-54.
72. Weber DM, Rankin K, Gavino M, Delasalle K, Alexanian R. Thalidomide with dexamethasone for resistant multiple myeloma. Blood 2000;96:167a-167a. abstract.
73. Palumbo A, Giaccone L, Bertola A, et al. Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma. Haematologica 2001;86:399-403.
74. Anagnostopoulos A, Weber D, Rankin K, Delasalle K, Alexanian R. Thalidomide and dexamethasone for resistant multiple myeloma. Br J Haematol 2003;121:768-71.
75. Ghobrial IM, Rajkumar SV. Management of thalidomide toxicity. J Support Oncol 2003;1:194-205.
76. Eriksson T, Bjorkman S, Hoglund P. Clinical pharmacology of thalidomide. Eur J Clin Pharmacol 2001;57:365-76.
77. Orlowski RZ, Stinchcombe TE, Mitchell BS, et al. Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies. J Clin Oncol 2002;20:4420-27.
78. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003;348:2609-17.
79. Berenson JR, Jagannath S, Barlogie B, et al. Experience with long-term therapy using the proteasome inhibitor, bortezomib, in advanced multiple myeloma (MM). Prog Proc Am Soc Clin Oncol 2003;22:581. abstract
80. Dredge K, Marriott JB, Macdonald CD, et al. Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects. Br J Cancer 2002;87:1166-72.
81. Zangari M, Tricot G, Zeldis J, Eddlemon P, Saghafifar F, Barlogie B. Results of phase I study of CC-5013 for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (HDCT). Blood 2001;98:775a-5a. abstract.
82. Richardson PG, Schlossman RL, Weller E, et al. Immuno-modulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood 2002;100:3063-67.