

Biology and Treatment of Multiple Myeloma

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Received August 30, 2005; accepted September 29, 2005

ABSTRACT

Multiple myeloma (MM) is a B cell malignancy that accounts for 10% of all hematologic cancers. In recent years much has been learned regarding the biology of the myeloma clone; specifically on the chromosomal alterations that can be more frequently found and on the involved oncogenes. It has been also demonstrated that, in MM, bone marrow microenvironment, both in its cellular (stromal cells, osteoblasts, osteoclasts, endothelia) and protein (extracellular matrix) components, plays an important role in promoting growth and survival of malignant plasma cells. Much of this knowledge will be translated into a better patients treatment; although high-dose therapy programs can be considered the treatment of choice for patients aged 70 or younger, novel drugs, targeting MM clone in its microenvironment can be incorporated into these therapeutic programs improving response rate and patients survival.

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KEY WORDS

Myeloma • Oncogenes • Microenvironment • Stem cell transplantation

INTRODUCTION

Multiple myeloma (MM) is a B-cell malignancy characterized by proliferation and accumulation of B lymphocytes and plasma cells, secreting monoclonal immunoglobulins, in the bone marrow and, less frequently, at extramedullary sites [1]. MM accounts for more than 10% of all hematologic malignancies. The male-female ratio is 1.5:1, and the median age at diagnosis is 70 years [2]. Clinical symptoms at diagnosis include bone pain as a result of osteolytic lesions or fractures; fatigue due to anemia; renal failure; and recurrent infections. Peripheral neuropathy, bleeding, and hyperviscosity syndrome are less commonly observed [3]. Bone marrow aspirate shows $\geq 30\%$ monoclonal plasma cells, and serum or urine monoclonal protein can be detected in $>97\%$ of the patients, whereas in 3% of cases no monoclonal protein component can be identified with conventional laboratory investigations. This percentage further decreases when the more sensitive immunoglobulin free-light chain assay is used. Criteria for the classification of monoclonal gammopathies, MM, and related disorders have been provided elsewhere [4]. The clinical course of the disease is extremely variable but progressive; through the years, many prognostic factors have been identified

that are either related to patient characteristics (poor performance status or renal failure) or related to the disease burden and activity (β_2 -microglobulin, C-reactive protein, and plasma cell labeling index). Recently, the International Myeloma Foundation promoted data collection from $>11\ 000$ patients from Asia, America, and Europe; a staging system was thus proposed that was based on β_2 -microglobulin and serum albumin. Three risk groups with significantly different survival can be identified [5] (Table 1). Furthermore, cytogenetic abnormalities seem to be increasingly important in defining patients' prognosis, as will be described in the following section.

THE MYELOMA CLONE

The genetic basis of the pathogenesis of MM is not unique; neoplastic cells can show a hyperdiploid karyotype with rare translocations or other structural abnormalities or a nonhyperdiploid karyotype with chromosomal translocations that frequently involve the immunoglobulin heavy-chain locus (IgH; 14q32). These alterations, which are often cryptic for conventional cytogenetics, involve different chromosomal partners, some of which are common to other B-cell

Table 1. International Staging System for Multiple Myeloma

Stage	Parameters	Median Survival (mos)
I	β_2 -Microglobulin <3.5 mg/L and albumin >3.5 mg/dL	62
II	No I or III	44
III	β_2 -Microglobulin >3.5 mg/L	29

neoplastic disorders, such as the 11q23 locus, where the *BCL1/cyclin D1* oncogene is located. Conversely, other chromosomal partners, such as 4p16.3, 6p21, and 16q23, seem to be peculiarly involved in MM. As a consequence of the chromosomal translocations outlined previously, the proto-oncogenes located on the partner chromosome of 14q32 (*BCL1/cyclin D1*, *FGFR3*, *cyclin D3*, and *c-maf*) are placed under transcriptional control of the potent IgH enhancer, thus resulting in their overexpression. Although the biologic significance of the overexpression of the different proto-oncogenes in the framework of MM pathogenesis is presently under investigation, it seems now clear that some of the chromosomal alterations described previously do possess prognostic implications. A better prognosis is observed in patients carrying the t(11;14)(q13,q32) alteration [6], whereas t(4;14)(p16.3,q32) is an unfavorable prognostic factor [7]. In the telomeric region of the short arm of chromosome 4 are several putative transcriptional units containing the *MMSET*, *TACC3*, and *LETM1* genes; of these, *MMSET* seems to possess a major role in favoring the clonal expansion of malignant cells. A poor prognosis is also associated with chromosome 13 deletion, which can be detected in 50% of patients by interphase fluorescence in situ hybridization analysis [7]. Genetic alterations that are most frequently found in MM are reported in Table 2. No cytogenetic marker can distinguish monoclonal gammopathies of undetermined significance (MGUS) from MM; however, it has been hypothesized that in MM, as in other tumors, the dysregulation of oncogenes and tumor-suppressor genes controlling cell proliferation, growth arrest, and apoptosis contributes to the progression of the disease. Secondary chromosomal translocations involving *c-myc*, activating mutations of the family of *ras* oncogenes (*n-ras* and *k-ras*), mutation, or monoallelic p53 deletions are extremely rare in MGUS or smoldering MM, whereas the highest frequency occurs in advanced phases of MM. This finding lends support to the notion that these genetic alterations can play a role in driving the progression of MM.

A consistent advance in understanding the biology of MM is presently being obtained through the evaluation of gene expression profiling; this technology has allowed identification of genes differently expressed in normal versus malignant plasma cells [8] to separate MM patients into different subgroups whose gene

expression profiling pattern is related to cytogenetic abnormalities, clinical picture, and response to therapy [9] and to provide insights into the mechanism of response or resistance to different drugs [10].

MM-MICROENVIRONMENT CROSS TALK

It has been recently demonstrated that cellular (stromal cells, osteoclasts, and osteoblasts) and protein (extracellular matrix) components of the bone marrow microenvironment play a crucial role in the pathogenesis of MM. It is well known, for example, that adhesion to extracellular matrix confers resistance to FAS-mediated apoptosis to neoplastic plasma cells [11]. Even more important for the pathogenesis, growth, and progression of MM is adhesion of plasma cells to bone marrow stromal cells that induce transcription and secretion of cytokines (interleukin [IL]-6, insulin-like growth factor 1, and tumor necrosis factor α) that mediate cell proliferation and migration, together with mechanisms that control drug resistance and apoptosis. In particular, IL-6 is the major growth factor of MM, and it promotes proliferation, elicits dexamethasone resistance, and induces expression and secretion of vascular endothelial growth factor (VEGF) in neoplastic plasma cells [12].

In MM patients, bone marrow angiogenesis is remarkably increased as compared with what is observed in MGUS, and it is well known that patients with nonactive MM (complete or partial remission [plateau phase]) show reduced bone marrow angiogenesis in comparison to patients with active disease (newly diagnosed MM, relapse phase, or plasma cell leukemia) [13]. Neoplastic plasma cells induce their own microvascular system through the secretion of fibroblast growth factor 2 and enzymes that display proteolytic activity on the matrix, such as metalloproteinases 2 and 9 and urokinase-type plasminogen activator. VEGF, however, plays a central role in the induction of bone marrow angiogenesis in MM, because messenger RNA encoding VEGF has been identified in plasma cells from MM patients and in MM cell lines. Furthermore, VEGF can in turn induce the secretion of IL-6 by bone marrow stromal cells, so a paracrine and

Table 2. Chromosomal Abnormalities in MM

Alteration	Method	% Patients	Prognosis
$\Delta 13$	Conventional FISH	10-20 30-35	Adverse Adverse*
IgH translocations			
t(11;14)	Conventional/FISH	15-20	Good*
t(4;14)	FISH	15-20	Adverse
t(14;16)	FISH	2-10	Adverse

FISH indicates fluorescence in situ hybridization.

*Still under debate.

autocrine mechanism supporting plasma cell growth can be hypothesized [14].

Skeletal involvement is observed in approximately 80% of patients with newly diagnosed MM; this complication is attributed to an alteration in the mechanisms of bone remodeling induced by neoplastic plasma cells, as demonstrated by *in vitro* coculture experiments [15], so that bone resorption is promoted (osteoclast activity) and bone formation is inhibited (osteoblast activity). It is well known that osteoclasts are recruited and undergo normal maturation through the interaction of their receptor RANK (receptor activator of nuclear factor- κ B) with its ligand (RANK-L) produced by stromal cells, preosteoblasts, and activated T lymphocytes. The activity of RANK-L is balanced by the presence of its decoy receptor, osteoprotegerin, which is produced by stromal cells and preosteoblasts [16]. In MM, osteoclast activity is promoted by an increased production of RANK-L by stromal cells and preosteoblasts, a reduced production of osteoprotegerin, and an upregulation of pro-osteoclastogenic cytokines, such as IL-1 α , macrophage colony-stimulating factor, and macrophage inflammatory protein 1 α [15,16]. The activity of osteoblasts is concomitantly reduced; in fact, malignant bone marrow plasma cells express and secrete the soluble wnt inhibitor DKK-1, which could potentially impair the maturation of osteoblasts [17]. Osteoclasts can in turn promote plasma cell growth through an increased production of IL-6 [18], thus contributing to the maintenance of the vicious circle.

MM THERAPY

Autologous Stem Cell Transplantation

High-dose chemotherapy followed by autologous stem cell transplantation is presently the treatment of choice for MM patients younger than 60 to 65 years. This recommendation derives from the results of 2 prospective randomized studies [19,20] that have demonstrated that single autologous stem cell transplantation is superior to conventional chemotherapy because it results in a significantly longer patient survival. To further improve these results, 2 sequential lines of high-dose chemotherapy followed by double autologous stem cell transplantation have been applied; the clinical advantage obtained with this procedure, as compared with a single transplantation, has been recently demonstrated by 2 prospective randomized studies [21,22] that showed a longer response duration and disease-free survival in patients treated with double autologous stem cell transplantation. A survival advantage is mostly evident in patients who were primarily refractory to conventional induction chemotherapy and in those who did not reach complete remission either after the first transplantation or at the end of the entire therapeutic program to which

they were assigned (single or double autologous stem cell transplantation). Autologous stem cell transplantation has been also used in patients with MM and chronic renal failure; because of the higher incidence of complications, an appropriate dose reduction has been proposed. Results are encouraging in terms of treatment-related mortality and survival [23].

Novel Therapies

In addition to the clinical benefit offered by a double autologous stem cell transplantation, the therapeutic strategies for MM can be improved by the availability of drugs that are active both on neoplastic plasma cells and on the bone marrow microenvironment. Thalidomide, a glutamic acid derivative with sedative properties, has been demonstrated to be able to induce an objective response in 30% to 40% of patients with advanced, relapsed, or refractory MM [24], and it is presently proposed as first-line therapy in patients with newly diagnosed disease and, in combination with dexamethasone or conventional chemotherapy, as preparation for high-dose therapy programs [25,26]. The mechanism of action of thalidomide has not yet been fully elucidated. Although this compound is a potent inhibitor of angiogenesis, its activity in MM and other hematologic disorders is more likely to be due to its interaction with bone marrow stromal cells and to the subsequent inhibition of the secretion of tumor necrosis factor α and IL-6 and to the down-regulation of adhesion molecules. Furthermore, thalidomide modulates the immune system, promoting the growth of natural killer and T lymphocytes and increasing the production of IL-2 and interferon γ . A major drawback of thalidomide is represented by its side effects: more than half of the patients complain of lethargy and constipation, deep venous thromboses occur in up to 15% to 20% of newly diagnosed patients treated with thalidomide/dexamethasone unless proper prophylaxis is administered, and World Health Organization grade ≥ 2 peripheral neuropathy is reported in 60% of patients treated longer than 1 year.

Thalidomide analogues were synthesized to obtain compounds displaying an antineoplastic activity comparable or superior to that of thalidomide, but with fewer side effects. Lenalidomide (Revlimid; CC5013; Celgene, Warren, NJ) is at present the most widely tested thalidomide analogue; in a phase II study performed in 222 patients [27], an objective (or better) response was observed in 28% of the cases, and, importantly, the incidence of neuropathy was markedly reduced as compared with what has been described in thalidomide-treated patients. Proteasome inhibitors are another class of drugs that act both on MM clones and on the microenvironment. The proteasome is a multicatalytic protease that degrades >80% of intracellular proteins and, specifically, cell cycle-regulatory

proteins, oncogenes, tumor-suppressor genes, transcriptional activators, and inhibitors. Neoplastic cells and, in particular, MM cells are very sensitive to proteasome inhibitors because the subsequent accumulation of regulatory proteins leads to cell-cycle arrest and apoptosis. Bortezomib, a boronic acid derivative, is the proteasome inhibitor that has so far been revealed as the most promising in vitro and has been subsequently widely used in the clinic; >30% objective responses have been obtained in patients with relapsed/refractory disease [28]. Also, in a multicenter randomized trial conducted in 669 relapsed MM patients, a significantly higher response rate (38% versus 18%) and a longer time to progression and survival were observed, as compared with high-dose dexamethasone [29].

Allogeneic Stem Cell Transplantation

Myeloablative allogeneic bone marrow transplantation (allo-BMT) for the treatment of MM was introduced in the early 1980s by several institutions [30]. Conventional preparative regimens consisted of total body irradiation (10 Gy with lung shielding) or, less frequently, high-dose busulfan [31] plus high-dose cyclophosphamide or melphalan. This procedure was initially offered to heavily pretreated patients with advanced refractory disease, and despite a treatment-related mortality exceeding 40%, it allowed demonstration that high-dose chemotherapy/radiotherapy coupled with a graft-versus-myeloma (GVM) effect could overcome drug resistance and induce long-lasting complete remission. Transplant-related mortality (TRM), however, remained a major issue for almost 10 years: most trials reported mortality rates ranging from 37% to 57%. A retrospective case-matched study performed by the European Group for Blood and Marrow Transplantation in 1996 [32], aimed at comparing the outcome of MM patients who underwent autologous or allogeneic stem cell transplantation between 1983 and 1994, showed that survival was poorer in the allografted group as a result of a significantly higher TRM (41% versus 13%).

A comparison of myeloablative transplantation reported by the European Group for Blood and Marrow Transplantation registry during 2 time periods (1983-1993 and 1994-1998), however, showed a significant reduction in TRM during the later time period (21% versus 38% observed before 1994) [33]. This can be attributed to an improvement in patient care, because more effective bacterial, fungal, and viral treatments were made available through the years, whereas the increasingly frequent use of peripheral blood as a stem cell source did not seem to favorably affect patient outcome. Favorable prognostic factors for survival after myeloablative allo-BMT in MM are younger age, low β_2 -microglobulin, stage I disease at diagnosis, and

chemosensitive disease; the relapse rate, however, does still average 30%, and this raises the issue of whether allo-BMT can potentially cure MM.

To address this, we have retrospectively analyzed the presence of minimal residual disease in serial post-transplantation bone marrow samples obtained from patients in sustained complete remission after allogeneic stem cell transplantation [34]. For this purpose, patient-specific primers were generated from complementarity-determining regions 2 and 3 of the rearranged IgH gene; it was found that 75% of the patients who were analyzed remained persistently polymerase chain reaction negative for a median of 3 years, with some polymerase chain reaction-negative patients at 4 to 10 years after allogeneic stem cell transplantation. It can thus be concluded that allogeneic stem cell transplantation is associated with a GVM effect that results in more frequent molecular complete responses and a decreased probability of relapse as compared with autologous stem cell transplantation [35]. Therefore, allogeneic stem cell transplantation is probably the only therapeutic approach that has the potential ability to eradicate the myeloma clone; however, presently available results do not allow its consideration as the treatment of choice for MM. The challenge for clinical investigators will be to further reduce TRM by an improved patient selection and better supportive care and to increase the complete response rate. A decrease in TRM could be achieved by the use of nonmyeloablative preparative regimens (reduced intensity conditioning-allo-BMT) aimed at reducing conditioning-related toxicity while sparing the GVM effect. A great variety of preparative regimens have been proposed that include either low-dose (2 Gy) total body irradiation with fludarabine or intermediate-dose melphalan plus fludarabine. A favorable outcome is more frequently observed in nonheavily pretreated patients and in chemosensitive disease [36]. Presently, a tandem strategy of high-dose melphalan and autologous stem cell transplantation followed by reduced intensity conditioning-allo-BMT is being used by several groups to further decrease the tumor burden before inducing a GVM effect. Mature data evaluating the long-term outcome of this strategy will be available soon.

Supportive Therapy

The global treatment approach to MM should also include supportive therapy; the main fields of intervention include treatment of anemia, prevention of infections, and treatment/prevention of bone disease. Anemia is present in almost two thirds of patients at diagnosis: it improves when disease is controlled by treatment, and it worsens in progressive or resistant disease. After exclusion of iron or vitamin deficiency, recombinant erythropoietin should be used, because it

increases the hemoglobin concentration, reduces transfusion requirements, and improves quality of life. Patients with a hemoglobin level <10 g/dL should receive erythropoietin at a dose of 10 000 U 3 times a week or 30 to 40 000 U once a week [37]. Alternatively, darbepoetin α can be used, at 150 $\mu\text{g}/\text{wk}$. Infections are a primary cause of death in MM, and risk increases during chemotherapy, long-term therapy with steroids, and autologous and, above all, allogeneic stem cell transplantation. Intravenous immunoglobulins should not be routinely used as general prophylaxis for bacterial infection in MM patients; their use should be reserved for patients with recurrent infections and polyclonal hypogammaglobulinemia and for recipients of allogeneic stem cell transplants showing severe hypogammaglobulinemia. Prophylactic antibiotics should not be routinely used during conventional chemotherapy; trimethoprim-sulfamethoxazole is recommended to prevent *Pneumocystis carinii* pneumonia in patients treated with high-dose dexamethasone. Seasonal influenza vaccination should be recommended for all MM patients, whereas *Haemophilus influenzae* type B vaccine and 23-valent pneumococcal polysaccharide vaccine should be used in patients treated with autologous or allogeneic stem cell transplantation [37]. Skeletal involvement is a common feature of MM. Up to 80% of newly diagnosed MM patients present with osteopenia, osteolysis, and pathologic fractures, and the latter can severely impair patients' quality of life. Bisphosphonates are presently the only clinically available drugs capable of inhibiting osteoclast activity; MM patients with bone lesions or severe osteopenia should thus be treated with bisphosphonates. These compounds have been proven to reduce skeletal-related events and bone pain both in early-stage and advanced disease [37]. Because absorption after oral administration is poor, intravenous treatment should be preferred, either with pamidronate 90 mg/4 weeks in at least a 2-hour infusion or with zoledronic acid 4 mg/4 weeks in a 15-minute infusion.

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