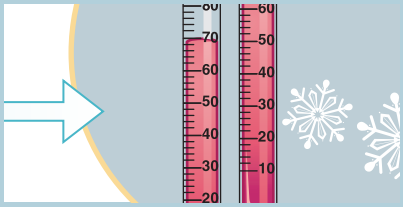
abstract



Multiple myeloma (MM) is a neoplasm of plasma cells that is characterized by tumour cell tropism of the bone marrow and production of monoclonal immunoglobulins (Ig) detectable in serum and/or urine. It often manifests as one or more of lytic bone lesions, monoclonal protein in the blood or urine, disease in the bone marrow, renal failure, anemia, and hypercalcemia. Better understanding of the biology of myeloma has led to the development of agents, such as bortezomib, CC-5013, and thalidomide, that target the myeloma cell and the bone-marrow microenvironment. Ongoing trials promise to define the roles of new agents, mini-allogeneic transplantation, and maintenance therapy.

Key words: *bone marrow, biology, transplant, chemotherapy, multiple myeloma*

Management of Multiple Myeloma

Manmeet S. Ahluwalia, MD, *Department of Internal Medicine, Fairview Hospital, Cleveland Clinic Health System, Cleveland, OH, USA.*

Hamed A. Daw, MD, *The Cleveland Clinic Cancer Center, Cleveland, OH, USA.*

Introduction

Multiple myeloma (MM) is a neoplastic disorder characterized by proliferation of a single clone of plasma cells derived from B cells.[1] There have been major changes in the treatment regimens in the last decade or so and, although MM still remains an incurable disease, new treatment options promise more hope for the people with this disorder.[2]

Epidemiology

MM represents one percent of all malignancies in whites and two percent in African-Americans. Among hematological malignancies, it constitutes 10% of the tumours and ranks as the second most frequently occurring hematological cancer in the United States after non-Hodgkin's lymphoma. An estimate of 15,980 new cases of multiple myeloma will occur in the United States in 2005, resulting in 11,300 deaths.[3] In Canada, approximately four to five new cases per 100,000 persons are diagnosed each year, and an estimated 590 people will die from this cancer in 2005.

The disease is twice as common in men as it is in women. The incidence is higher in African-Americans and lower in Asians than in Caucasians. The incidence of myeloma and other plasma cell disorders increases with advancing age. The median age at diagnosis is 68 years.[4]

Risk Factors

Exposure to ionizing radiation is the strongest single factor linked to an increased risk of MM. This has been documented in atomic bomb survivors with a five times greater incidence than the control group and a latent period of approximately 20 years from exposure. Exposure to metals, especially nickel; agricultural chemicals; benzene, petroleum products, and other aromatic hydrocarbons; and silicon have been considered as potential risk factors. Alcohol and tobacco consumption has not been clearly linked to myeloma. Among medications, only mineral oil used as a laxative has been reported to be associated with an increased risk of MM in some patients.

Clinical Manifestations

Patients with MM may be entirely asymptomatic and diagnosed on routine blood testing or may present with myriad symptoms including fatigue due to anemia, frequent infections due to low uninvolved immunoglobulin or low CD4 count, and bone pain due to pathologic fracture.[1] Renal failure can manifest as nausea and vomiting. Patients can present with paraplegia or nerve compression secondary to cord compression or neurological involvement (Table 1).

Biology of Multiple Myeloma

The bone-marrow microenvironment consists of extracellular matrix proteins, osteoblasts, osteoclasts, stromal cells, myeloma cells, vascular endothelial cells, and lymphophytes. The complex interactions between the myeloma cells, stromal cells, and adhesion molecules lead to production of cytokines and the factors involved in angiogenesis, thereby playing a key role in the pathogenesis of MM. Interleukin-6 (IL-6) is an important cytokine in myeloma cell growth and proliferation.[5] Interaction between myeloma cells and the bone marrow stromal cells leads to production of IL-6 that supports the growth of these cells

and also protects them from apoptosis. In addition, IL-6 enhances the effect of other osteoclastogenic factors, macrophage inflammatory protein-1a (MIP-1a), IL-1, and tumor necrosis factor a (TNFa).

Nuclear factor-kappa B (NF-kB) is a protein that is presently believed to be pivotal to the pathogenesis of MM and, hence, has become a major area of focus of myeloma treatment in the last few years. NF-kB is a p50/RelA heterodimer (p50/p65) present in the cytoplasm of almost all cells.[6,7] NF-kB regulates cell growth and apoptosis, as well as the expression of various cytokines, adhesion molecules, and their receptors.[8] Activated NF-kB leads to increased expression of various cytokines and chemokines, adhesion molecules, and cyclin D, promoting cell growth and survival.[9] It also increases expression of adhesion molecules

Table 1: Clinical Manifestations

Symptom	Mechanism	Treatment options
Fatigue	A normochromic normocytic anemia is usually observed in myeloma patients due to tumour cell involvement of the marrow, as well as inadequate erythropoietin responsiveness.	Erythropoietin administration is an important supportive care therapy for patients with symptomatic anemia.
Nausea, vomiting/uremia	The etiology of renal failure can be multifactorial and includes light-chain deposition disease, hypercalcemia and hypercalciuria leading to osmotic diuresis, volume depletion, and prerenal azotemia. In addition, light-chain tubular casts lead to interstitial nephritis (myeloma kidney).	Hydration and avoidance of nonsteroidal anti-inflammatory drugs and intravenous contrast agents that may aggravate the renal failure are recommended.
Loss of appetite, fatigue, muscle weakness, restlessness, difficulty in thinking or confusion, constipation	Hypercalcemia	Hydration with intravenous fluids, steroids, and furosemide are recommended.
Bone pain	Tiny fractures in the bones caused by accumulation of plasma cells and weakened bone structures. The mechanism of bone abnormalities in myeloma, especially destruction, is an unbalanced process of increased osteoclast activity and suppressed osteoblast activity. These changes are due to an increase in osteoclast-activating factors produced predominantly by the bone marrow microenvironment but also by myeloma cells.	Proper positioning and support; appropriate physical therapy; bisphosphonates; radiation therapy; and kyphoplasty or vertebroplasty for spinal fractures are recommended.
Recurrent infections	Deficiencies in both humoral and cellular immunity predispose patients to the development of recurrent bacterial infections. Various factors including high monoclonal Ig levels, soluble Fc receptor in serum, and transforming growth factor-β (TGF-β) lead to suppression of B-cell function, which in turn leads to depressed level of uninvolved Igs. Immunosuppressive cytokines, secreted by the microenvironment, such as TGF-, can lead to significant T-cell dysfunction. Corticosteroids that are often given as part of a treatment regimen also increase the risk of infection in these patients.	Antibiotic therapy and intravenous immunoglobulin therapy are recommended.

Source: Adapted from www.multiplemyeloma.org

Table 2: Initial Workup

Patient evaluation
Serum protein electrophoresis
Quantitative immunoglobulin
Serum-free light chains
24-hour urine for total protein and Bence Jones protein
Immunofixation of urine and serum protein
Complete blood cell count with reticulocyte and differential count
Blood chemistry renal function tests, calcium, albumin, uric acid, lactate dehydrogenase
β2-microglobulin levels
C-reactive protein
Bone marrow aspirate and biopsy for cytogenetics, flow cytometry (DNA-cIg), and plasma cell labelling index
Magnetic resonance imaging
Computerized axial tomography (CAT) scan
Skeletal survey
Bone densitometry

Adapted from: DeVita VT, Hellman S, Rosenberg S, Eds. Cancer: principles & practice of oncology, 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2005.

such as ICAM-1 and VCAM-1 by MM cells and upregulates IL-6 secretion by the stromal cells, contributing to drug resistance.[10,11] Therefore, strategies targeting NF-kB, the malignant cell-stroma interaction, angiogenesis, and the complex cytokine network have become the focus of MM treatment.

Diagnosis

The diagnosis of multiple myeloma is often made incidentally during routine blood tests for other conditions.[1] However, when an older patient presents with new onset of unexplained back pain or bone pain, fatigue secondary to anemia, renal failure, or recurrent infections, they should be screened for myeloma.[1] Additional laboratory findings such as hyperproteinemia or proteinuria, hypoalbuminemia, low Ig levels, or marked elevation of erythrocyte sedimentation rate should prompt a further complete evaluation for diagnosis of plasma cell dyscrasia. The workup of the patient should include a number of laboratory tests and medical procedures to help confirm a diagnosis of myeloma. These tests should be conducted on all patients as part of an initial evaluation. New diagnostic criteria requires the presence of at least 10% plasma cells on examination of the bone marrow (or biopsy of a tissue with monoclonal plasma cells), monoclonal protein in the serum or urine, and evidence of end-organ damage.[12] The end-organ damage is defined by a group of findings referred to as CRAB: calcium elevation in the blood, renal insufficiency, anemia, and bone lesions. Patients meeting these diagnostic criteria and lacking a detectable monoclonal protein are considered to have nonsecretory myeloma. Some of these tests are not only used to assess the extent of disease but also to plan and monitor treatment. Initial workup of the patient includes a number of tests (Table 2).

Staging Systems

Proper staging of myeloma is important not only when determining prognosis but also when developing a treatment plan. The Durie-Salmon system has been the most widely used staging system since 1975.[13] In this system, the clinical stage of disease is based on several measurements, including levels of M protein, the number of bone lesions, hemoglobin values, and serum calcium levels. Each stage can be further divided into subclass A or B according to renal function as determined by serum creatinine levels.

Recently, the Durie-Salmon staging system has been less frequently used and physicians have relied more on biologically relevant markers as prognostic indicators when making treatment choices. A new International Staging System (ISS) for myeloma, based on serum levels of beta-2 microglobulin (β2-M) and albumin, has been proposed. This system appears to better discriminate between staging groups and can be widely used since it is based on easily measured markers (Table 3).[14]

Prognostic Factors

MM patients can have variable disease course with survival ranging from less than one year to more than 10 years. Several clinical and laboratory tests provide important prognostic information. These prognostic factors are crucial as they help determine tumour growth, extent of disease, tumour cell biology, overall health status of the patient, response to therapy, and, more importantly, help predict life expectancy after diagnosis (Table 4).[15]

Management Options

Therapy for MM is individually tailored according to each patient's need. There is no established standard therapy for MM. Treatment of myeloma is a complex process that involves many variables that must be taken into account, such as the patient's health status, disease course, previous therapy (if any), and response to previous therapy. Patients with newly diagnosed myeloma typically receive some form of initial therapy. In addition, they receive

bisphosphonates and supportive care as required to treat bone disease and other complications of the disease.

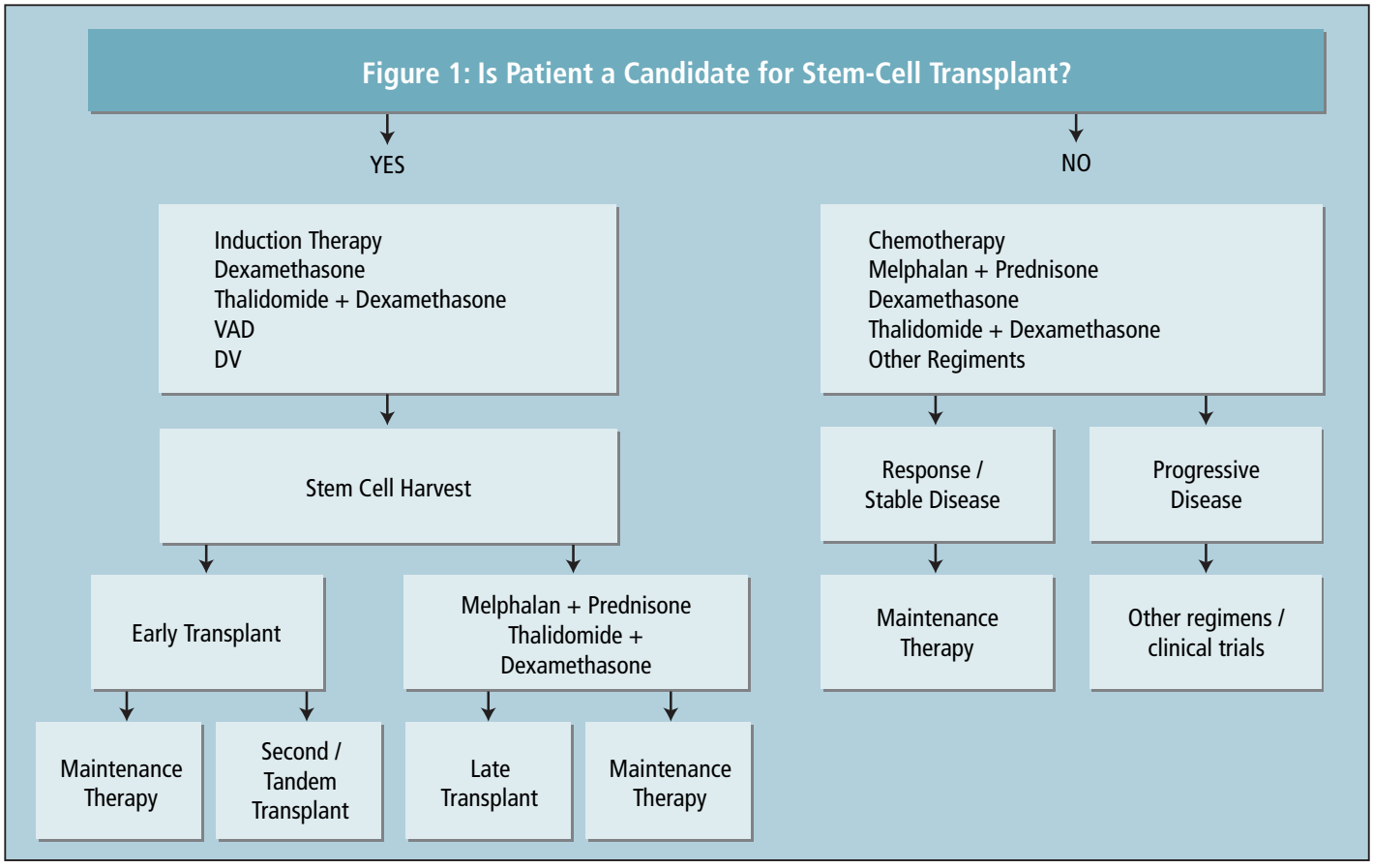
The choice of initial therapy is dependent on whether a patient is a candidate for stem cell transplant, a therapeutic strategy that, although not curative, has led to improved response rates, disease free survival, and overall survival in myeloma and is a major advance in myeloma treatment.[16] Patients under the age of 65 in good physical condition are generally considered to be good potential transplant candidates. However, older patients may be eligible if they are in very good health (Figure 1).

Transplant Candidates

Patients who are eligible for autologous stem-cell transplantation (Figure 2) are first treated with a regimen that is not toxic to hematopoietic stem cells. In these patients, an alkylating agent such as melphalan may impair the ability to collect stem cells for use in an autologous transplant and, hence, is best avoided or used very cautiously. These patients often receive a combination chemotherapy regimen such as VAD (vincristine, doxorubicin, and dexamethasone),[17] a modification of the VAD regimen such as DVd (liposomal doxorubicin, vincristine, and short-schedule dexamethasone), or alternatively, dexamethasone or a combination of thalidomide and dexamethasone. Stem cells are collected from the patient when reduced tumour burden is achieved after three or four cycles of induction therapy with any of the abovementioned regimens. After stem cell collection, transplant candidates may proceed directly to an autologous transplant, referred to as an early transplant. In an alternative approach, such patients continue to receive their initial therapy until plateau (minimum 12 months of therapy and achievement of stable disease for two months) is achieved. These patients then receive their transplant at the time of relapse (late transplant). Early transplantation is preferred as it not only minimizes a patient's time on chemotherapy but also aims to improve overall quality of life of the patient.

Tandem (Double) Transplant

In tandem stem-cell transplantation, patients undergo a second planned stem-cell transplantation after they have recovered from the first. Tandem transplantation was developed at the University of Arkansas by Dr. Barlogie and colleagues in an attempt to improve complete-response rates.[18] In a recent randomized trial conducted in France, event-free survival and overall survival were significantly better among recipients of tandem transplantation in comparison to those who underwent single autologous stem-cell transplantation (P=0.01).[19] However, preliminary data from other randomized trials failed to confirm any convincing improvement in overall survival among patients receiving tandem transplantation.[20,21] Tandem transplantation is an option for patients who do not have a very good partial



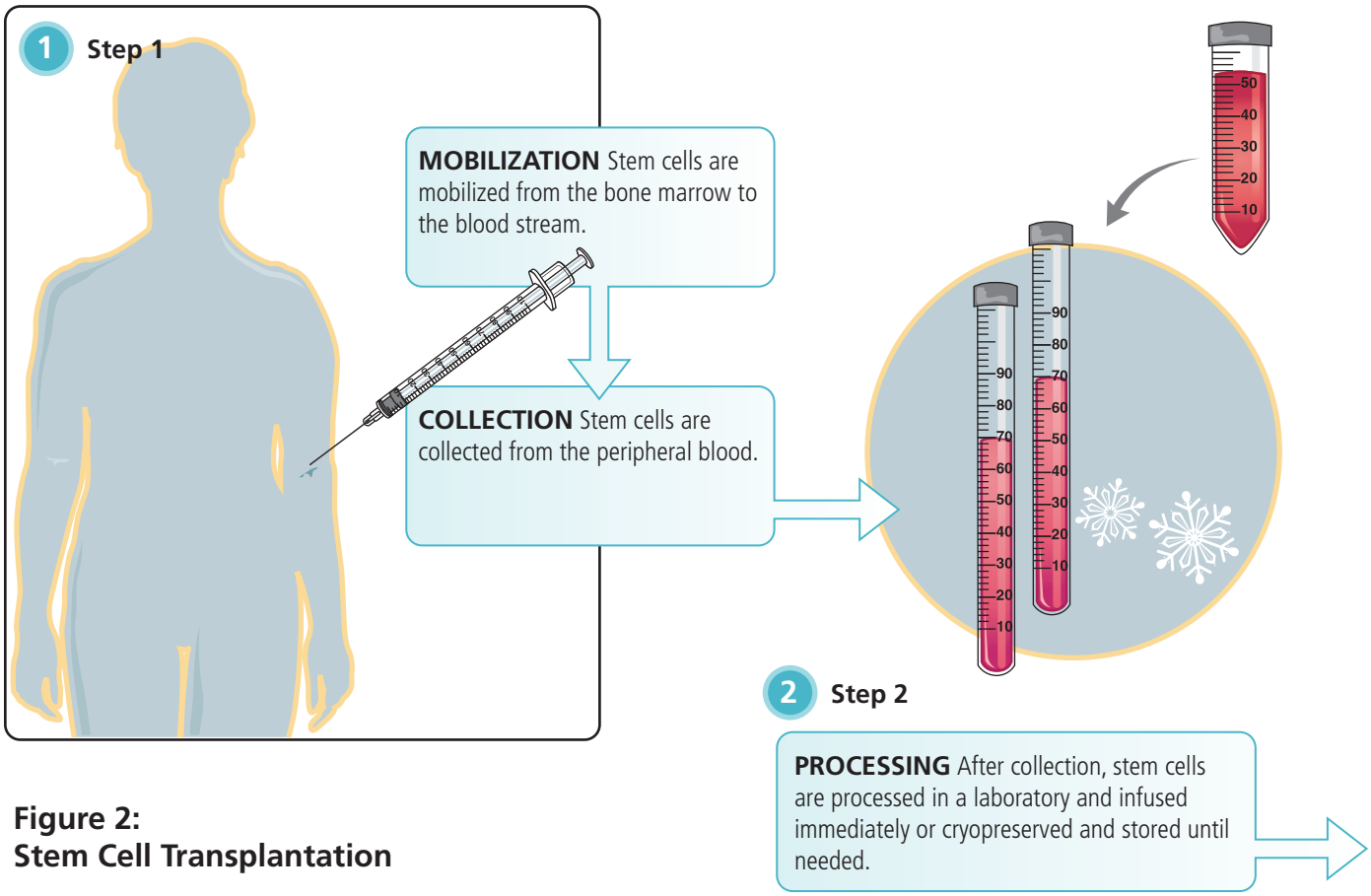


Figure 2:
Stem Cell Transplantation

response (defined as reduction of 90% or more in monoclonal protein levels) with the first transplantation. Until more convincing results are available, it may be a reasonable approach to collect enough stem cells to allow a patient to undergo two transplantations, reserving second autologous stem-cell transplantation for relapse.

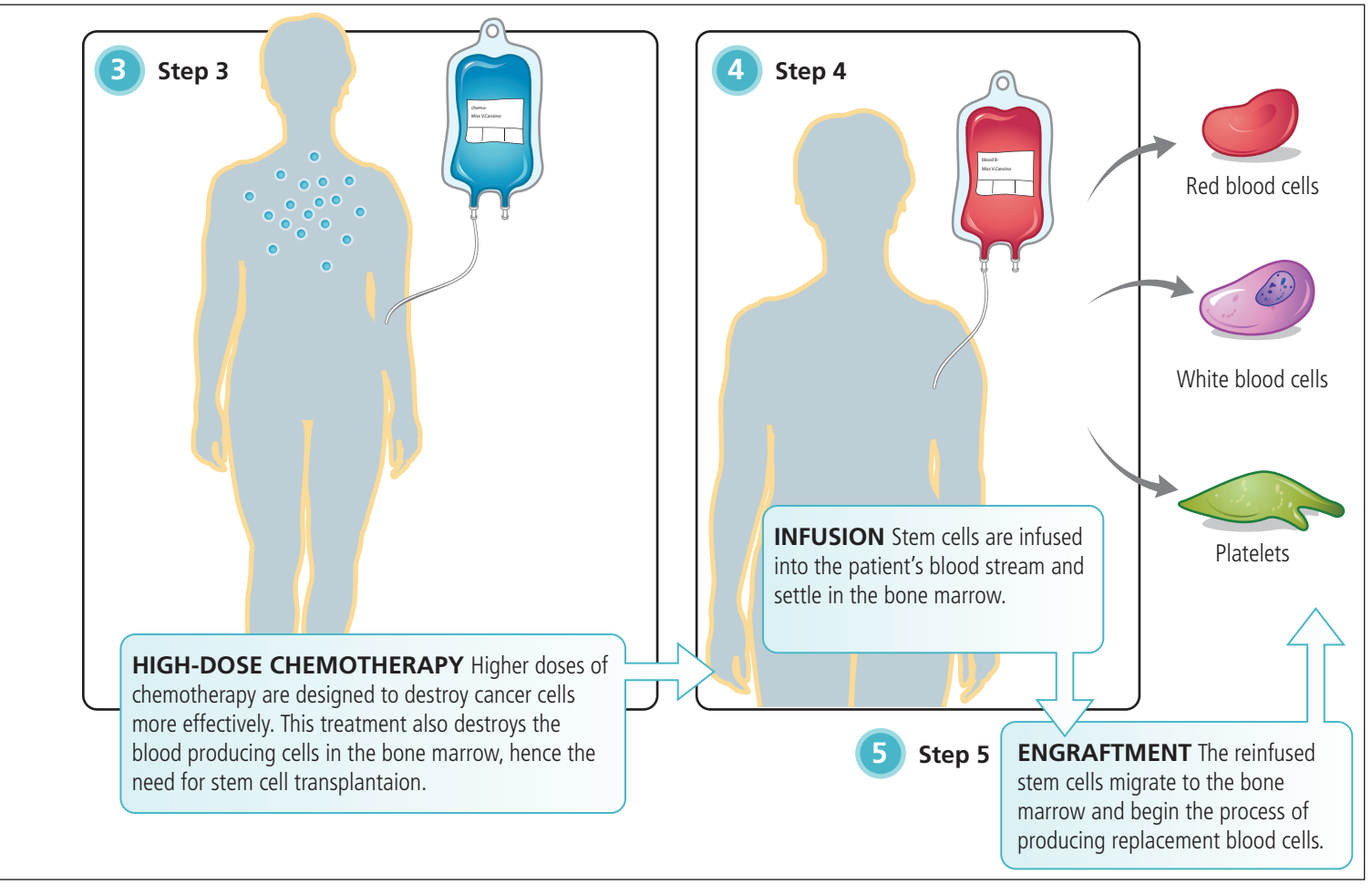
Nontransplant Candidates

In patients who are not eligible for transplantation because of age, poor physical condition, or coexisting comorbid conditions, the most commonly used initial treatment is a combination of melphalan and prednisone. Although VAD,[17] 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 such patients as it is less toxic.[2] Other combinations of agents such as cyclophosphamide and prednisone may also be used, but the better response rate that may be achieved with any of these more aggressive combination regimens in comparison to melphalan plus prednisone has not been shown to confer any additional survival benefit.[22] High-dose dexamethasone or a combination of thalidomide and dexamethasone is the preferred choice in older patients who may be not be able to tolerate other therapies. This initial therapy is continued for about a year until plateau is achieved. At that time the patient receives some form of maintenance therapy, such as corticosteroids or thalidomide, and continues to receive bisphosphonates and supportive care as required (Table 5).

Bisphosphonates and Kyphoplasty

Many MM patients have detectable bone disease (local destruction with osteolytic lesions or generalized osteoporosis) at the time of diagnosis. Despite the advances in treatment of MM, most patients with advanced myeloma develop clinical manifestations related to osteolytic bone destruction. With the spine, decompression might be needed and new techniques such as vertebroplasty or kyphoplasty are increasingly being used early. Kyphoplasty involves injection of cement (polymethylmethacrylate) into vertebral compression fractures. Patients treated with kyphoplasty have reported significant clinical improvement of pain and function.[23]

Bisphosphonates have an antiosteoclastic activity and have been shown to decrease skeletal events (e.g., bone complications such as fractures, radiation therapy to bone, surgery to bone, and spinal cord compression) in patients with MM.[24] There is growing evidence of direct antitumour action of bisphosphonates on MM cells. They do so by inhibition of the ubiquitous mevalonate pathway that induces apoptosis of tumour cells,



suppressing proliferation and migration of endothelial cells, and inhibiting angiogenesis. Bisphosphonates stimulate T cells that cause increased apoptosis of the MM cells.[25] They have also been shown to reduce production of the growth factor IL-6 in MM patients. IL-6 is known to play an important role in the growth and survival of myeloma cells. The immunomodulatory effects of bisphosphonates are under investigation.

Relapsed and Refractory MM

Despite several recent therapeutic advances, MM remains incurable. Most patients experience relapse after responding to initial therapies, including high-dose chemotherapy (Table 5) and stem-cell transplantation. Multiple regulatory pathways and complex interactions involving cytokines, adhesion molecules, angiogenesis, and resistance mechanisms contribute to the disease relapse after initial response. The complex pathophysiology of MM makes it difficult to manage the disease successfully.

If relapse occurs more than six months after conventional therapy is stopped, the initial chemotherapy regimen should be reinstituted. 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. Good responses have been achieved in relapsed myeloma with the use of intravenous vincristine, doxorubicin, and dexamethasone. Intravenous liposomal doxorubicin is a less cardiotoxic alternative to doxorubicin.[26] Either dexamethasone or intravenous pulsed methylprednisolone is also effective. The use of thalidomide and arrival of newer agents such as bortezomib have shown promising results, thereby providing hope for better management of the relapsed and refractory multiple myeloma.[27]

Recent Advances

Thalidomide

Of the several agents and molecules that are being evaluated either as a single agent or in combination with traditional therapy in multiple myeloma, thalidomide stands out as agent that maintains the same high response rates not only in newly diagnosed MM but also in the relapsed or refractory disease. Initially used as a sedative in the 1950s, thalidomide was withdrawn from the market after reports of teratogenicity. The recognition of the antiangiogenic properties of thalidomide led to the first clinical trial of this drug for the treatment of multiple myeloma which showed a response rate of 25% inpatients with relapsed disease.[28] Subsequent studies have shown response rates ranging from 25–35%.[29,30] The responses are durable, with a median duration of approximately 12 months. Promising results have been achieved

with the combination of thalidomide and corticosteroids (approximately 50%), and a three-drug combination of thalidomide, dexamethasone, and an alkylating agent such as melphalan or cyclophosphamide (with response rate of up to 70%).[31]

Overall, thalidomide as a single agent or in combination is well tolerated. The tolerability of the therapy with this agent depends on the starting dose of therapy, the maximal target dose, and the cumulative dose. The most common side effects observed with use of thalidomide in myeloma include drowsiness or fatigue, peripheral neuropathy, constipation, dizziness, dry skin or rash, impotence, hypothyroidism, and leukopenia. Drowsiness and neuropathy are the most common reasons for discontinuation of the therapy or a dose reduction. The most critical side effect is the increased incidence of deep venous thrombosis that ranges from 1–3% in patients receiving thalidomide alone but increases to 10–15 % in patients receiving the drug in combination with dexamethasone.[32] When thalidomide is used in combination with chemotherapy, especially anthracyclines, the incidence of deep venous thrombosis is significantly increased (up to 25%), and could be reduced to baseline by the use of low-dose acetylsalicylic acid or low molecular weight heparin.

Proteasome Inhibitor: Bortezomib

Bortezomib (N-pyrazine carbonyl-L-phenylalanine-L-leucine boronic acid; previously known as PS-341 or MLN-341), a boronic acid dipeptide, is a specific inhibitor of the proteasome pathway.[33] The proteasome pathway is important for the activation of NF-kB by regulating the degradation of the NF-kB inhibitor, I-kB. In view of the encouraging *in vitro* data, a phase I study using bortezomib was initiated in patients with refractory hematologic malignancies (i.e., MM or lymphoma).[34] Its efficacy against myeloma was noted in a phase I dose-finding study. Based on promising results in the preclinical and phase I activity in multiple myeloma, a phase II study (SUMMIT) was initiated in patients with relapsed and refractory MM.[35] A total of 202 heavily pretreated patients were enrolled, of which 193 were able to be evaluated. The overall response rate (complete response ([CR]) + partial response ([PR]) + minimal response ([MR]) was 35% (67 of 193 patients). An additional 34 patients (18%) achieved a PR and 14 (7%) an MR.[35] The median duration of response in several studies has been around 12 months, and the responses were associated with improvement in cytopenia, renal function, and quality of life. Lower response rate was seen in patients above 65 years and those with extensive marrow involvement. The most common adverse effects of bortezomib are gastrointestinal symptoms, cytopenia, fatigue, peripheral neuropathy, and thrombocytopenia.

Table 3: Staging Systems

Stage	Durie-Salmon system	International Staging System (ISS)
I	All of the following: – Hemoglobin value >10g/dL – Serum calcium value normal or ≤12mg/dL – Bone x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only – Low M-component production rate—IgG value <5g/dL; IgA value <3g/dL. Bence Jones protein<4g/24 h	β2-M <3.5 and Albumin ≥3.5
II	Neither stage I nor stage III	Neither stage I nor stage III
III	One or more of the following: – Hemoglobin value <8.5g/dL – Serum calcium value >12mg/dL – Advanced lytic bone lesions (scale 3) – High M-component production rate—IgG value >7g/dL; IgA value >5g/dL. Bence Jones protein >12g/24 h Durie-Salmon subclassifications (either A or B) A: Relatively normal renal function (serum creatinine value <2mg/dL) B: Abnormal renal function (serum creatinine value ≥2mg/dL)	β2-M >5.5

Source: Reprinted with permission from www.multiplemyeloma.org

Immunomodulatory Drugs

Immunomodulatory drugs (IMiDs) are a group of oral drugs that are chemically similar to thalidomide. They are more potent than thalidomide and appear to lack some of the more common side effects seen with thalidomide. Two IMiDs are currently being evaluated in patients with relapsed or refractory myeloma, including CC-5013 (lenalidomide) and CC-4047. These ImiDs have shown more promising preclinical activity than thalidomide. These drugs induce apoptosis, decrease the binding of myeloma cells to stromal cells in bone marrow, and inhibit angiogenesis.[36] CC-5013 has shown promise in the initial phase II trials and is now undergoing phase III trials.[37] The most common side effects seen are thrombocytopenia and neutropenia. Sedation, constipation, and neuropathy are seen much less frequently as compared to thalidomide.

Novel Agents

Novel agents that are under investigation for their role in treatment of MM include those that act by interrupting the intracellular signalling pathways including the inhibitors of insulin growth factor 1 (IGF-1) receptor, inhibitors of the heat shock protein 90, and soluble NF-kB ligand (RANKL) antagonists to decrease bone resorption. Inhibitors of lysophosphatidic acid acyltransferase-b (CT-32176, CT-32458, and CT-32615) in combination with histone deacetylase (HDAC) inhibitors are under study for their role in MM treatment (Table 6).[38]

Salvage Therapies

Salvage therapies are employed in patients with relapsed or refractory disease. Salvage therapies include combination chemotherapy of vincristine, adriamycin, and dexamethasone (VAD).[39] The other combinations that have shown efficacy include DCEP, comprising dexamethasone pulsing and four-day continuous infusion of cyclophosphamide, etoposide, and cisplatin, or DT-PACE, in which thalidomide and adriamycin are added to DCEP (especially in relapsed or refractory myeloma with high proliferate activity).[40]

Summary

Disease progression in multiple myeloma is associated with complex biological pathways and processes, making it difficult to manage the disease successfully and increasing the probability of relapse. The development of the drugs bortezomib, CC-5013 and thalidomide, and the use of single and tandem transplants, provides more hope for patients with MM. Further novel treatment strategies are needed to target the underlying pathogenic mechanisms, but they must be demonstrated to be safe for a predomi-

Table 4: Prognostic Variables

β2-microglobulin level
Hemoglobin level
Serum calcium level
Lactate dehydrogenase level
C-reactive protein level
Serum immunoglobulin level
Number of lytic bone lesions
Plasma cell labelling index
Serum immunoglobulin level
Albumin level
Plasma cell labelling index
Bone marrow plasmacytosis (%)
Renal failure
Bone marrow microvessel density
Chromosomal analysis (monosomy 13)

Source: Adapted from DeVita VT, Hellman S, Rosenberg S, Eds. Cancer: principles & practice of oncology, 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2005.

Table 5: Chemotherapeutic Agents/Regimens used in MM

Melphalan, prednisone*
Dexamethasone*
Thalidomide, dexamethasone*
Vincristine, doxorubicin, dexamethasone*
liposomal doxorubicin, vincristine, reduced-dose dexamethasone*
Cyclophosphamide, prednisone*
Vincristine, melphalan, cyclophosphamide, prednisone/vincristine, BCNU, doxorubicin, prednisone
Dexamethasone, cyclophosphamide, etoposide, cisplatin
Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide
Cyclophosphamide, thalidomide
Liposomal doxorubicin, vincristine, reduced-dose dexamethasone, thalidomide

* used as induction therapy

Source: Adapted from www.multiplemyeloma.org

Table 6: Novel Agents

Immunomodulatory derivatives (IMiDs)—CC-5013, CC-4047
Arsenic trioxide
Heat shock proteins
Antivascular endothelial growth factor (VEGF) antibodies
Farnesyl transferase inhibitors
Histone deacetylase inhibitors
Bcl-2 antisense molecules
2-methoxyestradiol
Bisphosphonates
IGF-1 receptor inhibitors
RANKL antagonist
Lysophosphatidic acid acyltransferase-b inhibitors
Vaccines

Source: Ahluwalia MS, Hussein MA. Treatment of relapsed / refractory multiple myeloma and new frontiers in multiple myeloma therapy. In: Sekeres M, Kalaycio M, Bolwell B. Clinical malignant hematology. (in press)

nantly older patient population. Further research is ongoing to target multiple pathways of the disease simultaneously for more efficient and durable treatment of the disease. ◆

No competing financial interests declared

References

1. Kyle RA, Rajkumar SV. Plasma cell disorders. In: Goldman L, Ausiello DA, eds. Cecil textbook of medicine, 22nd ed. Philadelphia: W.B. Saunders, 2004:1184–95.
2. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med 2004;351:1860–73.
3. American Cancer Society. Cancer facts and figures 2005. Atlanta, GA: American Cancer Society, 2005.
4. Sirohi B, Powles R. Multiple myeloma. Lancet. 2004 Mar 13;363: 875-87
5. Anderson KC, Lust JA. Role of cytokines in multiple myeloma. Semin Hematol 1999;36:14–20.
6. Karin M. How NF-kappaB is activated: the role of the I kappaB kinase (IKK) complex. Oncogene 1999;18:6867–74.
7. Mitsiades N, Mitsiades CS, Poulaki V, et al. Biologic sequelae of nuclear factor-kappaB blockade in multiple myeloma: therapeutic applications. Blood 2002;99:4079–86.
8. Almond J, Cohen GM. The proteasome: a novel target for cancer chemotherapy. Leukemia 2002;16:433–43.
9. Karin M, Ben-Neriah Y. Phosphorylation meets ubiquitination: the control of NF-[kappa]B activity. Annu Rev Immunol 2000;18:621–63.
10. Chauhan D, Uchiyama H, Akbarali Y, et al. Multiple myeloma cell adhesion-induced interleukin-6 expression in bone marrow stromal cells involves activation of NF-kappa B. Blood 1996;87:1104–12.
11. Hazlehurst LA, Damiano JS, Buyuksal I, et al. Adhesion to fibronectin via beta1 integrins regulates p27kip1 levels and contributes to cell adhesion mediated drug resistance (CAM-DR). Oncogene 2000;19:4319–27.
12. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 2003;121:749–57.
13. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975;36:842–54.
14. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. J Clin Oncol 2005;23:3412–20.
15. Rajkumar SV, Greipp PR. Prognostic factors in multiple myeloma. Hematol Oncol Clin North Am 1999;13:1295–1314.
16. Bladé J, Vesole DH, Gertz M. Transplantation for multiple myeloma: who, when, how often? Patient selection and goals. Blood 2003;102:3469–77.
17. Alexanian R, Barlogie B, Tucker S. VAD-based regimens as primary treatment for multiple myeloma. Am J Hematol 1990;33:86–9.
18. 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.
19. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 2003;349:2495–502. [Erratum, N Engl J Med 2004;350:2628.]
20. Cavo M, Tosi P, Zamagni E, et al. The "Bologna 96" clinical trial of single vs. double autotransplants for previously untreated multiple myeloma patients [abstract]. Blood 2002;100:179.
21. 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) [abstract]. Hematol J 2003;4(1 Suppl):S59.
22. 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.
23. Dudeney S, Lieberman IH, Reinhardt MK, et al. Kyphoplasty in the treatment of osteolytic vertebral compression fractures as a result of multiple myeloma. J Clin Oncol 2002;9:2382–7.
24. Ashcroft AJ, Davies FE, Morgan GJ. Aetiology of bone disease and the role of bisphosphonates in multiple myeloma. Lancet Oncol 2003;4:284–92.
25. Kunzmann V, Bauer E, Feurle J, et al. Stimulation of gammadelta T cells by aminobisphosphonates and induction of antiplasma cell activity in multiple myeloma. Blood 2000;96:384–92.
26. 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;95:2160–8.
27. Ahluwalia MS, Hussein MA. Treatment of relapsed/refractory multiple myeloma and new frontiers in multiple myeloma therapy. In: Sekeres M, Kalaycio M, Bolwell B, eds. Clinical Malignant Hematology Book. [in press]
28. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999;341:1565–71.
29. 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.
30. Rajkumar SV, Fonseca R, Dispenzieri A, et al. Thalidomide in the treatment of relapsed multiple myeloma. Mayo Clin Proc 2000;75:897–901.
31. Srkalovic G, Elson P, Trebisky B, et al. Use of melphalan, thalidomide, and dexamethasone in treatment of refractory and relapsed multiple myeloma. Med Oncol 2002;19:219–26.
32. Zangari M, Anaissie E, Barlogie B, et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. Blood 2001;98:1614–15.
33. Adams J, Palombella VJ, Sausville EA, et al. Proteasome inhibitors: a novel class of potent and effective antitumor agents. Cancer Res 1999;59:2615–22.
34. 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;20:4420–7.
35. 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.
36. 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.
37. Richardson PG, Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood 2002;100:3063–7.
38. Bruno B, Rotta M, Giaccone L, et al. New drugs for treatment of multiple myeloma. Lancet Oncol 2004;5:430–42.
39. Barlogie B, Smith L, Alexanian R. Effective treatment of advanced multiple myeloma refractory to alkylating agents. N Engl J Med 1984; 310:1353–6.
40. Lee CK, Barlogie B, Munshi N, et al. DTPACE: an effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. J Clin Oncol 2003;21:2732–9.