Multiple myeloma: An update on biology and treatment

H. Ludwig, J. Meran & N. Zojer
First Department of Internal Medicine with Medical Oncology, Wilhelminenspital, Vienna, Austria

Summary
Recently, several advances have been made in understanding the pathogenesis of multiple myeloma. Increasing evidence favours a pre-switched, but somatically mutated B-cell as myeloma stem cell to give rise to the malignant clone. Deletions of the p53-gene, partial or total loss of chromosome 13 and rearrangements of band 14q32 and 11q13 are frequently found in multiple myeloma, and were shown to harbour prognostic significance. Presence or absence of distinct chromosomal aberrations may guide selection of treatment strategies in the future.

Although melphalan/prednisolone remains the standard of myeloma treatment in elderly patients, significant improvement has been achieved in antimyeloma and in supportive therapy. High dose therapy with autologous stem cell transplantation enhances survival in younger patients and several trials are ongoing to substantiate these results. The effect of interferon maintenance treatment on overall survival is significant in metaanalysis, although the gain achieved is limited. Newer treatment strategies - targeting the molecular level - have just entered clinical trials, and may further improve outcome of myeloma patients.

Key words: autologous transplantation, chromosomal aberration, myeloma, review

1. Biology of multiple myeloma

All malignant plasma cells show identical rearrangement and mutation of Ig variable (Vh) genes and thus produce an identical (monoclonal) protein, which can be detected by serum electrophoresis as narrow based peak of γ-mobility (rarely the M-protein is detected in the α- or β-range). In the course of disease the CDRs remain stable, i.e., there is no evidence of ongoing somatic hypermutation.

Normal B-cell development

The normal B-cell precursors have to undergo three differentiation steps to ultimately produce specific immunoglobulins [1,2]. First, the constant (Ch), joining (Jh), variable (Vh) and diversity gene segments rearrange to encode the heavy chain of the immunoglobulin, which is followed by a similar rearrangement of the light chain genes. IgM is the first immunoglobulin which appears on the surface of early B-cells. In a second step, hypermutation of the antigen-binding region takes place to further enhance antibody specificity and binding stringency. During this germinal-center reaction, B-cells with high affinity to antigens presented by follicular dendritic cells escape apoptosis to differentiate to memory B-cells or plasma cells. Finally, in a third step, individual B-cells from the same antigen induced clone exchange their Ig heavy chain constant region, which also changes the effector function of the immunoglobulin. Whereas pre-switched B-cells express IgM on their surface, the Ig heavy chain switch is followed by expression of IgG, IgA, IgE or IgD. The resultant plasmablasts then adhere to the bone marrow stromal cells and differentiate to plasma cells.

Pathogenesis of multiple myeloma

The malignant clone for multiple myeloma is derived from a cell which is somatically hypermutated. The Vh genes show no clonal diversity and the Vh sequence remains stable during the course of the disease [3-5]. Thus, it is generally believed that the initial neoplastic event in multiple myeloma occurs in a single post germinal-center B-cell (Figure 1). Although the malignant clone has undergone isotype switch in most cases of myeloma, IgM positive B-cells with identical Vh-sequence to the isotype-switched cells have been identified in the bone marrow and peripheral blood of myeloma patients [6,7]. This finding provides evidence for the involvement of pre-switched B-cells in the malignant process. The clonotypic IgM-positive B-cells may represent a population that has undergone a neoplastic event and that is still capable of isotype switching. To reach full malignant status, a second genetic event may be necessary, and this may occur in a single isotype switched cell. Otherwise, the clonotypic IgM positive cells may be subject to programmed switching, which also will result in a population of myeloma cells uniformly expressing the same Ig class.

While the myeloma stem cell seems to be a post germinal-center B-cell or plasmablast, the situation differs in monoclonal gammopathy of undetermined significance
deletions are found in a variety of tumours and have been described to occur in multiple myeloma. By fluorescence in situ hybridisation (FISH) with a p53 specific probe, deletions were found in 33% of myeloma patients with newly diagnosed disease (see Table 1). Furthermore, this aberration was proposed as novel prognostic factor, since survival time was only 13.9 months from diagnosis for patients with a deletion of the p53 gene versus 38.7 months for patients with absence of this abnormality [11]. However, p53 aberrations do not seem to be the initiating event in multiple myeloma. In monoclonal gammopathy of undetermined significance, p53 deletions are a rare event, being absent in 15 patients studied by interphase FISH with a probe to 17p13 (p53 locus) and to the centromere of chromosome 17 [12].

Table 1: Molecular mechanisms of malignant transformation in multiple myeloma. (See text for references.)

<table>
<thead>
<tr>
<th>Oncogene/tumor suppressor gene</th>
<th>Chromosomal aberration</th>
<th>Frequency [%]</th>
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<tbody>
<tr>
<td>retinoblastoma [Rb]</td>
<td>del 13q12</td>
<td>50%</td>
</tr>
<tr>
<td>ras-mutations</td>
<td>–</td>
<td>34%</td>
</tr>
<tr>
<td>p53</td>
<td>del 17p13</td>
<td>33%</td>
</tr>
<tr>
<td>FGFR3</td>
<td>t(4;14) (p16q32)</td>
<td>25%</td>
</tr>
<tr>
<td>bcl-1/myel D1</td>
<td>t(11;14) (q13q32)</td>
<td>20%</td>
</tr>
<tr>
<td>bcl-2</td>
<td>t(14;18) (q21q21)</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>c-myc</td>
<td>t(8;14) (q24q32)</td>
<td>&lt;5%</td>
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Interleukin-6 and other cytokines stimulating factors in the bone marrow micro-environment.

Retinoblastoma-gene

Negative prognostic relevance has also been described for Rb-deletions in myeloma patients [13, 14]. For those receiving standard treatment, deletion of Rb (13q12) or monosomy 13 was associated with a median survival of 10 months versus 34 months for patients with other abnormalities [14]. In an extensive study of 427 patients undergoing high dose therapy (tandem transplants supported by mobilized peripheral stem cells), the presence of a partial or complete deletion of chromosome 13 and/or 11q-abnormalities and/or any translocation portended a poor clinical outcome [15]. The absence of such karyotype was the most favourable variable for event free and overall survival on multivariate analysis. Patients with an unfavourable karyotype had a median overall survival of 26 months versus 69+ months for patients with an abnormal karyotype but absence of translocations, deletion of Rb, or 11q abnormalities.

14q-aberrations

Oncogene activation by translocations involving the Ig loci (IgH at 14q32 or, less frequently, the IgL loci at 2p12 and 22q11) are a hallmark genetic lesion in B-lymphocyte tumours. Translocations involving 14q32 can be detected by conventional karyotyping in 20%-40% of cases of multiple myeloma, but are reported to be more frequent using interphase cytogenetic analysis (74%) [16]. Using a Southern blot assay in addition to conventional karyotyping, translocations involving the IgH locus were shown to be present in 19 of 21 myeloma cell lines [17–19]. Notably, 7 of 9 cell lines with no karyotypically detectable 14q32 translocation had a translocation involving IgH by this assay. Hallek et al. [20] thus speculated, that IgH translocations may be a nearly universal and possibly early event in multiple myeloma. Two non-random partner loci have been identified for 14q32 translocations: 11q13 (cyclin D1) and 4p16 (fibroblast growth factor receptor 3, FGFR3). The remaining 50% of cases involve a promiscuous array of partner chromosomes, including 6p21, 8q24 (c-myc), 16q23 (c-maf) and 18q21 (bcl-2).

11q-aberrations

Other cytogenetic features which have been reported to be associated with a poor prognosis are hypodiploidy [15, 21, 22], 22q11 rearrangements [22] and 11q abnormalities [15, 23].

1.2. Bone marrow microenvironment

Interleukin-6 and other cytokines

The growth of myeloma cells depends on the presence of stimulating factors in the bone marrow micro-environment. Interleukin 6 (II-6) has a pleiotropic effect on hematopoietic and non-hematopoietic cells and promotes normal B-cell differentiation into Ig secreting plasma cells. The pathogenetic role of II-6 for multiple myeloma development was first discovered when it was shown that II-6 could induce in vitro growth of myeloma cells freshly isolated from patients.

Bone marrow (stromal, monocytoid and myeloid) cells secrete II-6, which then acts on myeloma cells in a paracrine fashion, although an autocrine loop of II-6 stimulation of myeloma cells has also been described [24]. When II-6 binds to its cellular receptors, the latter combine with a 130 kDa transmembrane glycoprotein [gp130], which further activates intracellular signalling pathways. As a result, expansion of the myeloma clone is supported by II-6 stimulation of cell division, and also by prevention of programmed cell death (apoptosis). High serum levels of II-6 have been predominantly found in patients with aggressive disease [25] and they correlated inversely with prognosis [26].

II-6 is also an important mediator of myeloma bone disease by acting on osteoclasts to increase bone resorption. Adjacent to malignant plasma cells, osteoclastic bone resorption is increased and bone formation decreased, which ultimately leads to the characteristic osteolytic bone lesions.

Other cytokines, which have been reported to support myeloma cell growth are II-11, oncostatin M, leukemia inhibitory factor (LIF) and ciliary neurotropic factor (CNTF), the receptors which have in common the signal transducing subunit gp130 [27]. II-10 stimulates myeloma growth by increasing the responsiveness to II-11 and oncostatin M [28].

Mechanisms of bone lesions

Bone disease is one of the major diagnostic criteria of multiple myeloma. Characteristic osteolytic lesions are commonly present, but myeloma can also lead to a more diffuse bone destruction with osteoporotic like appearance on X-ray. Osteodestruction is restricted to the vicinity of tumour cells and mediated by osteoclast stimulating factors like II-6, II-1 or TNF [29]. Bone formation was found to be increased only in early myeloma. In later myeloma bone lesions, not only bone resorption is increased, but also bone formation decreased, which is in contrast to bone lesions from different solid tumours, where osteoblastic bone formation is increased in response to increased bone resorption. This dysbalance in bone turnover in myeloma patients is reflected in low serum levels of the bone formation marker osteocalcin. On the other hand, urinary pyridinium crosslinks of collagen [markers of bone resorption] are increased in later stage multiple myeloma and can be used to determine the extent of bone destruction [30]. Levels of urinary cross links are elevated even in early myeloma and MGUS, although differentiation between the two is not possible by determination of these markers. However, data obtained by invasive procedures such as histomorphometry suggest, that an increase in bone resorption can predict the transition from MGUS to multiple myeloma [31]. Magnetic resonance imaging has also been used to detect these early changes in myeloma development [32].
Immunophenotype

has long been considered the same as that of normal plasma cells. Only recently has the differential expression of surface B4, CD-38 and CD 138 [42]. The phenotype of myeloma cells cultures were derived from the bone marrow mononuclear cells. Although the stromal cell gammopathy of undetermined significance (MGUS), which CD19+, whereas most myeloma cells were CD56+/CD19-. markers on normal versus malignant plasma cells been de-

Ig and surface membrane antigens such as PC-1,  PCA-1, B-

Plasma cells are characterised by expression of cytoplasmatic Ig and surface membrane antigens such as PC-1, PCA-1, B-B4, CD-38 and CD138 [42]. The phenotype of myeloma cells has long been considered the same as that of normal plasma cells. Only recently has the differential expression of surface markers on normal versus malignant plasma cells been described [43]. Normal plasma cells were shown to be CD56-/CD19+, whereas most myeloma cells were CD56+/CD19-. Interestingly, both populations are found in monoclonal gammapathy of undetermined significance (MGUS), which indicates that a varying percentage of monoclonal and normal plasma cells can be detected concomitantly in this disease [44].

CD56 (neural cell adhesion molecule, NCAM) is frequently lost or down-modulated in extramedullary myeloma and peripheral myeloma cells [45, 46], which suggests that loss of this adhesion molecule may act as transmigratory signal, permitting the exit of malignant plasma cells out of the bone marrow. Malignant plasma cells can be detected in the peripheral blood of patients with advanced disease, and were shown to be of adverse prognostic significance. CD44, VLA-1 and ICAM-1 are surface molecules which are implicated in directing the myeloma cells to the bone marrow and mediating interactions with the extracellular matrix and stromal cells. Adhesion of myeloma cells was shown to stimulate II-6 secretion by bone-marrow stromal cells [47], thus providing a potent stimulatory signal for myeloma cell growth. Binding of CD40 on myeloma cells by its ligand, CD40L, triggers II-6 secretion by the malignant cells themselves, which may provide an autocrine loop of growth support [48]. CD40 also plays an important role in the germinal center (GC) reaction, where concomitant CD40L- and antigen-binding rescues the GC B-cells from fas-induced apoptotic cell death.

As identified by their hyperdiploid DNA content, malignant plasma cells were shown to co-express markers of lymphoid (CD10), megakaryocytic (Gpi1b/IIa), erythroid (glycophorin A) and myelomonocytic lineage (CD11b, CD33) [49]. Other investigators have confirmed the expression of multiple hematopoetic lineage-associated antigens on myelomatous plasma cells [42]. In addition to CD38, the most typical plasma cell marker, the B-cell antigens CD9, CD10 and CD20 can be found on myeloma cells. Furthermore, malignant plasma cells may express myeloid markers: CD13, CD4, CD15, CD33, CD41; T-cell markers: CD2, CD4; natural-killer associated antigens: CD56; as well as HLA-DR, glycophorin A, CD23, CD24, CD25, CD37, CD39, CD40, CD45R, and CD71[42].

Definitive proof of expression of the stem-cell antigen CD34 on the malignant cell population is still lacking. Two studies have suggested the existence of a CD34+ tumour cell in multiple myeloma, by using a PCR-based assay with primers derived from the unique CDRs expressed by the patient's malignant clone [50, 51]. However, other investigators could not detect tumour cells in the CD34+ positive bone marrow cells or stem cell harvests from myeloma patients [52–54].

1.3. Involvement of peripheral blood

There is still considerable controversy regarding the involvement of circulating clonotypic B-cells (i.e., B-cells bearing the same immungenotype as myeloma cells, which identifies them as part of the malignant clone) in the development, progression and response to therapy of multiple myeloma. Since malignant plasma cells show little proliferative activity and are confined to the bone marrow in early stages of the disease, myeloma precursor cells have been implicated in the spread of the malignant cells to distant skeletal sites and dis-
ease progression [55]. The frequency at which clonotypic B-cells were found in the peripheral blood of myeloma patients vary to a large extent. Some investigators [56, 57] found that peripheral B-cells in myeloma patients express the surface marker CD34 and that the majority (74%-94%) of these phenotypically aberrant cells have clonotypic Ig rearrangements, as shown by in situ RT-PCR with patient specific primers. These data suggest that a large fraction of the peripheral B-cells in myeloma are part of the malignant clone.

However, other investigators could not reproduce these results. Chen and Epstein [58] reported frequencies of clonotypic cells among CD19 positive peripheral cells in myeloma patients of only 0.04-5% (mean 1.33%). These results were confirmed by Joshua et al. [59], who used mRNA in situ hybridisation with patient specific primers to quantitate clonotypic B-cells. Furthermore, aneuploidy as detected by flow cytometry was shown to be entirely confined to CD38 (=plasma cell marker) positive cells, while CD19 positive cells were diploid [60]. By FISH with centromeric probes, chromosome changes in peripheral B-cells could be found in only 2 of 15 patients [61].

2. Therapy of multiple myeloma

2.1. Conventional dose treatment

Despite the new developments in myeloma therapy, conventional dose treatment still is the mainstay of therapy for most myeloma patients. Indications for chemotherapy are presence of symptomatic disease or and/or stage II myeloma. In early myeloma a watch and wait strategy is feasible.

First-line treatment

Only one randomised study to date addressed the issue of delayed treatment for patients with early stage myeloma [62]. Fifty patients with asymptomatic stage I myeloma were randomised to initial treatment with MP or a watch and wait policy with treatment instituted on disease progression. The median time from diagnosis to start of treatment was 12 months in the watch and wait group, with symptomatic bone lesions, increasing M-protein and anaemia being the reasons to start therapy. There were no significant differences in response rate, response duration and survival compared with the group with initial MP treatment. These data support the policy of delayed treatment for stage I patients, although a close follow up was recommended by the authors to prevent potentially disabling complications of myeloma bone disease.

For more than 30 years newly diagnosed patients with symptomatic multiple myeloma have been treated with induction chemotherapy involving a small number of cytostatic agents. Median survival after conventional chemotherapy has not improved since introduction of the combination melphalan/prednisone (median: 30 months; range 24-38 months [63]). Only 5% of myeloma patients treated with standard dose chemotherapy achieve true complete remissions (CR) as defined by the absence on immunofixation-analysis of paraprotein in serum and urine and negative bone-marrow aspirate and biopsy. Partial remissions are obtained in 30%-70% of patients with standard dose treatment.

As compared to melphalan/prednisone (MP), combination chemotherapy with the addition of anthracycline, nitrosourea, cyclophosphamide and/or vincristine has led to improved remission rates (60% vs 53%, respectively), but to no improvement in survival [64, 65]. Moreover, not even subgroups of patients could be identified who achieve a survival-benefit from polychemotherapy. Recently, the final results of an ECOG trial, comparing MP to combination chemotherapy (VBMC) with 479 patients enrolled, were published [66]. Overall response with VBMC was significantly superior (72% vs 51% with MP), as well as response duration (24 months vs 18 months with MP). However, overall survival did not differ between the two regimens, thus confirming the results of the meta-analyses by Gregory et al. [64] and the MTCG [65].

The optimal duration of therapy has not been investigated systematically to date, although it is generally accepted that treatment should be given for 8-12 months.

The addition of interferon-a (INF) to induction chemotherapy protocols yielded promising results in the initial phase I and phase II trials. These results could not be unequivocally confirmed in subsequent randomised studies, where the outcome ranged from higher response rates and/or prolonged progression free and overall survival to little or no advantage from the addition of INF to standard chemotherapy protocols. However, a meta-analysis of 16 randomised trials, involving 2286 patients, shows a small but significant gain (10%) in overall response rate and improvement of relapse free and overall survival [63, 67]. This was recently confirmed with higher patient numbers [68].

<table>
<thead>
<tr>
<th>Table 2 Newer therapies for relapsed/refractory myeloma.</th>
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<tbody>
<tr>
<td>Therapeutic regimen</td>
</tr>
<tr>
<td>Dexmethasone, cyclophosphamide, idarubicin, etoposide (DC-IE)</td>
</tr>
<tr>
<td>Vincristine, epirubicin, cyclophosphamide, dexmethasone (VECD)</td>
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<tr>
<td>High-dose melphalan</td>
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<tr>
<td>Idarubicin, dexmethasone, interferon-α (I-Dexa)</td>
</tr>
<tr>
<td>Navelbine-monotherapy</td>
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<td>Topotecan-monotherapy</td>
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Relapsed/refractory disease

For patients with disease refractory to alkylating agents, a therapy combining high dose oral glucocorticoids with continuous infusion of vincristine and adriamycin (VAD) has proved effective [69]. Overall response rate is 50%-75% in relapsing and about 30% in refractory disease. High dose dexamethasone is the most active single agent in refractory myeloma, and continuous exposure to cytostatic drugs showed greater myeloma cell kill in vitro than short time exposure, two findings which provided the rationale for treatment with VAD. Due to relatively low toxicity and a stem cell sparing effect compared to melphalan based treatments, VAD was also introduced as preparative regimen before stem cell collection and high dose therapy [70]. Other treatment strategies for relapsed myeloma are summarised in Table 2.

2.2 Intensive treatment strategies

Growth factor support after high dose therapy

Several treatment strategies have been used to date to accomplish dose intensification in myeloma patients. The first trials on high dose therapy (beginning with the pioneering studies by McElwain in 1983) investigated dose intensification without the support of hematopoetic growth factors or autologous bone marrow/peripheral blood stem cells. Responses could be induced in refractory patients, but a high toxic death rate was observed, ranging from 17%-31% in the initial series. With autologous bone marrow or peripheral blood stem cell transplantation the death rate has now decreased to < 3% in most studies. One placebo-controlled trial investigated the supportive effect of granulocyte-macrophage-colony stimulating factor (GM-CSF) without stem cells, beginning with the day after melphalan 140 mg/m^2 [77]. This approach was shown to reduce neutropenia after high-dose therapy (23.5 vs 29 days in patients without GM-CSF support), with a trend to reduce the duration of the hospital stay. However, frequency of infectious complications and treatment related mortality (11.5%) were not different from the patients without growth factor support. It was concluded that high dose therapy with stem cell support is preferable to high dose therapy with GM-CSF, due to the lower treatment related morbidity and mortality.

Autologous bone marrow and PBSC-transplantation

Autologous bone marrow transplantation in the intensive treatment of multiple myeloma has been progressively replaced by the use of peripheral stem cells since their introduction as source of hematopoetic rescue in 1989 [78]. High dose therapy with PBSC support for myeloma was demonstrated to be equally effective as high dose therapy with autologous bone marrow transplantation in terms of CR rate, progression free and overall survival. In the PBSC group, hematopoetic recovery was faster (platelet recovery 19 vs 33 days), and the duration of the hospital stay shorter (20 vs 27 days) [79]. The reduced costs of the transplantation procedure with PBSC greatly facilitated high dose treatment strategies for myeloma patients and made possible even more intensive regimens (tandem transplantsations).

Conditioning regimens

Conditioning regimens before stem cell transplantation mostly include melphalan (140 mg/m^2 or 200 mg/m^2). There is a clear dose response relationship for this drug in multiple myeloma. In some studies melphalan 140 mg/m^2 was combined with total body irradiation (TBI) or other alkylating agents. The role of TBI in this setting is not well defined. A retrospective analysis on autologous transplantation found outcome to be better without TBI [80]. Alternative conditioning regimens have rarely been tested and include busulfan and/or cyclophosphamide instead of melphalan.

Autologous transplantation in newly diagnosed patients

Intensive therapy with stem cell support is most successful in previously untreated myeloma patients. Summarising the published studies, the overall response rate is about 80%, with a complete response (CR) rate of 20%-30% if strict criteria are used. The median time to progression is 2 to 3 years and the median survival approximately 5 years, which may increase in patients with a CR [81].

Figure 2. Overall survival of myeloma patients <65 years is significantly improved with high dose therapy and autologous transplantation compared to standard therapy. (Attal et al., N Engl J Med 1996 [82], reproduced with permission of authors. Copyright © 1996 Massachusetts Medical Society. All rights reserved.)
Randomised French trial

In 1990 the Intergroupe Francais du Myelome (IFM) initiated a randomised study comparing conventional chemotherapy and high-dose therapy with autologous bone marrow transplantation [82]. This study was the first to prove the superiority of high dose therapy over conventional dose therapy for myeloma patients. Prior to publication of these results it was unclear to what extent the selection of patients for intensive treatment regimens contributes to the favourable outcome of these patients [83].

Two hundred patients under 65 years were randomly assigned in the two treatment arms. The response rate among patients who received high-dose therapy was 81% (including complete responses in 22%), whereas it was 57% (complete responses in 5%) in the group treated with conventional chemotherapy. The estimated rate of survival for 5 years was 52% in the high dose group and 12% in the conventional dose group. Thus it was concluded that high dose therapy can improve response rate and survival in patients with myeloma (Figure 2). Subgroup analysis showed that autologous transplantation may be more feasible for patients under 60 years, since 82% of this group completed the treatment protocol, whereas only 58% of the patients older than 60 years underwent transplantation. Consistent with this, a retrospective analysis demonstrated a survival advantage with autologous transplantation only for good risk patients, i.e., patients younger than 60 years and with low β2-microglobulin levels (Attal et al., personal communication). On the other hand, some groups have found no significant difference in outcome for patients <65 years compared to those ≥65 years with intensive therapy and thus advocate high dose treatment for patients up to 75 years [84].

Timing of transplantation

Compared to patients with delayed transplantation, patients undergoing autologous transplantation shortly after diagnosis have improved relapse free survival. However, overall survival is not different between these treatment strategies [85]. Further evidence supporting a strategy of early transplantation comes from several other large studies on high dose therapy for myeloma. More than two regimens of pretransplant therapy or ≥12 months of prior therapy were consistently shown to adversely affect outcome [86,87]. Additionally, stem cell apheresis is frequently inadequate after extensive therapy with melphalan [88]. Thus, present data suggest that patients eligible for intensive therapy should be transplanted early in the disease course.

Tandem transplantation

Considering the frequent relapses after a single transplant procedure, the University of Arkansas initiated tandem transplants in 1989 in an effort to further improve long-term outcome of myeloma patients [89]. Peripheral blood stem cells (PBSC) were collected after high dose cyclophosphamide and either GM-CSF or granulocyte colony stimulating factor (G-CSF). Patients who attained a partial response after the first induction with melphalan 200 mg/m² received an identical regimen with the second transplant. In the other cases, chemoradiotherapy with melphalan 140 mg/m² and TBI was applied preceding the second transplantation procedure. Patients with a HLA-identical sibling donor were offered an allotransplant for the second cycle of myeloablative therapy. The complete treatment protocol (‘total therapy’), which was administered to newly diagnosed patients, additionally included remission induction with non cross-resistant regimens and maintenance therapy with interferon-α. CR was achieved in 36% of patients and median durations of event free survival and overall survival were 26 and 41 months, respectively [90]. These results were shown to be superior compared to standard therapy in a retrospective analysis [89].

Low levels of β2-microglobulin (B2M) and C-reactive protein (CRP) had favourable prognostic implications for patients undergoing 'total therapy.' Furthermore a non-IgA isotype, the absence of unfavourable cytogenetic features (see ‘biology of multiple myeloma’), and a short duration of pretransplant standard chemotherapy (≤12 months) positively affected outcome. These and subsequent studies showed, that the CR rate can be augmented after a second transplant (CR 15% following cycle one, 55% following cycle two) [91]. However, whether this improved CR rate translates into prolonged survival remains to be determined. An interim analysis of a randomized trial suggests, that double transplants confer no survival benefit compared to single transplants [92].

Autologous transplantation in sensitive/resistant relapse

CR > 20% can also be achieved in chemosensitive relapse of myeloma after conventional dose chemotherapy. Alexanian et al. [70] reported a 54% overall response and 36% CR rate in relapsed patients treated with high dose melphalan, but no survival advantage could be demonstrated for the intensive therapy group in comparison to historical controls.

Remarkably, high dose therapy can even overcome drug resistance in some myeloma cases, an effect first illustrated by Barlogie et al. [93]. Responses were seen in 50% of cases of VAD refractory multiple myeloma. Response duration however was short.

CD34-selection to reduce tumour cell contamination

A frequent concern in autologous bone marrow or PBSC transplantation is the potential contamination of the transplant by tumour cells. Myeloma cells can be detected in autologous bone marrow grafts and in the peripheral blood apheresis product [94,95], even after extensive preparative chemotherapy. Therefore efforts have been made to reduce the residual tumour cells before the transplantation procedure. The most recent advance was achieved by positive selection for the stem cell antigen CD34, which is not expressed on myelomatous
Figure 3. Autologous transplantation was shown to be superior to allogeneic transplantation with regard to overall survival in a case matched analysis of myeloma patient. (Björkstrand et al., Blood 1996 [101], reproduced with permission of authors. Copyright © 1996 American Society of Hematology.)

plasma cells. Using a PCR-based technique to detect the tumour specific CDRs, no malignant cells were found in highly selected CD34+ cells from the peripheral blood of myeloma patients [52]. After transfusion of CD34 selected peripheral blood cells following myeloablative therapy, hematopoietic reconstitution was shown to be similar to unselected transplants [96, 97]. However, it is questionable whether the reduction in contaminating myeloma cells (by 2-4 log) by the positive selection procedure will ultimately be associated with an increase in event free or overall survival [98].

Allogeneic bone marrow transplantation

For allogeneic bone marrow transplantation, CR rate was reported to be as high as 44%, with a median event free survival of 36 months [99]. Unfortunately, this therapy is currently still complicated by a transplantation associated mortality of 40% [99, 100]. In a retrospective case matched analysis comparing 189 myeloma patients treated with allogeneic bone marrow transplantation with an equal number of patients who received autologous transplants [101], the results of the allogeneic approach were shown to be inferior. Median overall survival was 18 months for the patients treated by allogeneic transplantation versus 34 months for the group with autologous transplants (Figure 3). Since long term survivors are more frequent with allogeneic transplants, this therapy may be offered to younger patients. Prolonged remissions are achieved by a graft versus myeloma effect [102], which even holds the promise of cure. Donor lymphocyte infusions may be used in relapsing patients for reinduction of remission. Less aggressive conditioning regimens may reduce the treatment related mortality and make allogeneic transplants feasible for a greater number of patients in the future [103].

2.3. Maintenance treatment

Chemotherapy maintenance

Maintenance therapy with cytotoxic drugs has not yielded the expected improvement in survival. Four randomised trials showed no benefit of treatment beyond achievement of best remission but increased toxicity [104–107]. Patients in plateau phase of myeloma should be closely monitored and therapy re-instituted on disease progression.

Interferon-α maintenance

Mandelli et al. [108] conducted the first randomised trial to investigate the effects of interferon-α (INF) as maintenance therapy for multiple myeloma. Remission duration was substantially prolonged in the INF arm (26 months vs 14 months in controls). The survival data showed a tendency towards longer survival in patients maintained with INF (median: 52 months), as compared to unmaintained patients (median: 39 months). Subgroup analysis revealed, that significantly prolonged survival was only seen in patients who had responded to induction treatment with at least partial remissions, but not in those who had only achieved disease stabilization. The prolonged remission duration was associated with an improved quality of life.
In the following trials on INF maintenance, relapse-free survival was consistently prolonged in the INF arm, although the gains reached statistical significance in only a few studies. Conflicting results were reported regarding the effect of INF maintenance on overall survival, with some showing significant increases, but others not. In a meta-analysis involving 929 patients from 8 randomised trials, significant but only marginal gains — between 3 and 7 months — of relapse-free and overall survival were detected in the INF arm [63, 67]. Considering the aforementioned benefits of INF maintenance therapy, the toxicities and financial costs, treatment is agreeable to 32%–58% of myeloma patients [109]. The patient preference following comprehensive information about the expected benefits and risks of INF therapy should therefore play a decisive role in planning the actual treatment.

2.4. Symptomatic treatment

Radiotherapy

Half-body irradiation can be used as treatment alternative for patients with chemotherapy-resistant disease. Jacobs et al. [110] showed, that half body irradiation is at least equally effective as MP as second-line treatment for multiple myeloma. Localised radiotherapy is applied to painful osseous lesions (30 Gy) or if there is risk for fracture (40–50 Gy).

Bisphophonates

Bisphosphonates reduce bone resorption by inducing apoptotic cell death of osteoclasts and inhibiting II-6 production of osteoblasts. They have been used extensively to palliate myeloma bone disease, i.e., to slow progression of lytic lesions, reduce the frequency of pathologic fractures and bone pain, and to prevent or reverse hypercalcemia. Furthermore, recent data suggest that bisphosphonates also exert an anti-proliferative and cytotoxic effect on myeloma cells. Bisphosphonates lead to arrest of myeloma cells in S-phase of the cell cycle and to bcl-2 mediated apoptosis in vitro [111, 112]. It is unclear whether the latter effects are of significance clinically.

To date, 6 randomised trials on bisphosphonates for the standard care of myeloma patients have been published. A trial by Berenson et al. [113, 114] evaluated the efficacy of pamidronate 90 mg i.v. in monthly intervals on skeletal morbidity, hypercalcemia and bone pain of myeloma patients (n=392). Pamidronate i.v. was shown to reduce the frequency of skeletal events and decrease bone pain. Furthermore, for patients who received second line chemotherapy (in contrast to patients who received first line chemotherapy), survival was significantly superior in the pamidronate group. Similarly, clodronate 1600 mg p.o. daily [115, 116], or 2400 mg p.o. daily [117] (summarising all 3 trials: n=1056) slowed the progression of skeletal disease in multiple myeloma and decreased the associated morbidity. However, overall survival did not differ significantly to that of placebo treated patients in the latter studies.

Contrary to these results, oral pamidronate (300 mg/day) [118] and oral etidronate (5 mg/kg/day) [119] were less successful in palliating skeletal disease in myeloma patients. Oral pamidronate improved bone pain and reduced loss of height, but failed to reduce skeletal events.

Erythropoietin

Inadequate levels of erythropoietin (EPO) can be detected in at least 50% of patients with myeloma-associated anaemia. Substituting this growth hormone to treat anaemia was shown to be effective in 80% of myeloma patients, with a mean hemoglobin increase of more than 2 g/dl [120, 121]. A dose-response relationship can be seen by increasing EPO doses up to 300 U/kg s.c. three times a week. Current practice is to give absolute daily doses of 5,000–10,000 U EPO s.c. If after two weeks the serum EPO level exceeds 100 mU/ml and the hemoglobin has failed to increase by at least 0.5 g/dl, a lack of response can be predicted with 93% accuracy [122]. The patient should therefore be discontinued from treatment. On the other hand, a serum EPO level below 100 mU/ml and a hemoglobin increase more than 0.5 g/dl predict a response with 95% accuracy. In the absence of EPO measurements, serum ferritin may be used alternatively to predict outcome. Patients with low levels of serum ferritin (<400 ng/ml) after two weeks of EPO are likely to respond to treatment.

Immunoglobulin

Due to suppression of the polyclonal humoral immune response, myeloma patients have long been known to be at high risk for infections. Chapel et al. [123] showed, that monthly infusions of immunoglobulin (0.4 g/kg) can compensate for the immune-deficiency and reduce the frequency of life-threatening and serious infections in this population of patients. Thirty-eight serious infections occurred in 470 patient-months in the placebo group, compared with 19 in 449 patient-months in the study group. Furthermore, i.v. immunoglobulin also protected against recurrent infections. Immunoglobulins should be substituted in myeloma patients who underwent a serious infection or who are otherwise at high risk for acquiring infectious diseases.

2.5. Newer treatment strategies

Several experimental treatment strategies aim to elicit an immunogenic response to the myeloma cells. This is preferably done using the specific antigenic determinant (idiotype) of the monoclonal immunglobulin as target antigen. Immunization of myeloma patients with an autologous (idiotypic) vaccine generated from the monoclonal immunglobulin resulted in a T-cell response in all patients and a partial remis-
sion in 1 of 5 patients (when augmented with simultaneous administration of GM-CSF) [124]. Currently, the feasibility of immunotherapy with idiotype pulsed dendritic cells [125] or DNA-vaccines [126] is being investigated. The latter approach uses tumour-cell specific DNA-sequences, which are administered i.m. and taken up and expressed by muscle cells near the injection site. The expressed protein stimulates the humoral and cellular arms of the host immune response.

Other potential treatment strategies include the use of anti-plasma-cell (anti-CD38 or anti-HM1.24) monoclonal antibodies [127], anti-interleukin 6 monoclonal antibodies [129] [130] and monoclonal antibodies or immunotoxins directed against CD20 or CD19 positive myeloma precursor cells [131, 132]. Furthermore, bel-2 antisense oligonucleotides are currently being investigated as treatment for multiple myeloma.

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Correspondence to:
Prof. Dr. Heinz Ludwig
First Department of Internal Medicine with Medical Oncology
Wilhelminenspital
Montleartstr. 37
1160-Vienna, Austria