Section A-Research paper

A Brief Overview about Multiple Myeloma

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Abstract

Background: Multiple myeloma accounts for 1% of all cancers and approximately 10% of all hematologic malignancies. Each year over 32,000 new cases are diagnosed in the United States, and almost 13,000 patients die of the disease. The annual age-adjusted incidence in the United States has remained stable for decades at approximately 4 per 100,000. Multiple myeloma is slightly more common in men than in women, and is twice as common in African-Americans compared with Caucasians. The median age of patients at the time of diagnosis is about 65 years. Traditional diagnostic criteria for the diagnosis and indications for the introduction of therapy in myeloma have defined active myeloma by the presence of end organ effects. These have now been expanded by the International Myeloma Working Group from the analysis of the risk of progression in large cohorts of patients with smouldering multiple myeloma. These new criteria have extended the diagnostic criteria to include the presence of free light chain abnormality(ratio of involved free light chain to non-involved free light chain > 100 mg/L; reference interval, 0.26–1.65 mg/L), bone marrow involvement demonstrating more than 60% plasma cells and the presence of more than one lytic lesions on magnetic resonance imaging (MRI) scan, in addition to the previous standard criteria. Patients with a clonal plasma cell disease and signs of manifest or threatened organ damage must receive adequate systemic therapy. Although this does not generally lead to cure, modern treatment plans have now increased the 5-year survival rate for myeloma patients up to 75 years of age to over 50%. In3–20% of patients, complete remission can last for many years. In the absence of severe (cardiac and pulmonary) comorbidities, the standard treatment in Germany remains high-dose melphalan (200 mg/m2)followed by retrains fusion of autologous blood stem cells.

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Introduction

Multiple myeloma is a malignancy of plasma cells originating from the bone marrow; it is a clonal plasma cell disorder that produces excess monoclonal immunoglobulin. The disease most commonly presents with hypercalcemia, renal failure, anemia and bone lesions (CRAB features) **(1)**.

Myeloma accounts for about 10% of all hematological malignancies. The annual incidence of myeloma in Australia is about five cases per 100 000 population, and there are about 1200 new patients diagnosed each year; the median age of diagnosis is themid-60s.There is variation in incidence among the different ethnic groups, with myeloma being twice as common in African Americans than in white people and less common in Asians **(2)**.

Modulation of gene expression leading to progression of MGUS to MM also occurs by mechanisms other than structural genetic changes. Epigenetic changes, including alterations in DNA methylation and both the methylation and acetylation of histones, are more commonly found in later stages of MM. DNA methylation acts to regulate gene expression and follows a characteristic pattern as MM progresses **(3).**

In the early transition from MGUS to MM, global DNA hypomethylation predominates, whereas in late-stage disease, hypermethylation of specific target genes begins to occur. Such targets include genes linked to dexamethasone resistance, cell adhesion, and cell signaling. Histone demethylation, which results in globally increased gene transcription, is also more prevalent in late-stage disease and has been shown to increase the transcription and expression of several oncogenes **(4)**.

Myeloma cells grow and expand almost exclusively in the bone marrow, which underscores the importance of the bone marrow microenvironment in supporting myeloma cell growth and survival. In this microenvironment, there is a complex interaction involving bidirectional positive and negative communication among the many cell types present. The microenvironment can be functionally divided into a cellular and non-cellular compartment, each of which have components that play distinct but interacting roles in the progression of MM. The cellular compartment is composed of two cell types, the hematopoietic and non-hematopoietic cells **(5)**.

The first of these include myeloid cells, T and B lymphocytes, natural killer (NK) cells, and osteoclasts, while the nonhematopoietic cell types include bone marrow stromal cells, bone marrow–derived mesenchymal stromal cells, fibroblasts, osteoblasts, adipocytes, endothelial cells, and the blood vessels. The non-cellular compartment includes the extracellular matrix and the various cytokines, chemokines, growth factors, and exosomes that are produced by the cellular compartment **(6)**.

The two staging systems for MM include the Durie-Salmon system and International Staging System(ISS), the latter of which is preferred since it has much better prognostic capability. Multiple studies have shown that the ISS has prognostic value for all forms of therapy and it retains overall survival prognostic value at relapse. The original ISS stratified patients into three categories based on levels at diagnosis of both β2-microglobulin and albumin, which are surrogate markers of tumor burden.68 To create more robust measure of prognosis, the ISS was revised in 2015 by adding measures of genetic risk(the presence of t(4;14), t(14;16), and del (17p) mutations)to the elements of tumor burden found in theists along with the addition of LDH as an additional surrogate marker **(7)**.

Patients with a clonal plasma cell disease and signs of manifest or threatened organ damage must receive adequate systemic therapy. Although this does not generally lead to cure, modern treatment plans have now increased the 5-year survival rate for myeloma patients up to 75 years of age to over 50%. In3–20% of patients, complete remission can last for many years. In the absence of severe (cardiac and pulmonary) comorbidities, the standard treatment in Germany remains high-dose melphalan (200 mg/m2)followed by retrains fusion of autologous blood stem cells **(8)**.

The upper age limit of 65 or 70 years is determined not so much by age per se as by medical fitness and regulations. The treatment begins with induction chemotherapy. The principal active substances are the proteasome inhibitors Velarde (bortezomib) anddexamethasone (the VD protocol). In most cases, however, Velarde (bortezomib) and dexamethasone are combined with cyclophosphamide or Adriamycin, oralternatively with thalidomide (VTD), for the sake of improved efficacy. The European Medicines Agency extended the indication for bortezomib to cover non-pretreated patients before planned high-dose treatment and stem cell transplantation. After three to six cycles of induction therapy, 75–80% of patients achieve a partial remission **(8)**.

The induction therapy used for this indication in the USA, combining the immunomodulatory substance lenalidomide with dexamethasone, has not received European approval for use in patients suited for transplantation. In 2014 an Italian study group published the results of a trial comparing a tandem high-dose protocol (two courses of high-dose melphalan) with conventional treatment (six cycles of melphalan/prednisone and lenalidomide. The time that elapsed before the next occurrence of disease activity or death (progression free survival) was a median 20 months longer in the high-dose group. Overall survival after 4 years was82% for the high-dose group versus 65% in the conventionally treated group **(7)**.

Whether, in view of more effective induction regimens, single or tandem high-dose treatment is preferable remains to be established by prospective randomized controlled trials. The guidelines are inconsistent in this respect. The value of second course of high-dose treatment in the event of insufficient response (i.e., failure to achieve complete remission) is broadly accepted. Combined autologous/allogeneic stem cell transplantation has been shown to be advantageous in patients at very high risk (17p deletion, extramedullary disease) **(9)**.

Concepts for improvement or maintenance of remission are being investigated in the attempt to delay recurrence of multiple myeloma. Cytostatic drugs, steroids, interferon, and also thalidomide have been tested but largely abandoned owing to significant adverse effects and, in some cases, lack of sufficient efficacy. In several studies administration of lenalidomide up to the time of first progression has been shown to prolong progression-free survival **(10)**.

Because of an increased incidence of secondary malignancies, inconsistent results with regard to prolongation of overall survival, and the lack of approval by licensing authorities in Germany, maintenance treatment with lenalidomide has not yet become standard. Given its short duration and its potential to achieve extended progression-free interval, high-dose treatment should also be considered as a first-line treatment for patients aged 65 to 75 years whose cognitive and physical status is good. Although administration of 200mg/m^2 as standard dose for patients over 70 has been reported, a dose of 140 mg/m^2 can reduce toxicity. The adverse effects seem to increase sharply from the age of65 upward, and only small numbers of patients have been treated with the standard dose **(9)**.

Comprehensive evaluation with regard to comorbidities and cognitive and physical status may help to establish a patient's suitability for intensive forms of treatment as well as the adverse effects that are apt to occur **(7)**. A randomized controlled trial by the German Multiple Myeloma Study Group (*DeutscheStudiengruppe Multiples Myelom*) is close to completion. This study compares long-term administrationof lenalidomide/dexamethasone with tandem high-dose (140 mg/m^2) melphalan. So-called conventional therapy is the treatment of choice for patients over 75 years of age. A randomized controlled trial published in 2007showed that melphalan and prednisolone (MP) plus thalidomide (MPT) was superior to MP alone or greatly attenuated high-dose treatment with regard to progression-free survival and overall survival. Asa result, the MPT protocol was licensed for this indication. A year later, the results of another randomized controlled trial appeared: the combination of prednisolone and bortezomib showed clear superiority of them protocol (bortezomib, melphalan, prednisone)over the standard treatment in all time-related endpoints **(11)**.

In this first generation of studies, however, the high degree of efficacy was associated with high rates of discontinuation due to toxicity. For this reason, alternative ways of administering bortezomib were developed (e.g., once instead of twice weekly; subcutaneous instead of intravenous). Lenalidomide is more effective than thalidomide, but causes more hematological adverse effects. In a protocol no longer including melphalan, it was shown that lenalidomide could be successful in treating older patients: the French study group compared continuous administration of lenalidomide and dexamethasone up to the time of first

progression with 18 cycles of lenalidomide and dexamethasone and with the standard of 12 cycles of melphalan, prednisone, and thalidomide **(11)**.

Both progression-free survival and overall survival were better in the experimental arm of the study than with the hitherto standard treatment. Modified bortezomib, melphalan, prednisone (nine cycles) and continuous lenalidomide and dexamethasone until progression I detected are the first-line treatments of choice inpatients for whom high-dose treatment is not an option. Direct comparison of these two regimens would-be desirable to determine whether one is superior to the other **(9)**.

1.1.1. Treatment of recurrence:

The treatment of recurrent/refractory (r/r) multiple myeloma depends on age, comorbidities, and previous treatment. The best time to begin treatment is keenly debated. If paraprotein is increasing slowly, initiation of treatment can be delayed, but therapy should be initiated immediately in the presence of new myeloma related organ damage and/or a rapid increase in paraprotein **(10)**.

Patients with recurrent multiple myeloma whose general condition is good with no serious comorbidities can receive high-dose treatment with melphalan together with autologous stem cell transplantation. Proteasome inhibitors, immunomodulatory substances,and classical chemotherapy agents play a crucial role in the treatment of recurrent multiple myeloma. The proteasome inhibitor bortezomib is among the substances most frequently used in patients with r/multiple myeloma **(12)**.

Bortezomib combined with corticosteroids or other substances (e.g., bandmaster)has been tried in treatment of recurrences. Clinical trials have shown that bortezomib can be efficacious even in patients previously treated successfully with this substance **(13)**.

Novel proteasome inhibitors, e.g., carfilzomib and iZombie, have also achieved promising results in various combinations in patients with (r/r)multiple myeloma. A recently published randomized controlled trial showed better progression-free survival in patients with (r/r) multiple myeloma who received carfilzomib in combination with lenalidomide and dexamethasone than in those treated with lenalidomide and dexamethasone alone. On that basis this combination treatment was licensed for use in (r/r)multiple myeloma in December 2015.Lenalidomide and pomalidomide are among the immunomodulatory drugs approved for use in (r/r)multiple myeloma **(9)**.

Two large randomized controlled trials demonstrated that treatment with lenalidomide and dexamethasone is very effective, achieving significantly better overall survival than dexamethasone alone in patients with recurrent multiple myeloma **(14)**.

Pomalidomide was licensed on the basis of a randomized controlled trial that compared pomalidomide plus low-dose dexamethasone with high-dose dexamethasone in patients with r/r multiple myeloma **(15)**.

Bandmaster, doxorubicin, cyclophosphamide, andmelphalan are also frequently used in the treatment for/r multiple myeloma, mostly in combination with corticosteroids and/or one of the newer substances. Numerous novel substances with various mechanisms of action are currently undergoing investigation in clinical trials for their efficacy against r/r multiple myeloma. The anti-CS1-(SLAMF7) antibody veltuzumab and the histone-deacetylase inhibitor Panobinostat are among the substances at the forefront of clinical development. In a study that investigated lenalidomide plus dexamethasone with and without elotuzumab, patients treated with veltuzumab showed significantly longer progression-free survival **(15)**.

Detailed analyses of overall survival have yet to be published. In 2015 the European Medicines Agency approved the histone-deacetylase inhibitor Panobinostat in combination with bortezomib and dexamethasone for treatment of previously treated multiple myeloma. Veltuzumab has recently been licensed for treatment of recurrent multiple myeloma in Germany **(9)**

Patients considered eligible for stem cell transplantation undergo an induction period with a proteasome inhibitor-based regime (induction) followed by a stem cell transplant and maintenance therapy with thalidomide. Autologous bone marrow transplantation using high dose melphalan has been available for over 20 years and its safety and tolerability have dramatically increased.45 Recent studies have compared transplantation with novel agents in order to avoid the cytotoxicity associated with high dose melphalan. These studies have confirmed the place of transplantation a beneficial procedure, showing improved progression-freesurvival and higher rates of MRD **(16)**.

Allogeneic stem cell transplantation from a sibling or human leucocyte antigen-matcheddonor is rarely used, but may have palace in young patients with high-risk myeloma or who have had an early relapse after autologous stem cell transplantation. A recent large study from the United States showed no advantage in allogeneic transplantation compared with sequential autologous stem cell transplantation, but there remains disagreement in the literature concerning its value **(17)**.

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