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Minireview paper

Treatment of myeloma: recent developments

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Melphalan was the first described treatment for patients with multiple myeloma in the 1960s and is still being used in clinical practice. However, the use of melphalan in combination with prednisone resulted in a median survival of only 2–3 years. Therefore, the dose of melphalan has been intensified since then (140–200 mg/m^2). In order to diminish treatment-related morbidity and mortality due to severe myelosuppression induced by these regimens, high-dose melphalan is currently supported with autologous stem cells. Indications for high-dose therapy and the role of further intensification by performing second or allogeneic transplantations are discussed. Furthermore, new therapeutic modalities, such as inhibitors of angiogenesis, also showing direct antiproliferative, cytokine-related and immunomodulatory effects on plasma cells (thalidomide and its newer deratives), inhibitors of the transcription factor NF-κB (proteasome inhibitors) and immunotherapy are described. [© 2002 Lippincott Williams & Wilkins.]

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Introduction

Multiple myeloma (MM) belongs to the plasma cell disorders, characterized by expansion of monoclonal plasma cells producing heavy and/or light chain immunoglobulins (M-protein). IgG is produced in more than 50% of patients, IgA in 30% and IgD, IgM or IgE rarely. Excretion of light chains in the urine is found in about 60% of patients. The diagnosis of MM is based on a classic triad of an increased number of plasma cells in the bone marrow (above 10%) or histologic proof of a plasmacytoma and one of the following criteria: M-protein in serum, monoclonal light chains in urine or the presence of lytic bone lesions. The clinical symptoms are caused by skeletal destruction and by bone marrow infiltration compromising normal hematopoiesis. Furthermore, a high level of M-protein can cause hyperviscosity, renal failure and neuropathy. Suppression of production of normal immunoglobulins leads to a high incidence of infectious events.

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Epidemiology and etiology

MM accounts for 1% of all malignancies in Caucasians and 2% in US Blacks.[1] In the Netherlands there are about 2000 patients suffering from MM, of whom 50% are younger than 65 years at the moment of diagnosis.[2] The annual incidence in the Netherlands in 1995 was 4.9 in males and 3.6 in females.[3]

The most established risk factors for development of MM are acute exposure to high doses of radiation or chronic exposure to lower doses of radiation.[2] Many studies have examined the relationship between chemical exposure and MM, especially among agricultural workers. Various chemicals were found to increase the risk of developing MM 3- to 4-fold, such as consumption of dioxin-contaminated fish and proximity to dioxin-contaminated water sources.[4,5] More recently, the role of viral infections in initiating a clonal idiotypic expansion of plasma cells has been investigated. An increased risk of MM in HIV-infected patients has been described.[6] Furthermore, a role of human herpes virus-8 (HHV-8) in the onset of MM has been proposed.[7–9] However, other groups failed to detect HHV-8 sequences in bone marrow biopsies.[10,11] Recently, the presence of HHV-8 was shown to be relatively common in healthy donors, which does not support a role in MM.[12] Therefore, there is no proven link between viral infections and the development of MM.

Currently, a multi-step pathogenesis of MM is proposed. It is hypothesized that during specific DNA modification processes in B cell development Ig H

translocations occur, resulting in new fusion genes, leading to clonal expansion of cells. Subsequently, karyotypic instability and secondary translocations occur.[13]

Prognostic factors

Prognostic factors were defined in previous trials concerning conventional treatment strategies. From recent trials investigating the role of high-dose chemotherapy with stem cell support, it was learned that the presence of previously defined risk factors was also predictive for the effect of high-dose chemotherapy. Therefore, prognostic factors, as described in the following paragraphs, should be implicated in defining the best treatment strategy for individual patients.

Staging system proposed by Salmon and Durie

Salmon and Durie proposed a staging system in 1975 based on the correlation between clinical presentation and plasma cell burden. Patients are divided in three groups according to the level of hemoglobin, serum calcium, level of M-protein and the presence of skeletal lesions (stage I, II and III). Using conventional therapy, patients with stage III disease have a median survival of 2 years, whereas patients with stage I disease frequently survive more than 5 years.[14]

Plasma Cell Labeling Index (PCLI)

In several studies the PCLI has been found to be an independent risk factor.[15–19] In this assay the number of proliferating cells is determined by the use of bromodeoxyuridine, which is only incorporated in S phase. The use of this assay is hampered by not being incorporated in daily laboratory practice.

β_2-microglobulin and albumin

Levels of β_2-microglobulin predict survival in conventionally treated as well as transplanted MM patients.[18,20,21] In conventionally treated patients, according to studies of the Southwest Oncology Group, the median overall survival (OS) times could be determined combining β_2-microglobulin levels with albumin levels (ranging from 16 months in patients with β_2-microglobulin >5.5 mg/l and albumin <30 g/l to 58 months in patients with β_2-microglobulin <2.5 mg/l and albumin >30 g/l).[22]

Similarly, in a recent performed randomized trial in which conventional chemotherapy was compared with autologous stem cell transplantation a low β_2-microglobulin level independently predicted a complete or very good partial response in both groups.[23]

Chromosomal abnormalities

Chromosomal analysis became incorporated in the diagnosis and monitoring of a variety of hemato-oncological diseases. Recently its use was introduced in patients with MM. Using conventional cytogenetic analysis, in a high proportion of patients (43%) a variety of chromosomal abnormalities, such as numerical abnormalities, deletions and translocations were observed.[24] Some of these abnormalities were found to be of prognostic significance.[25,26] Abnormalities of 11q and partial or complete deletions of chromosome 13 were associated with a worse overall as well as event-free survival. Patients with abnormalities of both chromosome 11 and 13 had an OS of only 12 months.[26] The absence of abnormalities of chromosome 11 and 13 significantly affected the duration of complete remission (CR) in patients undergoing autologous stem cell transplantations (more than 69 months in patients without chromosome 11 or 13 abnormalities versus 26 months in patients with these abnormalities), which correlated with a prolonged event-free survival and OS.[27] Analysis of their extended study of 1000 patients who underwent high-dose therapy, especially the absence of chromosome 13 abnormalities was significantly correlated with a better survival.[28] Therefore, an unfavorable karyotype is currently defined as abnormalities of chromosome 13 and/or 11.

Combination of cytogenetics with conventional risk factors

In the Total Therapy programme of the University of Arkansas, in which patients are autotransplanted twice, OS is independently correlated with the number of risk factors. Risk stratification occurred by using β_2-microglobulin levels (>2.5 versus <2.5 mg/l), chromosome abnormalities (abnormalities of chromosome 11 and 13 versus absence of these abnormalities) and duration of prior therapy (>12 versus <12 months). Event-free survival varied from median 37 (no risk factors) to 7 months (three risk factors) (Table 1).[29]

Table 1.

No. of risk factors	Median event-free survival (in months)
0	37
1	26
2	14
3	7

Treatment

Conventional induction chemotherapy

Melphalan was the first described treatment for MM in the 1960s and has remained the mainstay of therapy since then. In 1969 addition of prednisone was found to improve outcome, with a median survival of about 2–3 years.[30,31] Efforts have been made to improve outcome by using various agents and combinations for induction and maintenance therapy. On the presumption that alternating use of chemotherapeutic drugs with different mode of actions would be more effective, other alkylating agents like cyclophosphamide and carmustine, were combined with adriamycin and prednisone with or without vincristine (VCAP, VBAP and CAP). These combinations were compared with regimens in which melphalan was combined with vincristine, cyclophosphamide and prednison (VMCP).[32] Although addition of vincristine improved the response rate, recent analysis showed no differences in long-term survival. Comparison of these regimens with standard melphalan/prednisone (MP) revealed a better median survival of VMCP/VCAP and VMCP/VBAP over standard MP (36 versus 25 months); however, again there was no effect on long-term survival.[22,33,34] The advantage of newer combination therapy over MP in median survival could not be confirmed by others.[35–38] A meta-analysis on 18 published trials with 3814 patients showed that standard MP and other combination therapeutic regimens are equally effective.[39,40] Therefore, MP is still standard induction therapy.

Nevertheless, current OS rates obtained with conventional chemotherapy require new forms of therapy. In older patients improving OS will merely be dependent on improving salvage treatment and supportive care. This was recently supported by a retrospective study showing response percentages of about 50% and median remission durations of about 20 months, independent on the type of induction therapy (MP versus combination chemotherapy). OS, however, was different in the period of 1983–1986 compared to the period of 1986–1994 (33 versus 43.2 months), suggesting a role for salvage chemotherapy and supportive care.[41]

Salvage chemotherapy for relapsing MM after conventional therapy

First evidence for the efficiency of vincristine, doxorubicin and dexamethasone (VAD) as salvage therapy for patients refractory to alkylating agents came from Barlogie,[42] showing remissions in about 30% of primary resistant patients and in about 65% of relapsing patients, which was confirmed by others.[43,44] Originally, vincristine (0.4 mg/day) and doxorubicin (9 mg/m^2/day) were administered as a 4-day continuous infusion via a central venous catheter. Recently, it was found that vincristine and doxorubicin could be administered as rapid infusion, thereby bypassing the need for admission to the hospital.[45,46] In primary resistant disease similar responses were reached with solitary treatment with dexamethasone. In relapsing patients VAD was found to be somewhat more effective than dexamethasone alone.[47,48]

High-dose chemotherapy with stem cell support in patients aged less than 65 years

To improve OS in younger patients several groups explored much higher doses of melphalan with some source of stem cell support, which led to autologous stem cell transplantation becoming standard therapy in younger patients.

Autologous stem cell transplantation

Single transplants. The Royal Marsden Group was the first to explore high-dose melphalan (HDM) (140 mg/m^2) in patients with resistant disease or high-risk untreated disease. The dose of melphalan was indeed found to correlate with higher CR rates and response rates. However, the high CR rate of 32% was reached at the cost of a high treatment-related mortality rate of 16%, due to severe myelosuppression.[49] Therefore, HDM was subsequently supported with stem cells. Several groups have now treated MM patients with HDM with stem cell support after induction chemotherapy consisting mainly of VAD-like regimens. Although these phase II studies describe heterogeneous patient populations, conditioning regimens and definitions of response, progression-free survival, disease-free survival, as well as OS appear to be significantly better in

patients treated with HDM as compared with historical control groups treated with conventional chemotherapy.[50–53] Only in the study of Bladé, patients who were eligible for HDM, but did not receive it, had the same survival as compared to patients receiving high-dose chemotherapy.[54] The first prove that HDM was indeed superior as compared to conventional therapy came from the randomized study of the Intergroupe Myeloma Française.[23] CR was reached in a significantly higher percentage of patients treated with HDM compared to with conventional therapy, resulting in a better OS (for all patients: CR, 22 versus 5% and 5-year OS, 52 versus 12%; for patients aged less than 60 years, 5-year OS; 70 versus 18%).[23]

Double transplants. In view of the fact that HDM with stem cell support resulted in higher CR rates, it was hypothesized that further dose intensification would improve CR percentages even more and would be translated in better clinical outcome. In the Total Therapy program of the University of Arkansas MM patients were double transplanted using HDM (200 mg/m^2) as a first conditioning regimen and total body irradiation and cyclophosphamide as a second conditioning regimen. It was shown that CR rates increased during treatment, from 15% after induction therapy, 26% after the first to 41% after the second transplant.[27] The increase in CR percentages after the second transplant has also been shown by Harousseau,[55] Bjorkstrand,[56] Weaver[57] and ourselves.[53] In view of the hypothesis that achievement of a CR results in a longer event-free survival and better OS, double-transplant programmes might be shown to be more effective than single transplants in MM patients. Again from the Intergroupe Myeloma Française there came indications that higher CR rates obtained by double transplantations are indeed translated into a better OS. Although an earlier performed analysis of their randomized study comparing single transplantation (HDM 140/TBI) with double transplantation (HDM 140 followed by HDM140/TBI), only showed an advantage in OS in low risk patients with a β_2-microglobulin of below 3 mg/l,[58] a recent interim analysis showed that the significantly higher percentage of CRs and very good partial remissions in double-transplanted patients as compared to single-transplanted patients was not limited to low risk patients (61 versus 50%). After the first randomization (single versus double transplantation) a second randomization occurred (bone marrow versus peripheral stem cells). The 5-year post-second randomization survival was significantly higher in patients transplanted twice with the use of peripheral stem cells compared to patients transplanted once or transplanted with bone marrow (60 versus 40% for patients transplanted with peripheral stem cells, 43 versus 35% for patients transplanted with bone marrow). A second transplant could be performed in 75% of patients with a first transplant.[59] However, to determine the role of double transplantation, the final results of this and other randomized studies have to be awaited.

Allogeneic stem cell transplantation

Although CR rates and OS increased after the introduction of autologous transplantation protocols compared with conventional chemotherapy, all patients eventually relapse and molecular remissions are rare. Considerably higher percentages of molecular remissions have been described after allogeneic transplantations. Using clonal markers based on rearrangement immunoglobulin heavy chain genes, in allogeneic transplanted MM patients in complete clinical remission, molecular remission rates of 27–75% have been reported.[60–62] These percentages were higher as compared to autologous transplanted MM patients (up to 16%).[60,61] Moreover, patients who achieved a molecular remission had significantly lower relapse rates. Therefore, allogeneic transplantation might potentially cure patients.

However, in clinical practice allogeneic transplantation procedures were found to be complicated by high transplantation-related mortality rates up to 50%.[62–67] This is probably accounted for by inclusion of heavily pretreated MM patients and patients with refractory disease. The analysis performed by the European Group for Blood and Marrow Transplantation centers supports this hypothesis, as a significant reduction in transplantation-related mortality was found comparing results obtained during the period of 1983–1993 with 1994–1998 (38 versus 21%). Reasons for this decline were better results of transplantation earlier in the disease and better supportive care. Reduction in transplantation-related mortality was translated in a higher median OS; 10 months for patients transplanted in the earlier time period versus 50 months during the later period.[68]

Another strategy to diminish transplantation-related mortality may be performing allogeneic transplantation following treatment with non-myeloablative regimens instead of myeloablative regimens. The rationale is that the advantages of allogeneic transplatations are thought to be the

result of a graft versus myeloma (GVM) effect. Proof for that came from studies in which infusion of donor lymphocytes (DLI) resulted in partial and even complete clinical responses.[69,70] Therefore, in order to diminish direct toxicity of the myeloablative regimen, non-myeloablative regimens consisting of melphalan alone, total body irradiation alone, combinations of fludarabin, anti-thymocyte globulin and busulfan were explored.[71–73] In the studies of Badros *et al.*[71] and Garban *et al.*[73] patients were previously autotransplanted. Response rates of 75% were observed, of which 30% were CR. Even in patients with a refractory relapse remissions were observed. Transplantation-related mortality was found to be minimal.

However, it is currently unknown which patients will benefit from up-front allogeneic transplants, because of the lack of randomized protocols comparing autologous versus allogeneic transplantations. Only one retrospective case-matched study, describing patients treated during 1983–1994, compared the outcome of allogeneic transplants versus autologous transplants. It was found that OS was significantly better in autologous transplanted patients. This was due to the already mentioned high transplantation-related mortality of 41% in allogeneic transplanted patients,[64] which is expected to decline when transplanting patients up-front or using non-myeloablative regimens. This is not supported, however, by preliminary results obtained from the Dutch HOVON 24 study in which MM patients were transplanted allogeneic up-front. Median OS appeared to be worse in patients transplanted allogeneic as compared to patients transplanted autologous (21 versus 45 months).[74]

Maintenance therapy with interferon (IFN) after conventional therapy

Most studies in which the efficiency of treatment with IFN-α was investigated showed a improvement of remission durations of 6–9 months. However, in most studies this was not translated into an improvement of OS.[75–79] A recent meta-analysis concluded: 'the survival benefit, if any, is small and needs balancing against cost and toxicity'.[80]

Maintenance therapy with IFN after high-dose chemotherapy

In transplanted patients the role of IFN as maintenance therapy has been less extensively studied. Cunningham reported a significantly better OS at 4.5 years, which, however, ceased to exist at 7.5 years.[81] In a retrospective analysis of the EBMT registry, OS was better in patients treated with IFN. This analysis, however, was hampered by differences in prognostic factors between treated and untreated patients, and by the fact that only patients in CR or partial remission at 6 months after transplantation were analyzed.[82] Therefore, the value of interferon as maintenance therapy after high-dose chemotherapeutic regimens has yet to be determined.

New therapeutic modalities

Thalidomide

Several studies have shown an increased microvessel density in the bone marrow of MM patients, suggesting a role for angiogenesis in MM.[83–85] Thalidomide, originally a sedative which had become obsolete because of teratogenicity, was found to inhibit angiogenesis.[86] The first evidence for clinical efficacy of thalidomide in patients suffering from MM came from a study by the group of Barlogie, in which 89 refractory or relapsed MM patients showed a response rate of 32%.[84] Since then several studies have shown effectiveness of thalidomide in relapsed and refractory patients, with response rates varying up to 64%.[87,88]

The efficacy of thalidomide appeared not to be solely the result of inhibiting angiogenesis, as no correlation was found between microvessel density and response to therapy.[84] Therefore, research was focused on other mechanisms whereby thalidomide could affect the growth of plasma cells. First, thalidomide was found to diminish the expression of the adhesion molecule ICAM-1. As a consequence, less plasma cells adhered to stromal cells, resulting in inhibition of growth and survival.[89] Second, thalidomide was found to block the effect of cytokines important to growth of plasma cells [interleukin (IL)-6, tumor necrosis factor-α and IL-1].[90] Third, production of IFN-γ and IL-2 by cytotoxic T cells and natural killer cell number and function was enhanced by thalidomide.[91,92] Furthermore, research on the cause of teratogenicity of thalidomide showed free radical-mediated oxidative DNA damage.[85] In summary, thalidomide has proven to be effective in relapsed and refractory MM patients, although the mechanism is still unclear.

Future role of thalidomide

The value of combining thalidomide with other established treatment modalities for MM is currently

under investigation. There are already indications that the combination of thalidomide and dexamethasone is more effective than dexamethasone alone in patients relapsing after autologous stem cell transplantations (57 versus 27% response rate, respectively).[93] Also, in patients with a lack of continuing response to thalidomide alone or patients with a rash on thalidomide, addition of low-dose dexamethasone (4 mg) further reduced M-protein levels and was associated with fewer side effects.[94] The role of thalidomide in newly diagnosed patients, undergoing high-dose chemotherapy, in induction as well as maintenance therapy will be investigated in several protocols. For example, in the Netherlands the HOVON 50 protocol has started—a randomized study in which the value of thalidomide in the induction phase and in maintenance phase will be investigated. All patients will receive one or two courses of high-dose chemotherapy with stem cell support. Since a tendency to venous thrombosis has been reported, patients in the thalidomide arm will receive prophylactic low-molecular-weight heparin (LMWH).[93,95]

New thalidomide derivatives

New analogs [3-amino-phthalimido-glutaramide (S-3APG)] and derivatives (CC5013) of thalidomide are currently being investigated in *in vitro* (S-3APG) or *in vivo* (CC5013) phase I studies. *In vitro* and animal studies show better direct antiproliferative, cytokine-related and immunomodulatory effects against MM cells than thalidomide. Preliminary studies using CC5013 in MM patients show anti-tumor activity (greater than 25% response in 15 of 24 patients) with acceptable toxicity, mainly myelosuppression, but no somnolence and neuropathy as described in patients using thalidomide.[96,97]

Immunotherapy

Although immunotherapy has been reported in several meetings, abstracts and some reports, its usage at a large scale will probably not take place for several years.

Passive immunotherapy using monoclonal antibodies (mAb)

Plasma cells are known to express several antigens. Until now, however, no one antigen has been shown to be ultimately specific. CD20 is expressed on B cells from pre-B cells to mature B lymphocytes. On plasma cells, weak expression of CD20 was found to be present in 0–20%.[98–100] There might be a role for anti-CD20 mAb in selected patients with CD20-expressing plasma cells. At the moment the only preliminary results of clinical trials using a mAb against CD20 (rituximab) were described by Treon *et al.*[101] Among 18 treated patients, one experienced a partial response and five were reported to have stable disease. A patient with light chain disease was previously reported by the same authors, showing a partial response after one course of rituximab.[102]

Another candidate for mAb directed therapy might be CD138 (syndecan-1), which is a heparan sulfate proteoglycan, expressed on plasma cells. CD138 is also expressed on normal plasma cells, epithelial and endothelial cells, leading to cross reactivity. mAbs may be raised against specific regions within syndecan-1. As compared to syndecan-1 expression on normal cells, syndecan-1 on malignant plasma cells is underglycosylated, thereby uncovering epitopes which are normally not reachable for mAb, creating a possibility for therapeutic intervention.[103–105]

Vaccination therapy

Each malignant plasma cell clone has its own tumor-specific antigen, as each clone produces a specific monoclonal immunoglobulin (idiotype). Therefore, MM is an ideal candidate for anti-idiotype vaccination in order to generate a specific cytotoxic T cell response. Tumor-specific immune responses have been described in clinical practice, using vaccination with conjugated idiotypes or idiotype-primed dendritic cells obtained from leukapheresis material of patients.[106–111] Even shortly (2–4 months) after high-dose chemotherapy and peripheral stem cell transplantation the immunocompetence of patients was good enough to generate an immune response. Moreover, in some of these patients an idiotype-specific T cell proliferative response was observed.[108–110,112] It has been suggested that the ability to generate an anti-idiotype response is related to the extent of remission. The absence of a circulating M-protein might favor immune responses, as circulating immunoglobulins can induce anergy or deletion of idiotype specific T cells.[110,113] Specific cytotoxic T lymphocytes can also be generated *ex vivo* either by activated autologous plasma cells or by autologous dendritic cells and subsequently reinfused into the patients.[114]

Clinical use of vaccination therapy will be hampered by the fact that plasma cells do excrete immunoglobulins, thereby losing expression and furthermore by high levels of circulating immunoglobulins. It is therefore thought that the use of vaccination therapy will be especially effective in the setting of minimal residual disease.

NF-κB as a therapeutic target for MM

NF-κB is a transcription factor which upregulates the expression of IL-6, vascular endothelial growth factor, cell adhesion molecules and anti-apoptotic factors. Thereby activation of NF-κB confers survival potential for MM cells. It was already known that β_1-integrin-mediated adhesion of MM cells to fibronectin in the bone marrow environment resulted in drug resistance. As NF-κB activity was found to be dramatically increased in MM cells adhered to fibronectin, inhibition of signal transduction pathways initiated by cell adhesion may provide strategies to overcome drug resistance to chemotherapy. Irrespective the presence of drug resistance, inhibition of NF-κB might be a useful therapy in MM patients, as constitutive expression of NF-κB activity is present in MM cells. First indications that such intervention may be successful were presented at the American Society of Hematology meeting in December 2001. PS-341, a selective inhibitor of the proteasome, having numerous effects on regulatory proteins, including the blockade of NF-κB activation, was administered i.v. to heavily pretreated patients (including high-dose therapy), refractory to their most recent therapy. Preliminary evidence of antitumor activity was reported (52% of patients showed a response, 33% of patients had stable disease, after four cycles of PS-341).[115] Specific blockade of NF-κB activation by PS-1145 (a specific IκBα kinase inhibitor) or SN50 (a cell-permeable specific inhibitor of NF-κB nuclear translocation and activity) also exerted anti myeloma effects in *in vitro* studies. Dexamethasone, upregulating IκBá protein, was found to enhance blockade of NF-κB activation by PS-1145.[116,117]

Supportive care

Bone disease: treatment with bisphosphonates and osteoprotegerin

Almost all patients with MM will encounter skeletal events in the course of their disease. At diagnosis more than 50% of patients present with vertebral fractures and up to 30% with non-vertebral fractures due to the presence of osteolytic bone disease.[118] Furthermore, about 60% of patients have osteoporosis and 20–30% develop hypercalciema as a result of osteoclast-mediated bone resorption.[119] Osteoclast activation is thought to be the result of the production of osteoclast activating factors by plasma cells and bone marrow stromal cells. The precise nature of these factors (IL-1β, TNF-α, lymphotoxin) as well as the site of production (plasma cells or stromal cells) is still debated.[120] Recently, it was found that myeloma cells express RANKL (the ligand for receptor activator of NF-κB, also named osteoprotegerin ligand) or upregulated RANKL expression in preosteoblastic or stromal cells.[120,121] RANKL stimulates osteoclast activity and differentiation, and therefore it may be involved in the pathogenesis of MM-induced bone disease. Irrespectively of the underlying mechanisms, plasma cells are known to activate osteoclasts to produce IL-6.[120] Furthermore, plasma cell adhesion to bone marrow stromal cells initiate stromal IL-6 production.[122,123] Thereby the bone marrow environment and especially the environment created by resorbing bone is supportive for further growth of plasma cells. Therefore, it can be postulated that inhibiting osteoclasts by biphosphonates, not only leads to diminished bone resorption but, moreover, diminish proliferation of plasma cells. The effectiveness of clodronate and pamidronate in bone disease of MM patients has been observed by several, but not all, investigators. Clodronate, given orally, was found to decrease fractures in most studies.[124,125] In one study, no influence was observed on the incidence of fractures or pain, although less progression in lytic lesions was observed in the treatment arm in this study.[118] Pamidronate, given i.v., was also found to decrease the incidence of skeletal events, as well as increasing the quality of life.[126] In order to circumvent the inconvenience of i.v. administration of pamidronate during several hours, on the one hand, and the problem of poor resorption of oral biphosphonates, on the other hand, the third generation biphosphonates (zoledronate and ibandronate) which can be administered i.v. in a few minutes will probably be the best option. However, the effectiveness on clinical outcome has to be compared with conventional biphosphonates first.

Whether treatment with bisphosphonates will also affect disease progression or survival is not completely elucidated yet. In the extended above mentioned study of Berenson *et al.* a survival benefit was observed in these patients who received at least

two courses of pamidronate.[127] An anti-myeloma effect has been describes by others, *in vitro* as well as *in vivo*.[128,129]

In the future the role of osteoprotegerin, which inhibits osteoprotegerin ligand, and therefore inhibits osteoclast differentiation and activation, will probably be investigated as a new treatment option for bone disease in MM patients.[120,121]

Erythropoietin

The pathogenesis of anemia in patients suffering from MM is diverse. Inadequate production of erythropoietin led to investigating the role of epoetin α in the treatment of anemia in patients with multiple myeloma.[130] Since then several studies has been reported, showing effect in untreated patients with smoldering MM without symptoms, except for anemia,[131] in patients on chemotherapeutic treatment[132] and in patients with progressive myeloma resistant or refractory to chemotherapy.[133–135] Increases of 2 g/dl or more in Hb level (responders) were noted in about 70% of patients. In 30–50% of patients transfusions were no longer required. A recent large randomized study, describing 145 patients, confirmed earlier results: 57.6% of epoetin treated patients responded versus 9.1% in untreated patients. From epoetin-treated patients, 45.5% achieved Hb levels of more than 12 g/dl, versus 3.0% of untreated patients.[136] Furthermore, the quality of life increased during erythropoieitin treatment.[130,136]

It is not known whom to treat and how long to continue before deciding that treatment is not effective. Concerning whom to treat, patients with low endogenous erythropoietin levels were found to respond to treatment with erythropoietin. By relating erythropoietin levels to the predicted serum erythropoetin level for the degree of anemia, it could be determined that approximately 75% of patients with low levels for the degree of anemia responded to treatment with erythropoietin, whereas in patients with adequate levels only about 25% responded.[137] In the light of risks of blood transfusions and the necessity of hospital visits, it can be advocated to perform a trial in all MM patients with anemia with erythropoietin, irrespective the level of endogenous erythropoietin. Based on the maximum times to respond to treatment of about 3–4 months in most studies, such a trial of erythropoietin treatment should take about 4 months, before deciding erythropoietin treatment being not effective.[130,136,138]

Conclusions and future directions

Patients aged 65 years or younger

The introduction of high-dose chemotherapy with autologous stem cell support has significantly improved the outcome of patients with MM, compared to conventional chemotherapy. Therefore, upfront treatment with high-dose chemotherapy is the standard of care now. From ongoing randomized trials, it might be expected that the higher complete clinical and molecular remission rates reached with double transplant procedures will be translated in better OS. However, before becoming standard therapy the final results have to be awaited. In patients under 55 years, with high-risk multiple myeloma (i.e. with high β_2-microglobulin levels and abnormalities of chromosome 13), the role of allogeneic transplantations (after myeloablative pre-transplant regimens as well as non-myeloablative pre-transplant regimens followed by donor lymphocyte infusions) has to be determined. Future trials will be directed to the role of concomitant treatment with thalidomide or its derivatives in induction and maintenance therapy, and on the effect of immunotherapy in a situation of minimal residual disease after high-dose chemotherapy.

Patients aged over 65 years

Although high-dose chemotherapy has been performed in patients older than 65 year,[139] in most centers it is current strategy to give conventional chemotherapy in older patients. Although various agents in several combinations have been investigated in the past, melphalan/prednisone has remained standard therapy. However, an OS rate of about 2–3 years necessitates exploring new forms of therapy. Thalidomide or its derivatives will probably be introduced earlier in treatment strategies, combining it with conventional chemotherapy.

New targets for therapy

Activation of NF-κB, a transcription factor, confers a survival advantage to tumor cells, including MM cells. Proteasome inhibitors, such as PS-341, block NF-κB activation and were indeed found to possess anti-myeloma effects in ongoing phase II trials. New drugs inhibiting signal transduction pathways will be explored.

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