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REVIEW ARTICLE

MULTIPLE MYELOMA - A REVIEW

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ABSTRACT

Aim: To review the pathophysiology, diagnostic and investigatory approach and treatment for multiple myeloma.
Objective: To enumerate the various aspects in relation to multiple myeloma.
Background: Multiple myeloma is a hematologic malignancy characterized by the clonal proliferation of plasma cells in the bone marrow and, usually, the presence of a monoclonal Ig in the blood and/or urine. It is the second most commonly diagnosed hematologic malignancy with an annual incidence and prevalence in the various parts of the world.
Reason: To understand the disease and its course as well its management in the human body.

INTRODUCTION

Multiple myeloma (MM) is a malignancy of clonal plasma cells characterized by the presence of paraproteinemia, destructive bone disease, hypercalcemia, renal failure, and/or hematologic dysfunction [1]. Although MM is rarely, if ever, cured, high-dose melphalan and autologous transplant prolong survival compared with standard chemotherapy [2]. The growth and resistance to treatment of malignant plasma cells are dependent, in part, upon the interaction between the bone marrow microenvironment and the clonal plasma cells themselves. Indeed, the bone marrow microenvironment seems to be key, supporting the growth of myeloma by secreting growth and antiapoptotic cytokines such as interleukin-6 (IL-6), TNFa, insulin like growth factor-1 (IGF-1), and VEGF [3]. In addition, direct interaction of the bone marrow microenvironment with MM through integrins and cell adhesion molecules promotes growth, inhibits apoptosis, and is responsible for resistance to conventional chemotherapy and corticosteroids[4]. Novel agents that target both the MM cell and bone marrow microenvironment interaction [5] are essential in order to effect meaningful remissions and responses for most patients. The development of bortezomib, thalidomide, lenalidomide, and other new targeted molecules represents a paradigm shift in the treatment of MM [6,7].

In this review, we discuss the preclinical rationale, derived clinical studies, and combination strategies in the context of new drug development for relapsed and refractory MM. Plasma cells form an important central function in the context of our normal immune system. They are the cells that are responsible for both short- and long-lived antibody responses following antigenic stimulation. Normally, clones of plasma cells come and go via immune regulatory pathways that include the local secretion of cytokines and stromal factors, which are necessary for the survival of plasma cells and for antibody secretion. The clonal evolution of a malignant plasma cell is thought to occur when primary genetic events transform a normal postgerminal center B cell into the malignant plasma cell. Functionally, these cells are no longer regulated by normal senescencemechanisms, with the net result being the development ofan enlarging clone of cells that support their own growth and proliferation via local secretion of cytokines such asIL6, IGF-1, TNF-a, and others that are secreted by plasma cells themselves or by the stromal microenvironment within the bone marrow. Over time, additional genetic events occur that further provide the impetus for growth and proliferation, which eventually lead to drugresistance[8].

Pathophysiology

There is a growing realization that the evolution of the disease involves sequential and complex changes in both the malignant cell and in the surrounding bone marrow microenvironment, including bone. The evolution from MGUS to active myeloma seems to be a multistep, stochastic progression that can occur over a few months to decades [9]. The pathogenetic switch or switches that lead to conversion of normal plasma cell populations to MGUS have not been elucidated. The sequence of events that lead to progression from MGUS to active

myeloma has been researched intensely with a resultant glimpse into the various genetic abnormalities and the bone marrow microenvironment disturbances that exist in the various stages of progression. Considerable interpatient heterogeneity in these disturbances has been shown to exist, and this has led to proposed new classifications of the disease on the basis of differences in disease biology.

The tools for the study of the cytogenetic makeup of myeloma cells mainly have been conventional karyotyping, fluorescence *in situ* hybridization, and, more recently, gene expression profiling. There is no characteristic genetic signature that is diagnostic of the disease. However, activation of one of the three cyclin D genes has been shown to be present in nearly all myeloma cases. Almost half of patients with myeloma have translocations that nonrandomly involve the Ig heavy chain locus on chromosome 14q32 and one of five well-defined chromosomal partners: 11q13 (cyclin D1), 6p21 (cyclin D3), 4p16 (fibroblast growth factor receptor 3 and multiple myeloma SET domain), 16q23 (c-maf), and 20q11 (mafB) [10,11]. All Ig heavy chain locus translocations except t(11;14) seem to have unfavorable prognosis. Deletions of chromosomes 13 and 17 (17p13; the p53 locus) also are unfavorable. Hypodiploid myeloma also is associated with poorer survival compared with hyperdiploid myeloma. Bone lesions in myeloma are thought to be a result of imbalance between the two opposing processes: Bone formation by osteoblasts and bone resorption by osteoclasts. Myeloma cells are thought to increase production of pro-osteoclastogenic cytokines such as macrophage inflammatory protein 1 (MIP-1_), parathyroid hormone-related protein (PTHr-P), vascular endothelial growth factor (VEGF), and IL-6. An increase in expression of RANKL (receptor activator of NF-B ligand) by osteoblasts and a decrease in the level of its decoy receptor osteoprotegerin result in activation of osteoclasts. Levels of dickkopf 1 (DKK-1), an inhibitor of Wnt signaling that inhibits differentiation of osteoblast precursors, also are increased [11,12].

Interactions between the myeloma cell and other cells in the marrow microenvironment, such as stromal cells and hematopoietic stem cells, and also the extracellular matrix activate multiple signaling pathways, resulting in proliferation/antiapoptosis of the myeloma cell. The autocrine/paracrine survival factors that are involved in these interactions include IL-6, IGF, VEGF, and TNF[11]. These complex relationships also contribute to drug resistance, and therapeutic strategies that simultaneously target both the malignant cell and the microenvironment are being designed. It is interesting that only 60% of patients with myeloma have bone lesions. In these patients, the resorption of bone seems to be required for fueling disease progression through release of myeloma survival factors. Other patients with myeloma do not develop disease-mediated bone destruction even in advanced stages of the disease. This suggests that the degree of dependence of myeloma cells on the marrow microenvironment is variable.

Diagnosis and Investigations

Some patients' myeloma is diagnosed incidentally because of elevated serum protein levels, but most patients present with symptoms related to anemia, bone lesions, kidney dysfunction, infections, or hypercalcemia. Various blood, urine, bone marrow, and imaging studies are required to diagnose, stage, and monitor the disease and determine prognosis. The diagnostic criteria for myelomais followed[13]. A critical element of making a correct diagnosis is ensuring that plasmacytosis is clonal, particularly when other typical features are not present.

Classification and Staging Systems

The time-honored Durie-Salmon staging system correlates well with tumor burden[14]. However, the new international staging system[15], based on 2-microglobulin and albumin, correlates better with prognosis. The translocation and cyclin D classification proposed by Bergsagel and Kuehl [16] has five groups that can be ' on the basis of recurrent Ig translocations and cyclin D expression. In a recent proposed molecular classification, seven disease subtypes were identified [17]. The last two classifications still have to be validated but seem to have promising prognostic and therapeutic relevance.

Prognosis

The international staging system, the translocation and cyclin D classification, and the molecular classification discussed in the previous paragraph seem to correlate with survival. However, the international staging system is most easily applicable practically because of its simplicity. Other investigations that are practically feasible and have been shown to correlate with outcome include karyotype and some biochemical parameters. Cytogenetic abnormalities such as partial or complete deletion of chromosome 13 and t(4;14) indicate high-risk disease. Other adverse features include plasmablastic morphology and elevated lactate dehydrogenase, plasma cell labeling index, and C-reactive protein [18].

Treatment

Advances in therapy have resulted in improvement in the survival of patients with myeloma over the years. Without therapy, the median survival of a patient with active myeloma is approximately 6 months. With oral melphalan-prednisone (MP) therapy, median survival improves to 3 years. High-dosage therapy with HSCT further improves median survival to 5 years, Tandem autologous transplantation is superior to single in selected patients. Now the newer agents, such as thalidomide[19,20], raise a possible challenge to the established approach of evermore aggressive dose escalation. To maximize chances for prolonged survival, it is important to plan therapy for each patient in a manner that uses all agents appropriately and sequentially without adversely affecting future treatment options. The dilemma that clinical researchers face is whether to go forward with trials that combine all available agents to increase chances of tumor cell kill while increasing the possibility of drug resistance or to reserve new agents for salvage therapy of relapsed and refractory disease. The treatment of myeloma comprises disease-specific therapy and supportive care. The general principle is to reserve disease-specific therapy for active disease. The new diagnostic criteria for myeloma identify the patients who have active disease, who almost always need therapy. Definitive therapy is required when the patient is symptomatic or when organ dysfunction is present or impending. There is no evidence that starting definitive therapy in patients with smoldering or indolent myeloma improves survival. Patients with Durie-Salmon stage I myeloma also can be watched without antitumor therapy for a period of time.

Supportive Therapy

Supportive therapy comprises management of hypercalcemia, skeletal complications, anemia, infections, and pain[21].

Regular administration of bisphosphonates such as pamidronate (90 mg once a month) or zoledronate (4 mg once a month) in patients with skeletal lesions is important [22]. These drugs arrest and reverse the disturbance of balance between bone formation and resorption. Possible direct and indirect (through effect on the bone marrow microenvironment) anti-myeloma activity of these drugs led to their open-ended use in myeloma. However, the potential for renal damage and increasing concern about osteonecrosis of the jaw warrants periodic reassessment of the need for continued bisphosphonates after 2 yr rather than the previous approach of long-term therapy. Any symptoms that involve the jaw should be investigated carefully, and a careful dental evaluation and corrective work should be performed before starting bisphosphonates or early in the course of therapy.

Disease-Specific Therapy

The current standard approach consists of initial induction therapy, consolidation with high-dosage chemotherapy and autologous HSCT, maintenance therapy, and salvage therapy.

Initial Therapy. As HSCT is being used increasingly in myeloma [23,24], the choice of initial therapy is based on whether the patient is a transplant candidate. Patients who are transplant candidates receive induction therapy that does not cause permanent stem cell damage. Patients who are ineligible for HSCT can receive MP or similar therapy. More intensive alkylating agent-based combinations improve response rates without prolonging survival. However, MP and other alkylating agent-based combinations damage normal hematopoietic stem cells, making stem cell collection for HSCT difficult if not impossible and increasing the risk for myelodys plastic syndrome. The complete remission (CR) rate with MP is 5%, and the overall response rate is 40 to50%. The addition of low-dosage thalidomide to MP in elderly patients with myeloma improves response rates and event-free survival (EFS) but increases toxicity significantly compared with MP[25]. Longer follow-up is required to assess effect on overall survival (OS).

The usual induction therapy for patients who are eligible for HSCT is based on high-dosage dexamethasone or methylprednisolone. There is no compelling evidence that regimens that combine modestly active intravenous agents with high-dosagedexamethasone are better than dexamethasone alone with its convenience of oral administration[26]. Lack of response to induction therapy does not necessarily signify a poor prognosis because subsequent HSCT can result in substantial cytoreduction[27]. Two recent randomized studies suggested that the wide spread adoption of thalidomide-containing induction therapy as the new standard may not be beneficial, because the addition of thalidomide results in higher response rates but increases serious toxicity significantly and does not prolong survival. Ina study [28] that compared thalidomide-dexamethasone (TD) with dexamethasone alone, overall response with four cycles was significantly higher with TD (63 *versus* 41%; *P* _ 0.002), but CR rates were comparable (4 *versus* 0%). The incidence of grade3 to 5 deep vein thrombosis (DVT), rash, sinus bradycardia, neuropathy, and any grade 4 to 5 toxicity within 4 cycles was significantly more common with TD (45 *versus* 21%; *P* _ 0.001). OS was identical during the first 2 yr. In another study[29], patients received intensive induction therapy followed by tandem auto transplantation and post transplantation consolidation and maintenance, with or without thalidomide. Although CR rates and 5-yr EFS were better with thalidomide (62 and 56%, respectively) than without (43 and 44%, respectively), the 5-yrOS was similar at 65%. Despite comparable salvage therapy, median survival after relapse was only 1.1 yr in the thalidomide group compared with 2.7 yr in the control group (*P* _ 0.001) because of resistance to all types of salvage therapy in thalidomide-treated patients. Severe peripheral neuropathy and DVT occurred more frequently with thalidomide.

Therefore, a reasonable approach may be to use single-agent dexamethasone, with consideration being given to the addition of thalidomide if there is no response to dexamethasone. This will minimize toxicity and expense without compromising outcome and likely will reduce the development of resistant disease. DVT prophylaxis is essential if TD is used, although the optimum mode of prophylaxis is unclear. The use of other newer agents, such as bortezomib and lenalidomide, as part of initial therapy currently is investigational, although the combination of lenalidomide and dexamethasone seems to be veryactive[30].

High-Dosage Chemotherapy. High-dosage melphalan with autologous HSCT may be administered as consolidation ntherapy after induction (early) or as salvage therapy after relapse (late). Two randomized studies showed higher response rates and prolongation of EFS and OS with early HSCT [23,24], whereas one did not [31]. Another randomized study showed that deferring HSCT to relapse after initial therapy did not compromise OS, although EFS was shorter compared with early transplantation [32]. Quality of life, as measured by the TWiSTT score (time without symptoms or treatment toxicity), was better in patients who underwent HSCT early. Another recent study that randomly assigned patients to early HSCT or continued standard-dosage chemotherapy with an option to undergo salvage HSCT at relapse showed no benefit for early HSCT in terms of response rates, EFS, or OS[33].

Despite these conflicting reports, the balance of opinion currently is that HSCT after high-dosage melphalan is beneficial [34]. The Arkansas group pioneered the approach of tandem autologous HSCT [35]. Long-term follow-up of the Total Therapy 1 study from Arkansas shows 10-yr OS and EFS probabilities of 33 and 15%, respectively [36]. Further intensification of the Total Therapy 1 regimen seemed to improve outcome in the Total Therapy 2 study[37], but improvement stemmed from intensified chemotherapy rather than added thalidomide [38]. Whether tandem HSCT is superior to single HSCT remains contentious. The only published, prospective, randomized study showed a doubling of the likelihood of OS and EFS at 6 yr for patients who underwent tandem HSCT [38]. In a subgroup analysis, this benefit was confined to patients who did not achieve at least a very good partial response to the first transplant. Ongoing studies may be able to answer this question definitively; early data from these studies favor tandem HSCT in terms of EFS, but there is no difference in OS yet. The similarities in long-term outcome between the Royal Marsden data and the long-term follow-up for the Total Therapy 1 group may be at least partly because 131 of the Marsden patients eventually underwent a second transplant as therapy of relapse.

Allogeneic stem cell transplantation potentially is curative because of immunologically mediated graft-*versus*-myeloma effects[39], but toxicity compromises survival and remains a concern [40]. Minitransplantation, whereby intensity of the

conditioning regimen is reduced substantially, may overcome the problem of toxicity in part by making the procedure safer. Here, there is much greater reliance on graft-*versus*-tumor reactions to eliminate the cancer[41]. Although a proportion of patients are alive disease-free for a decade or longer after HSCT with essentially normal quality of life ("operational cure")[42], most patients eventually relapse and need salvage therapy. Third and occasionally even fourth cycles of high-dosage chemotherapy have been used in selected patients. Therefore, it is important to collect enough stem cells at the outset for the planned number of transplants as well as for future salvage therapy. Administration of post transplantation maintenance therapy may help to delay disease recurrence. The agents used are corticosteroids, IFN, and thalidomide. Although the use of maintenance therapy may improve EFS, OS may not be affected beneficially because recurrent disease may not be sensitive to the agent used for maintenance. A greater worry is that recurrent disease may be resistant to other agents as well [13].

Salvage Therapy. The availability of thalidomide[19,20], bortezomib [43,44] and lenalidomide [45,46] has transformed the treatment of myeloma. It now is possible to achieve excellent cytoreduction including CR in patients whose disease relapses after extensive previous therapy and achieve prolonged survival after relapse. The appropriate approach for a patient with relapsed disease depends on previous therapy, including transplantation, response to previous therapy, the nature of the disease, age, organ function, bone marrow function, the availability of an allogeneic donor, and access to clinical trials of investigational agents [47].

Thalidomide. Thalidomide as a single agent is effective in approximately one third of patients with relapsed myeloma[19,20]. The exact mechanism of action is unknown, but the drug is thought to act directly on plasma cells, on the marrow microenvironment, and through cytokines that affect thegrowth of plasma cells. Some patients respond to as little as 50mg of the drug, but most require 200 mg or so. The addition ofother agents such as dexamethasone or multiagent chemotherapy improves response rates further and is effective in patients who have not responded to the agents used singly. The main adverse effects are sedation, fatigue, constipation, peripheral neuropathy, autonomic disturbances, and thromboembolicphenomena. Long-term follow-up of the Arkansas Total Therapy 1 study shows longer postrelapse survival for patients whose disease relapsed in the thalidomide era compared with those whose disease relapsedearlier[36], suggesting that the use of thalidomide as salvage therapy, in contrast to its use as initial therapy, does seem to prolong survival.

Bortezomib. Bortezomib, an inhibitor of the 26S proteasome(an intracellular organelle that is responsible for protein degradation),also is effective in 25 to 30% of patients with relapsedmyeloma[43]. For patients with relapsed disease, bortezomib is more effective than dexamethasone[44]. Combining bortezomib with other agents that are active in myeloma, such ascorticosteroids, thalidomide, and low-dosage melphalan, increases its efficacy. The main adverse effects are thrombocytopenia, gastrointestinal disturbances, and peripheral neuropathy. Bortezomib seems to be particularly effective in patients with light-chain disease and causes rapid cyto reduction that necessitates precautions against tumor lysis syndrome in patients with a high burden of rapidly proliferative disease.

Lenalidomide. Lenalidomide is a structural analog of thalidomidebut its *in vitro* biologic actions are more potent thanthalidomide. It is remarkably effective in patients with relapseddisease; including those who have failed prior thalidomide and bortezomib [45,46]. The combination of lenalidomide and dexamethasoneis superior to dexamethasone alone for relapsed disease[46]. While the 25 mg dose has been formally explored[46], the drug is active at doses as low as 5 mg per day[45]. The main side effects are myelosuppression, thromboembolic phenomena (particularly in combination with dexamethasone), and skin rash.

Combinations. All of these new agents have been combined with one or more conventional agents with varying degrees of success and toxicity. Similarly, combinations of more than one of the new agents are being studied. Although still investigational, these are reasonable choices in patients who have no other treatment options. To maximize chances for prolonged survival, it is important to plan therapy for each patient in a manner that utilizes all agents appropriately and sequentially without adversely impacting future treatment options.

CONCLUSION

Combinations of agents in relapsed and refractory MM are clearly moving forward. Advantages of combination therapy include higher ORRs and, in many cases, better depth of responses, as well as the ability to revisit "backbone" agents used earlier in treatment. Additional preclinical studies and derived clinical trials that prove the efficacy of combination therapy are needed in advanced MM and will likely be forthcoming in the near future to further improve patient outcome[48].

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