Advances in the Treatment of Multiple Myeloma: Long Awaited

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Pathogenesis of MM

Multiple myeloma (MM), a neoplastic proliferation of plasma cells, may evolve from monoclonal gammopathy of unknown significance (MGUS).1 MGUS occurs when limited number of immortalised plasma cells home to the bone marrow, adhere to the stroma, and trigger an autocrine/paracrine IL-6 cytokine loop that confers survival advantage to the myeloma plasma cells. With time, clonal evolution in the plasma cells develops, leading to metastasis of the neoplastic plasma cells to multiple sites of the bone marrow. Interaction of the plasma cell with the marrow micro-environment leads to osteolytic bone lesions, and thus symptomatic multiple myeloma.2 Therefore, MM is not only a disease of neoplastic plasma cells but also a disease where the micro-environment is of utmost importance to the development of complications and chemo-resistance. As a result, treatment of MM requires targeting of not only the neoplastic plasma cells but also the microenvironment. (Figure 1)

The most important initiation event in myeloma pathogenesis involves upregulation of D-type cyclins, majority by virtue of various chromosomal translocations involving the immunoglobulin heavy chain gene.3 Deletion of chromosome 13 occurs in about half of the patients with MGUS and MM, and is an important adverse prognostic factor that defies tumour cell kill by high-dose chemo-irradiation inherent with autologous bone marrow transplantation.

Diagnosis of MM and monitoring of disease activity

The diagnosis of MM is based on plasmacytosis (usually >10%) in the bone marrow, osteolytic bone lesions on skeletal survey, and presence of a monoclonal gammopathy in the serum. Therefore, the usual investigations in a case of suspected myeloma include serum protein electrophoresis, bone marrow aspiration and skeletal survey.1 New modalities that enable detection of occult bone disease include magnetic resonance imaging of the bone marrow and PET-scan.

While the detection of a monoclonal immunoglobulin in the serum usually raises the suspicion of MM, monoclonal gammopathy may also occur in other lymphoproliferative diseases such as CLL, indolent lymphoma, or even primary amyloidosis in the absence of MM. Moreover, the most common immunoglobulin subtypes in MM, in order of prevalence, are: IgG, IgA and then light chain disease.

Apart from clinical symptoms, disease activity is monitored by the level of monoclonal paraprotein (M-protein).1 Recently, serum free light chain has been shown to correlate with M-protein and is a useful adjunct to M-protein measurement for the monitoring of myeloma disease, especially in those with light chain myeloma.

Natural course of disease in MM

Clinically, patients with MGUS are entirely asymptomatic, which may progress to symptomatic MM at the rate of 1% per year.2 On the other hand, patients with MM are usually symptomatic with hypercalcaemia, Renal impairment, Anaemia or Bone pain/fracture (abbreviated as CRAB). Conventional treatment comprises combination of alkylators with steroid, usually in the form of melphalan + prednisolone, which induces a response rate of about 50% but complete remission in about 5% of patients. Treatment of patients with MP usually leads to plateau phase when a reduced amount of M-protein remains detectable but at stable levels. The disease inevitably progresses with escalation of M-protein and recurrence of clinical symptoms, which may be controlled with further chemotherapy. However, patients will eventually succumb due to refractory disease. Moreover, high-dose chemotherapy followed by stem cell rescue, i.e bone marrow transplantation (BMT) is only applicable to younger patients in view of its toxicity. Therefore, MM is regarded as a largely incurable disease.

Treatment goals and cytoreduction chemotherapy

The modalities of treatment in patients with MM depend on the age of the patients. For instance, cure is aimed at in young myeloma patients, prolongation of survival in myeloma patients entitled for autologous bone marrow transplantation, and symptomatic control in the elderly patients. Initial cytoreduction usually involve combination chemotherapy, followed by autologous BMT (ABMT) in those eligible patients. The median survival in MM is about 3-5 years, depending on if the patient has undergone ABMT.

Prognostic factors

1. Durie-Salmon versus International myeloma staging
Conventional chemotherapy in MM

MP (melphalan/prednisolone) has been the mainstay of treatment for decades. Subsequent intensification of treatment with additional chemotherapeutic agents did not improve survival. In the early 1990s, VAD (vincristine, adriamycin, dexamethasone) has been applied with an improvement in response rate. Importantly, VAD does not contain any alkylator, which will decrease the yield of stem cell harvest for subsequent autologous BMT. Moreover, VAD results in a rapid response and can be applied in patients with renal insufficiency. Therefore, myeloma patients who are eligible for autologous BMT will receive VAD.

Role of autologous BMT

In the last decade, one of the most important advances in the treatment of MM is the advent of autologous bone marrow transplantation (ABMT), which will enable increase in the rate of complete remission (CR), and prolonged disease-free and overall survival. However, the procedure is not curative but results in significant prolongation of survival. On the other hand, allogeneic bone marrow transplantation (Allo-BMT) with bone marrow rescue from HLA-identical siblings is probably the only curative modality of treatment but the treatment-related mortality is excessive, up to 30%. Therefore, mini-allogeneic BMT by virtue of non-myeloablative chemotherapy, which will render less treatment-related mortality, is currently under intensive research for its efficacy and safety in the treatment of MM.

New agents in MM: mechanisms, safety and efficacy

1. Thalidomide

Thalidomide has been banned in the 1960s as a sedative because of teratogenicity. Thalidomide was approved by FDA for the treatment of MM in 1998. Clinical trials showed that upfront use of thalidomide plus dexamethasone results in a high response rate (60%). The major side-effects are neuropathy, constipation, bradycardia and venous thrombosis (less common in the orientals). Revlimid is a derivative of thalidomide. However, the major side-effect is myelotoxicity instead of neuropathy. Early data showed a high response rate of revlimid plus dexamethasone when used as salvage therapy in relapsing myeloma patients.

2. Bortezomib (Velcade)

NF-kB is a transcription factor which upregulates genes protecting myeloma plasma cells from apoptosis. However, normally NF-kB is inhibited by IκB by forming a cytosolic complex with IκB, precluding its access to promoter region of its target genes. Bortezomib is a proteosome inhibitor which protects IκB from proteosomal degradation, and thus keeps NF-kB in the cytoplasm, thereby preventing activation of anti-apoptotic genes and leads to apoptosis of myeloma plasma cells. Bortezomib has been shown to be an effective salvage therapy in heavily pretreated, relapsing myeloma patients.

Impact of novel therapeutic agents on induction therapy of MM

Upfront use of some of these novel therapeutic agents, in particular in combination with conventional chemotherapy, has been shown to increase CR rate from about 5% to up to 30%, which is a major advance in the treatment of MM. Moreover, apart from Revlimid, these agents are not myelotoxic, and thus can be used together with myelotoxic chemotherapeutic agents such as melphalan, doxorubicin or cyclophosphamide. Indeed, MPT (melphalan, prednisolone and thalidomide) combination has resulted in a CR or near CR rate of about 25%, and importantly a prolonged survival compared to those receiving MP alone. Moreover, upfront use of bortezomib with MP results in high CR rate (32%) and total response rate of 89%, which is a major breakthrough in myeloma therapy. Similarly, combination of velcade with doxorubicin and dexamethasone resulted in a CR or near CR rate of 25%.

General treatment recommendations

Taking into account the difficulty in achieving CR in myeloma, which is a requisite to cure, the advances in the new therapeutic agents, and the survival advantage inherent with bone marrow transplantation, a general treatment recommendation may be devised based on the age of the patient (which limits the application of ABMT) and data from randomised clinical trials. (Figure 2)

1. MM patients <65 years: autologous BMT after initial cytoreduction. There is some studies showing that tandem autologous BMT results in superior survival to one autologous BMT. On the others hand, patients achieving > 90% reduction of M-protein do not benefit from tandem autologous BMT.

2. Elderly MM patients: induction therapy with MPT (melphalan, prednisolone and thalidomide), Velcade plus MP, or MP

Current Controversies

1. One autologous BMT versus tandem (double) ABMT

ABMT has been shown in multiple randomised clinical trials to result in higher CR rate, superior progression-free
and overall survivals when compared with conventional chemotherapy alone.\(^8\) (Hira et al, 2006) With ABMT, an additional 15%-25% of myeloma patients may achieve CR or near CR.

Moreover, in patients who failed to achieve >90% reduction in M-protein levels after a ABMT, a recent clinical trial has shown superior survival in patients undergoing tandem autologous BMT compared with those undergoing a single autologous BMT. Ongoing clinical studies are conducted to compare the outcome of tandem auto-allo BMT with tandem autologous BMT.

II. High-risk patients (with high β2-microglobulin and deletion of chromosome 13)

As yet, bortezomib is the only agent that appears to overcome the adverse prognostic impact of deletion 13, which impacts survival adversely even in the setting of super-intensive chemotherapy such as tandem autologous BMT. Tandem auto-allo BMT is potentially hazardous because of the inherent GVHD. Therefore, high-risk MM patients, such as those with high ISS stage or deletion 13 karyotype, should be enrolled into clinical trials. Moreover, maximal cytoreduction, preferably CR, should be achieved prior to autologous stem cell harvest, thereby minimising contamination of marrow graft with myeloma plasma cells. Achievement of CR has been largely impossible with conventional combination chemotherapy. Therefore, the increased CR rate associated with the use of these novel agents will hopefully render a high proportion of myeloma patients a CR, who may then undergo BMT with minimal amount of tumour cells.

Summary

MM has for a long time been an incurable disease but major advances in bone marrow transplantation and advent of novel therapeutic agents has enhanced the CR rate, the pre-requisite to cure. Optimisation of the application of BMT and novel agents will lead to prolonged survival and hopefully cure in the future. Moreover, bortezomib may overcome a hitherto unconquered adverse prognostic factor of deletion 13. Therefore, it is of utmost importance that chromosomal study has to be performed at diagnosis to risk-stratify the patient. Those with high-risk features may undergo clinical trials incorporating bortezomib induction, followed by auto-mini-allogeneic BMT at the time of minimal residual disease.

References