Therapy of Multiple Myeloma

H. Goldscheidt, F. W. Cremer, Th. Möhler, A. Krämer, M. Görner, G. Egerer, A. D. Ho

Summary  Multiple Myeloma (MM) is characterised by the accumulation of malignant plasma cells in the bone marrow producing a monoclonal immunoglobulin. The standard conventional therapy is the combination of melphalan and prednisone resulting in a response rate of 40% - 60% and in a median survival time of approximately 3 years. In order to improve the therapeutic efficacy various combination regimens have been tested. Most randomized trials have failed to show a significant improvement in survival time when combination chemotherapy is used instead of melphalan with or without prednisone. The benefit of maintenance therapy with interferon-alpha has been demonstrated. The toxicity of interferon-alpha, which may reduce the quality of life, should be considered. Recently, myeloma-treatment has been modified. High-dose chemotherapy accompanied by hematopoietic stem-cell support via autologous transplant is recommended up to the age of 65 - 70 years. First results from a French study comparing single versus double autologous transplantation have shown a benefit in terms of event-free survival for the sequential approach. Vaccinations as an adoptive immunotherapy to treat minimal residual disease are under way. The mortality rate of autologous transplantation of hematopoietic stem cells has been reduced in the last 5 years. The use of reduced conditioning regimens or the partial depletion of T cells in peripheral blood stem cell transplants in an effort to decrease transplant related mortality are promising approaches. Thalidomide and its derivates are a new class of agents with independent anti-turnout activity in MM. Encouraging results with this antiangiogenic therapy in phase II trials have been reported. Supportive therapies such as the treatment of anaemia with erythropoetin, the management of renal failure and the use of bisphosphonates, improve the life quality of MM patients.

Key words  multiple myeloma; treatment; transplantation; angiogenesis

Multiple Myeloma (MM) is characterised by the accumulation of malignant plasma cells in the bone marrow. These myeloma cells, derived from B-lymphocytes, produce an identical immunoglobulin known as monoclonal protein, the laboratory hallmark of MM. Patients suffer from the consequences of local tumour infiltration and bone destruction, abnormal cytokine production with anaemia, hypercalcemia, and suppression of normal immunoglobulin production. Monoclonal immunoglobulin production can be associated with deposition diseases, hyperviscosity, renal failure and coagulopathies. The incidence of MM in the United States and in Europe is four out of 100,000 people, with a median age at diagnosis of 65 years. MM accounts for about 1% of all types of cancer and slightly more than 10% of haematological malignancies. The cause of MM is unknown; however, radiation, exposure to environmental toxins, and a genetic component are considered possibilities.

Conventional chemotherapy

Prior to the introduction of melphalan and prednisone (MP), the average survival of MM patients was only a few months. Alexanian et al. published the results of treatment with oral melphalan with or without prednisone, and demonstrated a prolongation of survival. In numerous subsequent studies oral MP has been shown to prolong survival to 2 to 3 years. An equivalent dose of melphalan given intravenously was not found to further improve survival. Overall, 40% - 60% of patients will respond to MP. Complete remission, i. e. disappearance of the monoclonal protein with a plasma cell content of <5% in the bone marrow, is below 10%. Treatment should usually be stopped when a stable plateau of monoclonal immunoglobulin is reached. Further chemotherapy favours the development of drug resistance, myelodysplastic syndromes or acute leukaemia. Patients should be followed closely during the plateau phase, and MP chemotherapy should be reinstituted when relapse occurs later than 6 months after the end of initial treatment.

In comparison to MP, several studies have shown a higher objective response rate with combination chemotherapy, but in the majority of studies this has not translated into a significant improvement in survival. A meta-analysis of studies on 6,633 patients found no difference between MP and various combination chemotherapies in terms of overall survival. The VAD-treatment with vincristine, Adriamycin (doxorubicin) and high-dose dexamethasone, introduced by Barlogie et al., could significantly improve the rapidity and degree of response. Therefore patients with acute renal failure should be treated with this combination therapy. Because of the low toxicity of VAD to hematopoietic stem cells, it is widely used to induce remission before peripheral blood stem cell harvest followed by autologous transplantation.

In the standard VAD-regimen, vincristine and doxorubicin are given by continuous infusion via central line for four days and dexamethasone (40 mg daily) is administered on days 1 - 4, 9 - 12, and 17 - 20 each month. Modifications of VAD include the reduction of dexamethasone to day 1 - 4, the bolus infusion of vincristine and
dorubicin, the use of idarubicin or other anthracyclins instead of doxorubicin and the evaluation of navelbine, a new vincaalkaloid, instead of vincristine.

Most patients with MM responding to the initial chemotherapy enter into a plateau phase, that consists of a period of stability in which tumor progression does not occur, despite the persistence of a monoclonal protein and the presence of abnormal plasma cells. The stability of tumor burden during the plateau phase seems to be a result of immunological mechanisms and not being simply due to the reduction of tumor mass. There is no doubt that interferon-alpha (IFN-α) is the most promising agent in the maintenance treatment of MM. The Vienna Group of H. Ludwig [16] conducted a meta-analysis with IFN-α in induction and maintenance therapy. For maintenance therapy, treatment with IFN-α resulted in an increase in progression-free survival by 6 months and in overall-survival by 7 months. Considering the benefits of IFN-maintenance therapy, the toxicities and financial costs, treatment is agreeable to 32% - 58% of myeloma patients [7].

The patient preference following information about benefits and risks of IFN-therapy should therefore play a decisive role in planning the treatment. Our current practice is to use IFN-maintenance in all responding myeloma patients under the age of 70 years. Dose adjustments or even discontinuation of treatment are made in cases of toxicity in order not to decrease the patients’ quality of life.

**Autologous stem cell transplantation**

High-dose therapy followed by either autologous bone marrow transplantation (ABMT) or autologous peripheral blood stem cell transplantation (PBSCT) has increased the CR-rates from 10% after conventional therapy to 40% - 50%. The results of the IFM-90 trial showed a significantly longer event-free survival (EFS) and overall survival (OS) in patients treated with HD-melphalan and total body irradiation (TBI) followed by ABMT compared to patients treated with conventional polychemotherapy [8]. The survival advantage as a result of the HDT presented by the French study is of similar order of magnitude as that reported by Barlogie et al [9] and Lenhoff et al [10]. In the evaluation of patients treated at a single centre, age was not biologically adverse parameter. In an analysis including 350 patients treated with HDT at our centre, the mortality of patients up to 70 years is not higher compared to patients younger than 60 years. Although the designs of the trials are different, the results indicate that HDT can be recommended up the age of 65 - 70 years.

PBSCT’s are preferable to ABMT because engraftment is more rapid and the number of reinfused malignant cells is lower. A major goal for transplantation is to identify the HDT that best combines low toxicity with high anti-tumor effect. Comparing melphalan 140 mg/m² plus total body irradiation (TBI) with melphalan 200 mg/m², there were no differences in terms of response, EFS and OS [12]. However, since the toxicity of melphalan alone was lower than melphalan plus TBI, most investigators discontinued TBI [13]. A German multi-centre trial comparing total marrow irradiation plus busulfan/cyclophosphamide versus two courses of melphalan alone is still ongoing. To increase the response rates and to reduce the relapse rates highly purified CD34 positive blood stem cells have been used. Tumor cell purging did not improve the outcome after PBSCT in MM. The results of a randomized trial of the EBMT-group showed an increased rate of infections in the arm using purified CD34 positive blood cells compared to the arm with unselected cells, so that the purging of autografts is not recommended outside of prospective trials [14]. The role of double transplantation is under investigation. Barlogie et al first demonstrated the feasibility of this approach in high-risk refractory MM patients. The practicability of a double transplant in a multicentre setting was demonstrated in a German trial. First results from one study comparing single versus double autologous transplantation have shown a benefit in terms of event-free survival for the sequential approach [15].

Tries with vaccinations as an adoptive immunotherapy to treat minimal residual disease have been initiated [16]. One of the most potent means of stimulating immune response is through dendritic cells. Dendritic cells generated from myeloma patients are not different from those harvested in healthy donors [17]. Some groups have shown idiotype-specific T-cell responses or idiotype-specific antibody production in myeloma after vaccination. The clinical benefit of these immune-based therapies remains to be determined.

**Allogeneic stem cell transplantation for MM**

The potential graft-versus-melanoma effect of allogeneic stem cell transplantation can contribute to the elimination of residual tumour cells that have been resistant to chemo-therapy, increasing the chances of cure in MM. In addition, this approach offers the possibility of using HDT followed by rescue with healthy hematopoietic stem cells which have not been exposed to chemotherapeutic agents and are free of contaminating tumour cells. However, early attempts were hampered by a transplant related mortality up to 50%. In a recent registry study of the EBMT, it was shown that allogeneic transplantation results have improved significantly during the last 5 years and early transplant related mortality has been reduced from about 40% to somewhat more than 20% [18]. The use of reduced conditioning regimens may further decrease the treatment-related mortality. In an EBMT survey of alloge-