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Multiple Myeloma: An Old Disease with New Hope for the Future

Adnan A. Zaidi, MD; David H. Vesole, MD, PhD, FACP

ABSTRACT Multiple myeloma is a currently incurable malignancy of terminally differentiated plasma cells. It typically occurs in older patients (median age 71 years). Clinical manifestations result from monoclonal protein (immunoglobulin) production and its accumulation in the serum and/or urine, anemia, lytic bone disease, hypercalcemia, renal insufficiency, and immune deficiency. Myeloma cells have low proliferative activity—most myeloma experts opine that the initial oncogenic event occurs 10-15 years before clinical disease manifestation. In addition, myeloma cells develop multiple chromosomal abnormalities, which may explain the native resistance of myeloma patients to conventional therapy and our inability to completely eradicate the disease.

Indeed, with conventional therapy, only 5% of patients achieve complete response. Minimal improvement has been observed with conventional therapies over the past 20-30 years; the median duration of initial response remains approximately 18 months with median survival in the 36-month range. However, recent clinical trials have established high-dose therapy with autologous hematopoietic stem cell transplant as superior to conventional therapy: complete remission rates of 25-30% can be affected with median survival exceeding 5 years.

Newer approaches to improve treatment outcomes are in active clinical trials including: more potent induction regimens utilizing thalidomide, alone or in combination with dexamethasone; tandem transplants to improve complete remission rates; newer approaches to maintenance therapy using thalidomide with corticosteroids; non-myeloablative therapy with allogeneic transplant; and post-transplant vaccinations. (*CA Cancer J Clin* 2001;51:273-285.)

INTRODUCTION

Multiple myeloma is a malignancy of terminally differentiated B-lymphocytes. It is characterized by the clonal proliferation of plasma cells that are innately resistant to standard doses of chemotherapy. This systemic malignancy is highly treatable but rarely curable. Although skeletal evidence for the existence of multiple myeloma has been obtained from Egyptian mummies, the major clinical features of multiple myeloma were first described around 1850 in England. Recently, tremendous advances have been made in understanding the biology and developing treatments of multiple myeloma. This article deals with etiology, diagnosis, and the current treatment options for newly diagnosed and previously treated patients with multiple myeloma. It also discusses future treatment directions.

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ETIOLOGY

The etiology of multiple myeloma remains unknown. Risk factors are thought to include chronic immune stimulation, autoimmune disorders, exposure to ionizing radiation, occupational exposure to pesticides or herbicides, occupational exposure to dioxin, and perhaps, prolonged use of certain hair coloring products.^{1,2} Schwartz in his analysis of eight multiple myeloma “clusters,” observed an association between increased risk of multiple myeloma and proximity to dioxin-contaminated water sources and consumption of dioxin-contaminated fish.² Myeloma has been associated with exposure to Agent Orange during the Vietnam War.³ A number of viruses have been implicated in the pathogenesis of myeloma. Patients with HIV have a 4.5-fold increased likelihood of developing myeloma,⁴ although the exact mechanisms are unclear. The recent finding of human herpesvirus 8 (HHV-8) infection in bone marrow stromal cells in multiple myeloma patients may be associated with the development and progression of the disease.⁵ HHV-8 has also been identified in stromal cells of other plasma cell dyscrasias, such as monoclonal gammopathy of undetermined significance (MGUS) and primary systemic amyloidosis, implying a potential causal association. However, this association is not universally accepted.⁶ The Myeloma Intergroup of France has identified 20 families through myeloma family studies, where the risk of developing myeloma is as high as 5%.⁷

Hallek et al.⁸ proposed a model for the pathogenesis for multiple myeloma with an ordered progression from a normal plasma cell to MGUS to multiple myeloma. Cells are immortalized, but not transformed, when normal plasma cells progress to MGUS, and these do not progressively accumulate or cause bone destruction. Later this changes to intramedullary myeloma, where the cells are confined to the bone marrow micro-

environment where they accumulate and cause bone destruction via cytokine-induced increased osteoclast activity. In some patients, the disease evolves to extramedullary myeloma, where the cells proliferate more rapidly and circulate in the peripheral blood (plasma cell leukemia) or other extramedullary sites.

Interleukin-6 (IL-6) is essential for the survival and growth of myeloma cells, which express specific receptors for this cytokine.⁹ IL-6 was initially found to be a growth factor for myeloma cells, but recently it was also shown to promote the survival of myeloma cells by preventing spontaneous or dexamethasone-induced apoptosis. There is increasing evidence that IL-6 is an autocrine and paracrine growth factor. It is produced by the myeloma cells as well as stromal cells in the bone marrow microenvironment. Myeloma cells also shed the soluble form of IL-6 receptor, which can amplify the response of myeloma cells to interleukin-6. IL-6 receptor is present in high amounts in the serum of patients with myeloma, especially those with a poor prognosis. Finally, IL-6 also has a role in the pathogenesis of bone lesions in multiple myeloma. IL-6, soluble IL-6 receptor, and interleukin-1 (beta) activate osteoclasts in the vicinity of myeloma cells and, thus, provoke bone resorption. Other growth factors that seem to be important for multiple myeloma include granulocyte-colony stimulating factor, interferon- α and interleukin-10.

EPIDEMIOLOGY

The median age at diagnosis of multiple myeloma is 71 years. Age, race and gender significantly affect the incidence. There are approximately 14,400 new cases of multiple myeloma diagnosed each year and 11,200 deaths.¹⁰ The overall incidence rate in the United States is 4/100,000/year. The male/female ratio is 1:4. The incidence rate in African

Americans is 9.6/100,000/year.¹¹ With the aging of the US population, there is an increase in the cases of multiple myeloma. Myeloma accounts for 1% of all malignancies: 10% of all hematological malignancies in Caucasians and 20% in African Americans.¹² The reason for the higher incidence in women and African Americans is not known. It should be emphasized that MGUS is 80–100 times more common than multiple myeloma and three-fourths of these remain without conversion to multiple myeloma over 20+ years.

Signs and Symptoms

Signs and symptoms of multiple myeloma include bone pain, which may be present in three-fourths of patients. Osteolytic lesions and compression fractures may be seen in the axial skeleton and proximal long bones—the most common being the spine. There is an increased osteoclastic activity in myeloma patients mediated by osteoclastic stimulating factors including IL-1, IL-6 and TNF. These factors are produced locally in the bone marrow micro-environment by tumor and stromal cells.^{13,14} These cytokines may also serve as myeloma growth factors and prevent apoptosis.

Increased bone resorption may lead to hypercalcemia, which may present as lethargy, nausea, and constipation as well as renal insufficiency in one-third of patients. Renal insufficiency is often multi-factorial but is predominantly due to the development of “myeloma kidney” in which the distal convoluted tubules and collecting tubules become obstructed with casts consisting mainly of Bence Jones (monoclonal urinary light chain) protein. There is also light chain deposition in the mesangium. Renal insufficiency occurs in one-third of all patients. Hypercalcemia exacerbates the nephrotoxicity of Bence Jones proteins.

Cytokine dysregulation leads to impaired erythropoiesis, resulting in anemia in more than

75% of patients. Many patients have low levels of endogenous erythropoietin. IL-6 and other cytokines may inhibit erythroid lineage synthesis.⁹ Approximately 60% of multiple myeloma patients respond to exogenous erythropoietin.

Cellular and humoral immune dysfunction are commonly observed in multiple myeloma. Susceptibility to pneumococcal pneumonia and infections with other encapsulated bacteria, is enhanced in the setting of multiple myeloma in part due to diminished production of normal immunoglobulins and subsequent opsonization. Compromised cellular immunity is manifested as an increase in the incidence of herpes zoster in multiple myeloma patients.

Neurological dysfunction is common during the course of the disease. This may be from spinal cord compression (upper motor signs) manifested as back pain, sciatica, or muscle weakness as a result of epidural encroachment by plasmacytomas; hyperviscosity (headache, blurring of vision progressive obtundation, vertigo, hemiparesis, seizure); or a demyelinating neuropathy as a paraneoplastic manifestation of the myeloma paraprotein.

Laboratory Evaluation

The standard evaluation of a patient with suspected myeloma includes:

- complete blood count with differential.
- blood chemistry profile including calcium, creatinine, LDH, albumin, and uric acid.
- bone marrow aspirate and biopsy with cytogenetics and plasma cell labeling index (this may need a reference lab).
- complete skeletal survey.
- serum and urine electrophoresis with immunofixation to identify the M protein and quantification of this protein. Urine sample should be a 24-hour urine collection. Serum protein electrophoresis (SPEP) shows a monoclonal spike in 85% of multiple myeloma patients. Urine

TABLE 1

Diagnosis of Multiple Myeloma, Indolent Myeloma, Smoldering Myeloma, and Monoclonal Gammopathy of Undetermined Significance (MGUS)

Multiple Myeloma

Major Criteria

- I Plasmacytoma on tissue biopsy
- II Bone marrow plasmacytosis with > 30% plasma cells
- III Monoclonal globulin spike on serum electrophoresis
 - > 3.5 g/dl for IgG
 - >2 g/dl for IgA
 - ≥ 1 g/24 hr for κ or λ Bence Jones proteinuria

Minor Criteria

- a Bone marrow plasmacytosis 10-30%
- b Monoclonal globulin spike
 - < 3.5 g/dl for IgG
 - < 2 g/dl for IgA
 - ≤ 1 g/24 hr for κ or λ Bence Jones proteinuria
- c Lytic bone lesions
- d Uninvolved immunoglobulin levels IgM < 50 mg/dl, IgA < 100 mg/dl, or IgG < 600 mg/dl

Diagnosis of Multiple Myeloma

In a symptomatic patient requires a minimum of one major + one minor criterion
 I + b, I + c, I + d (not I + a)
 II + b, II + c, II + d
 III + a, III + c, III + d
 or three minor criteria that must include a + b
 a + b + c or a + b + d

Indolent Myeloma

No bone lesions or limited bone lesions (≤ 3 lytic lesions) no compression fractures
 M protein levels IgG ≤ 7 g/dl, IgA ≤ 5 g/dl
 No symptoms or associated disease features
 Performance status > 70%
 Hemoglobin > 10 g/dl
 Serum calcium normal
 Serum creatinine < 2 mg/dl
 No infections

Smoldering Myeloma

Same as indolent myeloma except:
 No bone lesions
 Bone marrow plasma cells ≤ 30%

Monoclonal Gammopathy of Undetermined Significance (MGUS)

Monoclonal gammopathy
 M protein level: IgG ≤ 3.5 g/dl, IgA ≤ 2 g/dl, BJ protein ≤ 1 g/24 hr
 Bone marrow plasma cells < 10%
 No bone lesions, no symptoms

electrophoresis shows a globulin spike in 75% of patients. Sixty percent of the patients have a monoclonal protein that is immunoglobulin G (IgG), 20% IgA, 1% IgD or non-secretory, and 15% are light chain only.

- serum beta-2 microglobulin, C-reactive protein.

Diagnosis

Table 1 provides the diagnostic criteria for multiple myeloma, smoldering myeloma, indolent myeloma and MGUS.¹⁵

CLASSICAL STAGING SYSTEM

In 1975, the Durie-Salmon Staging System was published to distinguish patients with low (Stage I), intermediate (Stage II) and high (Stage III) volumes of tumor mass before institution of therapy (Table 2).¹⁶ Each of these three stages are divided into substages A (serum creatinine < 2 mg/dl) and B (serum creatinine ≥ 2 mg/dl). It is included for the sake of completeness and is largely of historical value.

Prognostic Factors

Although the Durie-Salmon Staging System was the classic nomenclature to stage myeloma patients, recent advances in the biology and treatment of myeloma indicate that this staging system does not accurately predict event-free and overall survival. Other parameters as shown in Table 3, seem to have more clinical significance^{17,18} and when available should be done as part of the initial work-up. The strongest predictors of a favorable outcome that are routinely available are low beta-2 microglobulin and C-reactive protein. Other predictors of a favorable outcome, often only available at reference laboratories, are absence of chromosome 13 abnormalities on metaphase

cytogenetic karyotyping (or more recently by fluorescent in situ hybridization; FISH) and low plasma cell labeling index.

TREATMENT

Supportive Care

Skeletal involvement often leads to pain, pathological fractures, hypercalcemia, or cord compression. These complications result from increased osteoclastic bone resorption. Bisphosphonates are inhibitors of osteoclastic activity. Bisphosphonates may reduce tumor burden by changes in bone microenvironment, as well as promoting apoptosis of tumor cells and, thus, may have a direct effect on multiple myeloma.^{19,20} Therefore, patients with multiple myeloma who have lytic bone lesions or osteopenia should be given bisphosphonates. Pamidronate should also be used in cases of persistent hypercalcemia. The currently available bisphosphonate, pamidronate, has been shown to reduce skeletal complications and skeletal morbidity and to improve quality of life.²¹ Pamidronate is administered over 1-2 hours intravenously (90 mg) every four weeks. In addition to the reduction in skeletal events and bone pain, one randomized study suggests that some subgroups of patients treated with pamidronate have improved disease-free and overall survival compared with placebo.²² A newer bisphosphonate, zoledronic acid, will soon be available. This is a more potent bisphosphonate (100 to 1000-fold *in vitro*) that can be infused over a shorter period (15 minutes).²³

Anemia occurs in almost all multiple myeloma patients during their disease course. Up to 60% of patients respond to erythropoietin injections²⁴ even in the absence of renal insufficiency. There is a significant improvement in the patients' quality of life and sense of well being.²⁵

TABLE 2

Assessment of Tumor Mass
<p>High Tumor Mass (Stage III) ($> 1.2 \times 10^{12}$ tumor cells/m³)</p> <p>One of the following abnormalities must be present:</p> <ul style="list-style-type: none"> Hemoglobin < 8.5 g/dl Serum calcium > 12 mg/dl Very high myeloma protein production <ul style="list-style-type: none"> IgG peak > 7 g/dl IgA peak > 5 g/dl Bence Jones protein > 12 g/24 hour > 3 lytic lesions on bone survey (bone scan not acceptable)
<p>Low Tumor Mass (Stage I) ($< 0.6 \times 10^{12}$ malignant cells /m³)</p> <p>All of the following must be present:</p> <ul style="list-style-type: none"> Hemoglobin > 10.5 g/dl or hematocrit > 32 volume % Serum calcium normal Low myeloma protein production <ul style="list-style-type: none"> IgG peak < 5 g/dl IgA peak < 3 g/dl Bence Jones protein < 4 g/24 hour No bone lesions
<p>Intermediate Tumor Mass (Stage II) ($0.6-1.2 \times 10^{12}$ malignant cells/m³)</p> <p>All patients who do not qualify for high or low tumor mass are considered to have intermediate tumor mass.</p>

Infections are common in myeloma patients in part due to decreased production of normal immunoglobulins. Patients who present with fever should be evaluated with appropriate cultures and radiographic studies and started on antibiotics. Streptococcal infections are a particular concern. Fever is rarely due to myeloma itself and an infectious etiology should be sought. The use of daily oral trimethoprim-sulfamethoxazole (TMP-SMX) or some other broad-spectrum antibiotic such as a fluoroquinolone may be helpful when administered prophylactically during initial therapy.²⁶ To further investigate the importance of prophylactic antibiotics, there is an international randomized trial comparing fluoroquinolones versus TMP-SMX versus observation in newly diagnosed patients during the first two months of therapy (U1099).

TABLE 3

Favorable Prognostic Factors in Multiple Myeloma
Beta-2 microglobulin \leq 2.5 mg/l*
C-reactive protein \leq 4.0 mg/dl*
No -13/13q- chromosome abnormalities
Plasma cell labeling index less than 1%
Absence of plasmablastic morphology
\leq 12 months prior treatment
Chemotherapy sensitive disease
Any complete remission
Non IgA isotype (controversial)
Low Interleukin-6 receptor
* Routinely available to all physicians and should be done as part of initial work-up.

Patients who have IgA multiple myeloma have an increased risk for hyperviscosity due to the dimeric and polymeric forms of the IgA molecule. Hyperviscosity is characterized by oral bleeding, epistaxis, blurred vision, headache, sausageing of retinal veins, paresthesias, or congestive heart failure. Plasmapheresis should be promptly initiated if the patient has signs and symptoms of hyperviscosity.²⁷ Serum viscosity is measured by a blood test available in most hospital laboratories.

STANDARD CHEMOTHERAPY

The median survival in the pre-chemotherapy era was 7 months. After the introduction of chemotherapy, prognosis improved significantly with median survival of 24 to 30 months.²⁸ The mainstay of treatment for multiple myeloma includes glucocorticoids, which are most effective at higher doses, alkylating agents and local radiation. Melphalan and prednisone have been the gold standard for treatment for the last 30 years.²⁹ The addition of anthracyclines, combinations of alkylating agents, or interferon has resulted in minimal

improvement in treatment outcomes. A meta-analysis of 27 trials and 6,633 myeloma patients, comparing treatment with melphalan and prednisone to combination chemotherapy, revealed no significant difference in the survival of patients receiving either of these two forms of therapy.³⁰ Cumulative exposure to melphalan, however, is associated with an increasing risk of marrow toxicity, including myelodysplasia, acute leukemia and impaired stem cell production.³¹ This is an important consideration in patients who are candidates for high dose therapy with stem cell rescue (autologous transplants).

With conventional therapy, only 5% of patients achieve complete remission. Molecular analysis shows rapid development of MDR1 (multidrug resistance 1) gene expression in multiple myeloma patients. Attempts at overcoming drug resistance due to MDR1 activity (e.g., PSC 833, cyclosporine, quinine, verapamil) have met with limited success and are associated with increased toxicity.³²

Salvage therapy is needed for patients who have either relapsed or have primary refractory disease. VAD (vincristine + adriamycin + dexamethasone) benefits 40-50% of relapsing patients and about 30% of those with primary unresponsive disease.³³ The most active agent in the combination is dexamethasone. High dose dexamethasone pulsing alone induces responses in about 30-40% of patients regardless of prior response.³⁴

Thalidomide was recently reported as effective salvage therapy in patients with refractory multiple myeloma. Singhal et al.³⁵ reported a response rate of 32% in heavily pretreated patients with oral thalidomide as a single agent. Reduction in paraprotein was evident within 2 months in most responders. Thalidomide is reasonably well tolerated; the toxicities include somnolence, constipation, and occasionally peripheral neuropathy. The mode of action of thalidomide is unknown: Angiogenesis inhibition, possibly by down-regulation of VEGF (vascular endothelial

growth factor), immune modulation, by increasing NK cell activity, interleukin-2 and gamma interferon, and increasing apoptosis have been proposed. Thalidomide combined with dexamethasone pulsing has shown promising results in previously treated^{36,37} and in newly diagnosed patients.³⁸ Thalidomide combined with conventional chemotherapy agents as salvage therapy^{39,40} and induction therapy is under investigation. Thalidomide as maintenance therapy is also actively being studied.⁴¹

AUTOLOGOUS TRANSPLANTS

With conventional therapy, there has been minimal improvement in treatment outcomes for multiple myeloma in the past 15–20 years. To overcome the native (at the time of diagnosis) resistance of myeloma cells to conventional chemotherapy, high-dose therapy requiring autologous hematopoietic stem cell support was first evaluated in patients with refractory disease.^{42,43} This resulted in improved response rates and survival. This approach was then extended to newly diagnosed patients. In 1996, the seminal randomized study on symptomatic stage II and III patients by the French Myeloma Intergroup showed conclusively that high-dose therapy yielded a superior disease-free and overall survival outcome compared with conventional therapy.⁴⁴ The 5-year projected survival for the transplant group was 52% versus 12% for the conventional therapy group. Whereas complete responses were observed in only 5% of the conventional therapy group, 22% of the high-dose therapy group achieved complete remissions. The transplant-related mortality was only 2.7%. In a non-randomized trial, the University of Arkansas group has used tandem transplants as consolidation therapy for newly diagnosed multiple myeloma patients.⁴⁵ The researchers observed overall response rates

exceeding 75% and complete response rates (intent-to-treat) of 38% following tandem transplants. Transplant-related mortality was less than 8% at one year for all patients and for patients less than 65 it was closer to 1%. Patients achieving complete response had a median disease-free survival of 50 months and median overall survival more than 7 years.

In general, high-dose therapy with autologous transplant nearly doubles median survival for newly diagnosed patients. High-dose therapy with autologous stem cell transplantation is now considered appropriate care for front-line therapy in many newly diagnosed multiple myeloma patients, particularly those younger than 70 years of age. High-dose therapy with autologous transplant for patients with disease relapse has not been evaluated in randomized or pair-matched case controls. In previously treated patients with chemotherapy sensitive relapse, 75% of transplanted patients achieved 75% tumor reduction, including true complete responses of 10–15%.⁴⁶ The median relapse-free survival and overall survival is on the order of 2 and 3 years, respectively. In patients with refractory relapse, high-dose therapy with autologous stem cell transplant resulted in a median event-free survival and overall survival of 11 and 19 months, respectively.⁴⁷

Although high-dose therapy with autologous transplantation is now considered appropriate care for many newly diagnosed patients, there are still clinical investigations into the timing of transplant—either upfront as consolidation therapy or as salvage therapy at the time of relapse. A French Myeloma Intergroup study did not show a significant difference in overall survival when they randomized 184 patients to early versus late transplant (median survival approximately 5 years). They did observe a superior quality of life in the early transplant group since the disease-free survival was 39 months versus 13 months.⁴⁸ The North American Intergroup

study (S9321) comparing early to late transplant met its accrual goal in October 2000. Results of this trial are not expected for 2–3 years.

Another area of clinical research is whether tandem transplant is superior to single transplant. The Arkansas group has reported improved complete remissions with tandem transplant with the best results observed in patients with less than 12 months of prior therapy who received tandem transplants within 6 months.^{13,17,45} The French Myeloma Intergroup has completed a randomized trial comparing single with tandem transplant. The final analysis of this trial is not yet completed. The preliminary results show no difference in overall survival between groups at a median follow-up of 4 years.⁴⁹ However, in the most recent subgroup analysis, patients receiving tandem transplants with peripheral blood stem cell support had a superior outcome to patients receiving tandem bone marrow transplants or single stem cell or bone marrow transplants. In addition there are two other randomized trials comparing single to tandem transplant, which have not been completed. Until the final analysis of these trials is available, tandem transplants cannot be considered standard of care.

Transplant-related mortality is low, less than 3% in patients younger than 65 years and 5–8% in patients older than 65 years.⁵⁰ Unfortunately, even with tandem transplants, there does not appear to be a plateau in post-transplant survival curves indicating that cures are unlikely with this approach.^{17,43–48,38–43} Novel new approaches are imperative to improve outcomes.

ALLOGENEIC BONE MARROW TRANSPLANT

As indicated above, the use of high-dose therapy with autologous hematopoietic stem cell transplant has been shown to be superior to conventional therapy. However, there does not appear to be a plateau in the disease-free survival indicating that cures with autologous

transplantation are unlikely. This may be due to either infusion of stem cell grafts contaminated with myeloma cells and/or the inability to eradicate minimal residual disease even with tandem transplants.

Allogeneic transplantation offers two advantages: The absence of tumor-contaminated grafts and the benefit of a graft-versus-myeloma effect.^{51,52} Compared with autologous transplantation, fewer allogeneic transplants have been performed. This is due to the advanced age (median 71 years) at diagnosis and limited availability of histocompatible donors; less than 10% of patients are candidates for allotransplantation. Although long-term, disease-free survival has been observed following allotransplantation, the treatment-related mortality for multiple myeloma is excessively high, ranging from 20% to 50% in the first 100 days post-transplant.^{53,54} The North American Intergroup trial (S9321) allowed allogeneic transplantation in patients younger than 55 who had HLA identical sibling donors. Patients underwent allogeneic transplantation following four cycles of VAD and high-dose cyclophosphamide (4.5 g/m²). This arm of the study was prematurely closed when the transplant-related mortality was 41% in the first 36 patients (R. Kyle, personal communication).

Patients who survive the initial transplant-related toxicities have prolonged disease-free outcomes and may be cured. The European Blood and Marrow Transplant Registry (EBMT) have reported the largest database. Gharion et al.⁵⁵ reported an improvement in treatment outcomes with allogeneic bone marrow transplantation over the preceding 5 years due to a significant improvement in survival, which was the result of a reduction in transplant-related mortality. The median survival with allogeneic transplantation from 1984–1993 was 12 months and from 1994–1999, the median survival had improved to 43 months. Before 1994, transplant-related mortality at 12 months was 40% compared with 20% after 1994 due to de-

creased incidence in infectious pulmonary complications. An additional evaluation of the EBMT database compared the outcomes of syngeneic, allogeneic and autologous transplantation. The overall 4-year survival rate with syngeneic transplantation was 77%, with autotransplantation 46%, and with allotransplantation 31%.⁵⁶

There is evidence that immune regulation may be a vital component of the high response rates and low relapse rates following allogeneic transplantation for multiple myeloma. A number of small studies have observed a graft-versus-myeloma effect using donor leukocyte infusions or immunosuppression withdrawal for patients who have relapsed following allogeneic transplant.^{51,52} Approximately 50% of patients respond with a graft-versus-myeloma effect to donor leukocyte infusions. This was most frequently observed in patients with a concomitant graft-versus-host disease. Unfortunately, many of these responses were not durable.

As indicated above, the transplant-related mortality with allogeneic transplant is exceedingly high. No specific prognostic factor has been determined to explain the higher transplant-related mortality. Most clinicians are hesitant to subject a patient to this risk knowing that autologous transplants result in median overall survival of 5+ years. However, recently, a number of transplant centers have been using non-myeloablative transplants ("mini-transplants") for a number of hematologic malignancies including multiple myeloma.^{57,58} The basis of the 'mini-transplant' is to provide sufficient immune suppression to allow donor engraftment and subsequent graft-versus-tumor effect. Preliminary data showed a high rate of complete remission, even in heavily treated patients with resistant disease.⁵⁷ At the American Society of Hematology meeting in December 2000, there were 120 abstracts describing non-myeloablative therapy. A number of these included patients with multiple myeloma,

including one by Lalancette et al. that presented the European Bone Marrow Transplant Registry results from 50 patients.⁵⁸ All patients engrafted, 20 of 27 evaluable patients achieved 95% donor engraftment: New complete remission (CR) was observed in 16, continuous CR (CCR) 1, new partial remission (PR) 7, continuous PR 12. Transplant-related mortality at one year was 32%, relapse incidence 13%. The actuarial survival at one and two years was 54% and 40%, respectively. Unfortunately, most responses were not durable. To improve outcomes with this approach, the Eastern Cooperative Oncology Group will soon initiate a protocol using an autologous transplant for maximal tumor cytoreduction to be followed by a "mini-transplant" intended to eradicate minimal residual disease (E4A98). A pilot trial using this approach has shown high response rates (53% CR).⁵⁹

MAINTENANCE THERAPY

Interferon

The use of interferon for maintenance therapy following conventional chemotherapy is controversial. Although there are data that indicate interferon slightly improves relapse-free survival following conventional therapy, there is only a single study suggesting that interferon improves overall survival.⁶⁰ Although an initial study from the Italian Myeloma study group in 1990 reported improvement in relapse-free and overall survival with interferon maintenance therapy,⁶¹ a 10-year follow-up report by this group did not show any survival advantage.⁶² A meta-analysis of 24 randomized trials consisting of more than 4000 patients treated with interferon showed a minimal benefit in relapse-free and overall survival to the interferon-treated patients.⁶³ In autologous transplants, a single randomized trial of maintenance interferon following high-dose

melphalan initially suggested a survival benefit, but longer follow-up revealed no survival benefit.⁶⁴ Consequently, outside of a clinical trial, IFN therapy cannot be strongly recommended for maintenance therapy.

Steroids

The Southwest Oncology Group reported improved relapse-free and overall survival using prednisone maintenance therapy. Patients responding to VAD were randomized to either 10 mg or 50 mg of prednisone every other day until relapse. Patients receiving the higher prednisone dose (50 mg) had improved outcomes without any significant differences in toxicities.⁶⁵

FUTURE DIRECTIONS

Current clinical investigations are aimed at improving disease outcomes in each of the principle treatment phases: Induction therapy, high-dose therapy, maintenance and salvage therapy.

Induction Therapy

Since the Centers for Medicare and Medicaid Services (formerly the Health Care Financing Administration) now approves reimbursement of high-dose therapy with autologous transplant for newly diagnosed patients (and select previously treated patients) up to age 78, patients being considered for transplantation should not receive alkylating agent-based induction therapy, which may compromise future transplant options. Recent data indicate that thalidomide combined with high-dose dexamethasone pulsing results in response rates of more than 75%.³⁸ This combination alleviates the need of 96-hour chemotherapy infusions, insertion of in-dwelling catheters and the subsequent risk of

catheter-associated thrombosis in patients receiving VAD chemotherapy. The Eastern Cooperative Oncology Group is planning a Phase II clinical trial comparing induction therapy with dexamethasone alone versus dexamethasone/thalidomide. The Arkansas group is currently completing "Total Therapy II" which uses thalidomide for induction pre-transplant and as maintenance therapy post-transplant.

¹⁶⁶Holmium-DOTMP is referred to as a skeletal targeted radiotherapy (STR) product. The β radiation is provided by the ¹⁶⁶Holmium and is attached to DOTMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonic acid), which is a drug that is bone seeking. This selective radiation minimizes toxicity. ¹⁶⁶Holmium-DOTMP has been used with high-dose chemotherapy as preparation for auto-logous stem cell transplantation in patients with multiple myeloma; the therapy was well tolerated with a complete response rate of 53%.⁶⁶ Another skeletal targeted radiotherapeutic compound, ¹⁵³Samarium is also being combined with high-dose chemotherapy with autologous stem cell transplant.⁶⁷ Phase III studies will be needed to further assess the overall impact on remission rates and survival.

The regimen-related toxicities of most high-dose therapy regimens are oral mucositis and gastrointestinal toxicity. These prevent the full exploitation of the log-linear dose-response effect of certain antineoplastic agents. To increase the maximum tolerated dose of high-dose therapy, trials using cytoprotective agents, such as amifostine⁶⁸ or keratinocyte growth factor, are actively being pursued with promising preliminary results. It is hoped that increased dose intensity will result in higher response rates and improved survival.

Maintenance Therapy

Following the success of thalidomide in the salvage setting, thalidomide is now being

evaluated as maintenance therapy either alone or with corticosteroids.

Another new area is the development of vaccines. Several studies have demonstrated that myeloma protein, also called idiotype (Id), is sufficiently immunogenic and can be used to generate *in vivo* T-cell and B-cell responses in myeloma patients.⁶⁹⁻⁷¹ Clinical trials using Id-pulsed dendritic cells (DC) as a vaccine to treat minimal residual disease or relapsed myeloma are currently underway. Feasibility studies indicate that antigen-pulsed autologous DCs can be used to elicit *in vivo* Id-specific T-cell and B-cell responses. Additional studies are needed to optimize current DC vaccination protocols and determine clinical benefits associated with this approach. Interleukin-2 (IL-2) alone or with GM-CSF is also being used with or without vaccines to effect immunomodulation.⁷² Data suggest that high-serum levels of IL-2 correlate with longer survival in patients with multiple myeloma. Animal and laboratory studies indicate that IL-2 has anti-tumor activity. Non-myeloablative "mini transplants" are being refined and these may offer the potential for cure with reduced toxicity. Again, longer follow-ups are needed.⁵⁷⁻⁵⁹

Salvage Therapy

As discussed above, thalidomide has been shown to be an effective therapeutic modality in the setting of disease relapse. Thalidomide is now being used with other chemotherapeutic agents. The University of Arkansas group study of two combination chemotherapy regimens: DT-PACE (combining dexamethasone, thalidomide-cisplatin, adriamycin, cyclophosphamide, and etoposide)^{39,40} and DCEP (dexamethasone, cyclophosphamide, etoposide,

and cisplatin) indicated remarkable activity in far advanced and high-grade multiple myeloma.⁷³ Arsenic trioxide has also been shown to be active against high-risk refractory multiple myeloma with 23% response rates⁷⁴ when used alone or with butathione sulfoxime (BSO).⁷⁵ Pilot trials are in development including farnesyl transferase inhibitors (FTI),⁷⁶ angiogenesis inhibitors, such as immunomodulatory thalidomide derivatives (IMiDs), 2-methoxy estradiol (2-ME2), the proteasome inhibitor LDP-341,⁷⁷ shark cartilage derivatives (Neovastat; AE941), and agents to increase apoptosis such as bcl-2 oligo-nucleotide antisense proteins (Genasense).

CONCLUSION

Newly diagnosed patients up to the age of 78 (HCFA guidelines) should be considered for autologous stem cell transplantation. Patients under the age of 70 with an HLA compatible donor should be considered for a non-myeloablative "mini-transplant" in clinical trials. With relapsed patients, steroids with thalidomide appear to be the most promising intervention. Patients with chemosensitive disease should be considered for salvage high-dose therapy followed by autologous transplants or non-myeloablative allogeneic transplant. Patients should be sent to centers of excellence with a focus in multiple myeloma for clinical trials whenever possible. This will help advance our understanding of disease biology and refine treatment options. With an improved understanding of the myeloma biology, and with target therapy tailored to each patient, the goal of a cure in this disease has never been more promising. CA

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Erratum

In the September/October 2001 issue, in the article “Multiple Myeloma: An Old Disease with New Hope for the Future” (Zaidi AA, Vesole DH. *CA Cancer J Clin* 2001;51;273-285), an error appeared on page 274.

The statement which read: “The overall incidence rate in the United States is 4/100,000/year. The male/female ratio is 1:4,” was printed incorrectly. The statement should have read: “The overall incidence rate in the United States is 4/100,000/year. The male/female ratio is 1.4:1.”

We apologize for this error and any confusion it may have caused.