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Current Perspective

Changing concepts in multiple myeloma: from conventional chemotherapy to high-dose treatment

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Abstract

The treatment of Multiple Myeloma (MM), a malignant plasma cell disorder has changed considerably over the past decade. It has been convincingly shown that intensive treatment supported by autologous stem cell reinfusion is superior to conventional chemotherapy with alkylating agents or vincristine, doxorubicin and dexamethasone (VAD) alone in terms of a more rapid response and a longer disease-free survival. However, cure is not achieved in the majority of patients. Several trials have therefore focussed on repeated intensive treatments in order to improve the survival of these patients. Other approaches are aimed at identifying patients on the basis of prognostic factors, who may benefit from high-dose therapy. This review discusses the recent developments in intensive therapy for multiple myeloma.

Keywords: Multiple myeloma; Chemotherapy; Stem cell transplantation

1. Multiple myeloma

Multiple myeloma (MM) is a malignant plasma cell disorder which accounts for 1% of all malignant diseases and approximately 10% of haematological malignancies [1]. The annual incidence is approximately 0.003% and is increasing within the aging population. MM is characterised by an abundant clonal proliferation of plasma cells in the bone marrow, which produce a monoclonal heavy and/or light chain immunoglobulin (M-protein), usually IgG or IgA, occasionally IgM, IgD or IgE. This M-protein is present in the serum and/or urine. A M-protein may be present in the serum without evidence of MM. This so-called monoclonal gammopathy of unknown significance (MGUS) is present in 3% of persons older than 70 years. MGUS usually requires no treatment except when the M-protein autoreacts with tissues. Approximately one fourth of these patients ultimately progress into MM or related lymphoproliferative disorders [2,3]. Smoldering MM is diagnosed when patients have a M-component and $>10\%$ plasma cells in the bone marrow, but few bone lesions and no clinical symptoms. These patients should not be treated, since their condition can remain stable for years without therapy [4].

Common clinical features in MM include bone pain, anaemia, renal insufficiency and recurrent bacterial infections. Spinal cord compression, hyperviscosity and amyloidosis are relatively rare conditions in MM [1]. These features are used as prognostic indicators in the commonly used staging system [5].

Without treatment, the median overall survival (OS) in MM is only 17 months [6]. Local radiotherapy can be used for painful bone lesions, pathological fractures or spinal cord compression, but systemic chemotherapy is the treatment of choice. With melphalan and prednisolone (MP] as remission induction therapy the median survival of patients with MM has improved from 17 to 30 months [7,8]. Since then, several other combination chemotherapy regimens have been used in an attempt to improve the response rate and survival in newly diagnosed patients. However, these regimens were not superior to MP [9,10]. In 1983, McElwain and Powles first demonstrated the feasibility of high-dose therapy (HDT) in MM. An escalated dose of melphalan

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was used in an attempt to overcome primary resistance to alkylating agents. This approach resulted in a complete remission (CR) in approximately 35% of the patients, although at the cost of significant toxicity [11]. Since then HDT followed by haemopoietic stem cell rescue has been extensively used in the treatment of MM. Phase I/II trials have suggested a therapeutic benefit of HDT. However, selection of patients and the inconsistent criteria of response make it difficult to evaluate these studies. Recently, a prospective randomised trial demonstrated that HDT followed by autologous bone marrow transplantation (auto-SCT) improves the outcome of newly diagnosed patients with MM when compared with conventional combination chemotherapy (CCT) [12]. However, eventually all patients continue to relapse after HDT. Therefore, the place of intensified therapy in this disease needs to be defined in more detail.

In this article, we will review the changing concept of treatment in MM, from conventional chemotherapy to more aggressive approaches including HDT followed by auto-SCT.

2. Treatment of multiple myeloma

2.1. Response criteria

The first criteria of response were developed by the Committee of the Chronic Leukemia and Myeloma Task Force (CLMTF) of the US National Cancer Institute. The main parameter for objective response was a 50% reduction of the M-protein concentration in serum and urine [13].

In 1972, the South West Oncology Group (SWOG) defined objective response as at least 75% reduction of the serum M-protein synthesis rate and a decrease of at least 90% of the urinary light chain excretion. Patients with a reduction of the M-protein synthesis between 50 and 74% (SWOG criteria) and a M-protein decrease of less than 50%, but with clinical improvement were considered to have a partial remission (PR) [8]. In 1980, the concept of plateau phase was introduced by Durie and colleagues [14]. A plateau phase is a period of stable disease following chemotherapy of at least 4–6 months albeit with persistence of measurable disease with a stable M-protein and a significant number of plasma cells. This definition of plateau phase was later used in the United Kingdom Medical Research Council (MRC) Myelomatosis trials [15]. The CLMTF and SWOG criteria do not include complete response (CR) criteria because CR was rarely observed with the then existing regimens. Following the introduction of combination chemotherapy, CRs were achieved [16]. With the use of HDT followed by stem cell rescue a significant number of patients achieved a CR and different criteria of CR were needed. It is now agreed that a CR should require the absence of a M-protein in serum and/or urine with no detectable plasma cells in the bone marrow. New criteria of response, relapse and progression after HDT were recently proposed by 3 transplantation registries in order to bypass methodological inconsistencies [17]. More recently, prognostic factors that reflect the cellular and molecular characteristics of the malignant clone have been introduced. With more and better CRs being observed after HDT the need for the assessment of molecular remissions has emerged. With a quantitative polymerasechain reaction (PCR) based on the amplification of the unique heavy chain sequence of the tumour using patient allele-specific oligonucleotides (IgH ASO PCR) minimal residual disease can be quantified with a sensitivity of 10^{-4} cells [18,19].

Cytogenetic analysis has recently provided remarkable new insights into the prognosis of patients with MM, rendering the classical prognostic systems less adequate. Abnormalities of chromosome 13 are associated with poor event-free survival and overall survival after conventional dose chemotherapy [20, 21]. In addition, after high-dose therapy, deletions of chromosome 13 are associated with a poor outcome [22–25]. An example of the weight of this chromosomal abnormality is shown in the cumulative analysis of tandem transplantations. Among 1000 patients receiving melphalan-based tandem high-dose therapy, the presence of chromosome 13 abnormalities predicted a 5 year event-free survival of 0% versus 20% in patients without chromosome 13 abnormalities, and an overall survival of 16% compared with 44% (both $P<0.0001$). Thus, chromosome 13 deletions are not only associated with aggressive disease, but also with drug resistance to chemotherapy [24].

These findings have now convinced most clinicians that, analogous to studies in acute leukaemia, molecular and cytogenetic data should also be combined with traditional markers such as β_2M in MM in order to design a new staging system, that offers the opportunity to select patients for various treatment options.

In this issue of the *European Journal of Cancer*, the Italian MM87 study is published, which was designed to compare less or more aggressive induction therapy with respect to OS. In the study, a median survival of 40 months was achieved, which confirms that the limits of therapeutic benefit with conventional chemotherapy seem to be reached. A major achievement of this study, however, is the long follow-up which allows an analysis of some longstanding remissions and survival after conventional chemotherapy. As has been demonstrated before, certain patients may have a benefit from high-dose therapy, while others may not. In this era, for younger patients in general HDT is preferred because of the rapid response and longer disease-free interval. However, with HDT no cure can be achieved, and conventional therapy may be a serious option in some patients. In addition, elderly patients do not tolerate

HDT and they therefore depend on conventional chemotherapy for their treatment.

2.2. Conventional chemotherapy for the newly diagnosed patient

With the introduction 40 years ago by Alexanian and coworkers of melphalan and prednisolone as disease-specific chemotherapy in MM, responses were achieved in up to 60% of the patients. These response rates were associated with a median OS which improved from an average of 12 to 30 months [7,8]. Melphalan combined with prednisone has long since remained the hallmark of myeloma treatment. However, it has several disadvantages which prohibit its sustained use in elderly patients. First, this combination does not have any effect on the invalidating aspect of lytic bone disease in these patients. Second, in the early days patients were treated continuously with monthly or 6-weekly cycles of MP, leading to refractory disease and Cushing-like symptoms. Thirdly, melphalan proved to be extremely toxic for bone marrow stem cells, which resulted in bone marrow failure in many patients. Because of these limitations, several other combination chemotherapy regimens were developed in an attempt to improve survival and response rates, while avoiding the complications of MP. The M-2 protocol which combined melphalan (M] with cyclophosphamide (C), prednisone (P), carmustine (BCNU)(B) and vincristine (V) resulted in 87% objective responses and a median survival of 38 months, which seemed significantly better than MP [26]. In a Spanish randomised study in 487 patients a response benefit was observed for combination chemotherapy compared with MP [27]. The SWOG reported an improvement of response and survival in patients treated with VCMP/VBAP or VCMP/VCAP compared with MP [28]. However, other randomised trials failed to demonstrate a difference in survival using combination regimens compared with MP [10,27,29]. The combination of vincristine, doxorubicin and high-dose dexamethasone [VAD) was first introduced in patients with refractory MM [30]. In later studies, VAD has been used as first-line treatment in untreated patients. The response rate was higher (55–84%) and more rapid than with other combination regimens, but this did not result in a prolongation of survival (36–44 months) [16,31,32]. Dexamethasone alone may also induce rapid responses with a response rate of 43% and an OS similar to VAD [33]. Because of the rapid response induction, VAD is also often used as remission induction treatment prior to HDT and auto-SCT [12,34,35].

In 1998, the Myeloma Trialists' Collaborative Group published a meta-analysis of 6633 patients treated in 27 randomised trials in which CCT and MP were compared. There was no difference in mortality between these two therapies. The OS of combination chemotherapy and MP were equivalent (29 versus 29 months). However, there was a significantly higher response rate with CCT compared with MP (60% versus 53.2%, $P < 0.00001$) [10].

2.3. Conventional chemotherapy for refractory or relapsing patients

The poor prognosis of patients with refractory or relapsed myeloma has improved with the introduction of the VAD regimen [30]. VAD induced remissions in 32% of primary resistant patients and in 65% of relapsing patients even if they had been treated earlier with a doxorubicin-containing regimen [36,37].

Likewise, with alternative combination regimens, such as VBAD or VBAP (vincristine, BCNU, doxorubicin and dexamethasone or prednisone), approximately 30% of the patients respond, while higher responses are observed in primary resistant patients as compared with refractory relapse [38,39]. VMBCP has been shown to be equivalent to VAD for patients who relapse after cyclophosphamide and prednisone [40].

High-dose dexamethasone alone is also effective in the treatment of resistant myeloma. In patients unresponsive to previous treatment, the response is the same as with VAD. In relapsing patients, the response to VAD is superior to dexamethasone alone (65% versus 21%) [36].

By combining VAD with cyclophosphamide (HyperCVAD) resistance to VAD or dexamethasone may be overcome in 40% of VAD-resistant patients [41]. Failure of response to VAD may be the result of the multidrug resistance phenotype (MDR), which is characterised by the expression of P-glycoprotein. In drug-resistant malignant cells, P-glycoprotein lowers the intracellular concentration of cytotoxic drugs by pumping these out of the cell. Efforts to overcome MDR include high-dose therapy, regimens of non-cross-resistant cytotoxic drugs and the use of MDR modulators. The use of the non-cross-resistant agents etoposide, dexamethasone, cytarabine and cisplatin (EDAP) has resulted in responses of 40% in patients with advanced MM, however, with a short survival [42]. The use of verapamil, cyclosporin or quinine for MDR modulation was shown to be disappointing [43–45].

Taken together, it has become increasingly evident that with conventional chemotherapy the median OS in newly diagnosed patients has reached a plateau of 40–45 months. A further improvement can only be expected from new treatment modalities. Promising recently developed agents may open new possibilities for sustained remissions and one of these examples is Thalidomide that induces responses in up to 45% of refractory patients [46]. An alternative approach is the use of dose-escalation of currently

available, effective anti-myeloma drugs in high-dose regimens.

3. Intensive treatment for multiple myeloma

3.1. High-dose melphalan

Since CCT rarely leads to complete remissions with no major gain in survival, McElwain and Powles first explored the feasibility of HDT in an attempt to induce more CRs and prolonged OS. With high-dose melphalan (HDM 140 mg/m^2) 3 of 5 untreated patients and 1 of 4 previously treated patients achieved a CR. All patients responded to treatment [11]. HDM was then prospectively investigated and the majority of previously untreated patients entered a CR (27%) or a partial remission (51%). The median duration of remission was 19 months [47]. Myelosuppresion was severe and 10 patients died from sepsis or haemorrhage. Cunningham reported an overall response rate after HDM of 82% with 32% CRs in 63 previously untreated patients. The median duration of the response in this study was 18 months. Nine early deaths occurred due to toxicity (14%) [48]. A high response rate in newly diagnosed patients was also confirmed by Lokhorst and colleagues [49]. The toxicity of HDM due to severe myelosuppression can be reduced by the use of growth factors provided that there is enough adequate bone marrow reserve [50,51]. Several attempts have been made to administer an escalated dose of melphalan while avoiding severe myelosuppression. In a Dutch study, patients were treated with 2 cycles of intermediate dose melphalan (IDM or MF 70 mg/m^2) with growth factor support, followed by myeloablative treatment. The objective of this study was to reduce the toxicity of HDM, uphold its efficacy and preserve the possibility of stem cell transplantation. Eighty-five percent of previously untreated patients responded, 18% entered a CR. The overall toxicity was moderate and no serious infections occurred. The majority of patients were treated in the out-patient clinic [52]. The administration of IDM was also feasible in older patients with MM. Palumbo and colleagues described 71 patients (median age 64 years) who were treated with 2 or 3 cycles of 100 mg/m^2 melphalan (MF100) followed by stem cell support. Their outcome was compared with 71 matched controls who were treated with oral MP. Eighty-nine percent of the patients completed the entire programme. The complete remission rate was 47% after MF100 and 5% after MP. The median event-free survival was 34 months in the MF100 group compared with 17.7 months with MP ($P<0.001$). The median OS was 56 versus 48 months ($P<0.01$) [53]. These studies indicate that IDM or HDM are effective salvage regimens in relapsed patients and effective induction regimens in newly diagnosed patients. It has been an early and important step towards the development of HDT with stem cell rescue. HDM is now used as single agent or combined with total body irradiation (TBI) in most conditionings regimens [35,54,55].

3.2. Autologous stem cell transplantation for refractory multiple myeloma

Auto-SCT was first performed in primary refractory MM. Responses of 65 to 88% were reported with a median OS up to 42 months [56,57]. With repeated transplants, the median event-free survival (EFS) and OS were 37 months and $>$ 43 months, respectively [58]. This indicates that tumour resistance can be overcome with HDT. The results of transplantation at relapse, either sensitive or refractory, are significantly worse with a median OS of 21 months [56–58]. However, in a randomised trial comparing HDT and auto-SCT as upfront or rescue treatment in case of resistance to conventional chemotherapy, the OS was 64 months with both early or late HDT [59]. Since auto-SCT is now frequently performed, relapse from transplantation is a new problem. Tricot reported on 94 patients who had relapsed after auto-SCT. Transplantation performed as primary salvage therapy was associated with a significantly prolonged OS compared with chemotherapy ($P=0.009$), but selection bias may have been involved. Low β_2-microglobulin (<2.5 mg/l) and late relapse were favourable factors of good outcome [60].

3.3. Source of stem cells and conditioning regimen

The use of peripheral blood stem cells as an alternative source of stem cells for autologous bone marrow transplantation in MM was introduced in the late 1980s [61]. Peripheral blood stem cell transplantation has now almost completely replaced bone marrow transplantation. The main advantages of blood stem cells are easier availability, faster haemopoietic recovery and lower contamination of the graft. The most widely used conditioning regimens for transplantation nowadays are HDM200 alone or HDM140 combined with total body irradiation. Several studies have indicated that HDM200 or HDM140 may be preferred over TBI because of the lower toxicity and the better PFS and OS [62–65].

3.4. Time of transplant

Should patients with MM receive a transplant early or late in the course of their disease?

Gertz and colleagues collected stem cells in 118 patients within 6 months of diagnosis followed by transplantation at the time of progression. Of 118 patients, 67 had transplants, 9 died of progression of disease and 42 remained alive in plateau phase. The

median OS was 58.5 months. They concluded that early cryopreservation of stem cells followed by transplantation at progression is a feasible approach [66].

Fermand and colleagues randomised trial about the timing of auto-SCT in 202 patients. Patients received high-dose therapy with stem cell support at diagnosis after induction with VAMP courses or later at disease progression or resistance on VMCP courses or relapse in responders. In all patients stem cells were collected after one cycle of CHOP. At a median follow-up of 58 months, the estimated median OS was 64.6 months in the early transplanted group compared with 64 months in the late transplanted group. In this study, the only advantage of early high-dose treatment was a shorter period of chemotherapy and a better quality of life [59].

3.5. Autologous stem cell transplantation as intensification or consolidation treatment

Many phase II trials have studied the response rates and response duration after auto-SCT for consolidation or intensification after remission induction in newly diagnosed patients (Tables 1–3). In the majority of published studies only patients who had responded to induction chemotherapy were included. Harousseau and colleagues reported an OS of 54 months in 103 patients responding to induction therapy compared with 30 months in 30 non-responding patients [67]. The conditioning regimen was HDM with or without TBI in most studies. In general, the response rate after auto-SCT approximates 90%. A major benefit of this approach is the higher number of CRs which ranges from 22% to 77%. A high CR rate is frequently associated with a long PFS up to a median of 46 months and a median OS of 5 years. While the response rate and OS appear to be better than with conventional therapy, it is difficult to draw conclusions from non-randomised trials. Due to stricter eligibility, there may have been a selection bias regarding age, performance status and chaemosensitive disease. Blade and colleagues reported on 487 patients with symptomatic MM who had entered into a randomised trail to compare VCMP alternating VBAP with MP. A subgroup of 77 patients who could have been candidates for HDT because of age <65 years, stages II or III disease, performance status <3 and response to chemotherapy, but who had not received HDT were compared with selected patients treated with HDT. The OS after chemotherapy was 60 months, which was the same after HDT. The median OS of all 487 patients was 29 months [68]. This observation underlines the need for randomised trials.

In a prospective population-based study, Lenhoff and colleagues compared the impact of HDT with auto-SCT in 274 patients with matched historical controls derived from earlier trials with CCT. That analysis showed that OS at 4 years was 61% compared with 46% in the control group ($P<0.001$) [55]. Barlogie and colleagues compared double auto-SCT with case matched registry data for response rate (86 versus 52%, $P=0.0001$), EFS (49 versus 22 months, $P=0.0001$) and OS (61 versus 39%, $P=0.01$] [69].

Table 1
Autologous bone marrow stem cell transplantation in previously untreated patients

Author [Ref.]	No.	Situation at Tx	Conditioning regimen	CR (%)	CR + PR (%)	TRM (%)	PFS/EFS		OS	
							Median (months)	% (months)	Median (months)	% (months)
Harousseau [72]	35	Responsive	MF140 MF140±TBI	34	94	6	28/–	–	41	–
Attal [77]	31	Responsive to VCMP	MF140+TBI+IFN	48	94	3	NR/–	53% (33)	NR	85% (33)
Jagannath [78]	19	Responsive to VAD	MF140+TBI	37	58	5	21/–	–	54	–
Cunningham [54]	53	Post-VAMP	MF200	75	98	2	>20/–		>54	63% (54)
Harousseau [67]	81	Responsive (77%)	MF140±TBI	27	83	–	30/–	26% (48)	39	47% (48)
Alexanian [79]	45	Responsive to VAD	MF140+TBI ($n=24$), rest various	45	89	11	NR/–	58% (36)	50	77% (36)
Bjørkstrand [80]	189	Responsive ($n=143$) Unresponsive ($n=46$)	MF±TBI±Cy ($n=156$) Various ($n=33$)	40	86	13	20/–	21% (60)	34	38% (60)
Cunningham [81]	84	Post VAMP/C-VAMP	MF140–200 or Bu + IFN ($n=42$) − IFN ($n=42$)	77	88	0	46/39 27/27		78	
Attal [12]	100	Post-VCMP/VBAP	MF140 + TBI+IFN	22	81	2	–/27	28% (60)	NR	52% (60)

Tx = transplantation; CR = complete remission; PR = partial remission; TRM = treatment related mortality; PFS = progression free survival; OS = overall survival; MF = melphalan; TBI = total body irradiation; VCMP = vincristine, cyclophosphamide, melphalan, prednisone; IFN = interferon; NR = not reached; VAD = vincristine, doxorubicin, dexamethasone; VAMP = vincristine, doxorubicin, melphalan, dexamethasone; Cy = cyclophosphamide; Bu = busulphan; VBAP = vincristine, BCNU, doxorubicin, prednisone; EFS = event free survival.

Table 2
Autologous peripheral blood stem cell transplantation in previously untreated patients

Author [Ref.]	No.	Mobilization regimen	Conditioning regimen	CR (%)	CR + PR (%)	TRM (%)	PFS/EFS		OS	
							Median (months)	% (months)	Median (months)	% (months)
Boccadoro [82]	54	Cy 7 g/m^2 + G-CSF	MF140 + TBI	50	90	0	–/34.5	–	70	–
Fermand [83]	63	Mega-CHOP	HDC + TBI	20	100	11	43/–	42 (60)/–	59	54 (60)
Majolino [84]	290	Various	Various	40	90	3	–	–/28 (72)		47 (72)
Moreau [65]	142	Various	MF200	–	–	0	–/20.5			65.5 (45)
Marit [85]	73	Cy 7 g/m^2 + GM	MF140 + TBI	44	93	2	–	38 (27)/–	60	
Alegre [86]	259	Various	MF200 or MF + TBI	51	92	4	23	–	35	–
Gianni [87]	13	Cy 7 g/m^2 + G-CSF	MF120 + TBI	77	92	0	38	–	41	–
Lenhoff [55]	274	Cy 4 g/m^2 + G-CSF	MF200	41	89	4	27	39 (36)/–	NR	71 (36)
Harousseau [67]	133	Various	MF140 or MF + TBI	37	83	4	33	35 (48)/–	46	43 (60)

CR = complete remission; PR = partial remission; TRM = treatment related mortality; PFS = progression free survival; EFS = event free survival; OS = overall survival; Cy = cyclophosphamide; MF = melphalan; TBI = total body irradiation; HOP = cyclophosphamide, doxorubicin, vincristine, prednisone; HDC = carmustine, etoposide; NR = not reached. G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte macrophage colony stimulating factor.

Table 3
Autologous double transplantation for multiple myeloma

Author [Ref.]	No.	Type of resistance	Conditioning regimen	CR (%)	CR + PR (%)	TRM (%)	PFS/EFS		OS	
							Median (months)	% (months)	Median (months)	% (months)
Harouseau [72]	53	Newly diagnosed	MF140 (n = 97)	25	71	–	20	–	24	–
	44	Primary and relapse	MF140 + TBI (n = 38)	65	92	8	28	–	41	–
Björkstrand [88]	15	Newly diagnosed	MF200 (n = 15) MF140 + TBI (n = 11)	60	93	7	–	93 (20)/–	–	92 (20)
Weaver [73]	55	Newly diagnosed	MF200 (n = 55)	15	–	5	–	20 (18)/–	–	84 (18)
			MF200 (n = 38)	55						
Barlogie [35]	231	Newly diagnosed	MF200 (n = 195) MF200 or	26	75	2				
			MF140 + TBI (n = 165)	41	81	6	52	–	68	–
Fermand [66]	193	Newly diagnosed randomised	carmustine + etoposide + TBI + MF140 (n = 94) or MF140 and	42	–	9	–	57 (27)	–	72 (27)
			MF140 + etoposide + TBI (n = 99)	37	–	7	–	57 (27)	–	72 (27)
Attal [75]	402	Newly diagnosed, randomised	MF140 + TBI (n = 200) or	39		1.5	–/24	31 (36)	48	58 (36)
			MF140 and MF140 + TBI (n = 202)	49	–	3	–/30	39 (36)	54	66 (36)
Cavo [76]	192	Newly diagnosed randomised	MF 200 (n = 81) or MF 200 and	22	–	–	20.5/21.5	–	–	74 (prob. 48)
			MF 120 + Bu 12 mg/kg (n = 97)	26	–	–	31.5/29.5		–	71 (prob. 48)

CR = complete remission; PR = partial remission; TRM = treatment related mortality; PFS = progression free survival; EFS = event free survival; OS = overall survival; MF = melphalan; TBI = total body irradiation; Bu = busulphan.

The only prospective randomised trial for evaluation of HDT has been published by the IFM (Intergroup Français du Myélome). Conventional chemotherapy (4–6 cycles of alternating BVAP/VMCP) was used for remission induction in 200 patients. After induction, patients were randomised to receive either 4 (additional) courses of CCT or melphalan 140 mg/m^2 (HDM140 or MF140) and TBI (8Gy) followed by auto-SCT. HDT was superior to chemotherapy. In the high-dose therapy group, 38% of the patients had a complete or very good partial remission compared with 14% of the patients treated with CCT ($P < 0.001$). Twenty-six percent of the patients did not undergo the transplantation [12,70]. The EFS and OS were 18 and 42 months, respectively, with CCT and 28 ($P = 0.01$) months and 57 ($P = 0.03$) months with HDT [71].

3.6. Double transplantation

The achievement of a CR is of critical significance for EFS and OS [12]. In an attempt to increase the response rate and to reduce the relapse rate, dose escalation with repeated transplants was investigated. Harousseau and colleagues treated 97 patients, 44 with advanced MM including 14 primary resistant and 30 relapsing and 53 untreated patients with a first course of HDM without

stem cell support. In responding patients, a subsequent second course with stem cell support was administered. Overall response and CR rate were 71 and 25%, respectively after the first course. Only 36% of 69 responders proceeded to a second course due to toxicity. The OS of those patients was 41 months versus 24 months for all patients [72]. The Seattle group reported the results of a phase I-II study of tandem HDM 200 mg/m^2 in 55 patients. The CR rate improved from 15% after the first cycle to 55% after second cycle. The probability of EFS and OS at 18 months was 76% and 84%, respectively [73].

The largest experience with HDM and double transplants has been obtained by the group of Barlogie and colleagues. Newly diagnosed patients were treated with remission induction by VAD, high-dose cyclophosphamide, stem cell collection and a non-cross-resistant regimen. The first HDT consisted of HDM 200 mg/m^2 and was repeated if complete or partial remission was obtained. Eighty-eight percent of patients completed induction therapy, while 84% of the patients received a first and 71% a second transplant. After induction, a 65% response rate with a 15% CR rate was reached. The response rate increased to 75% (26% CR) after the first transplant and 83% (41% CR) after the second transplant. Median EFS and OS were 43 and 68 months, respectively. The absence of chromosome 11 and 13 abnormalities, low β_2-microglobulin levels at diagnosis and an early onset of CR were favourable prognostic factors [35]. These observations suggest that more intensive treatment results in a higher CR rate resulting in a prolonged PFS and OS. However, the role of double transplantation still has to be assessed in randomised trials. In 1994, the IFM started a randomised trial in 402 untreated patients comparing single transplantation (HDM140 + TBI) with double transplantation (HDM140 and HDM140-TBI) after induction with 3 to 4 cycles of VAD. In 2000, an interim analysis was performed with a median follow-up of 4 years. Eighty-five percent of patients received the first transplant and 78% of patients in the double transplantation group received a second transplant. CR or a very good partial remission was observed in 39% of patients in the single transplantation group versus 49% in the double transplantation group ($P = 0.06$). The EFS and OS were not significantly different. However, for patients with a β_2-microglobulin less than 3 mg/l at diagnosis, the 3-year overall survival was better after double intensification (69 versus 84%, $P = 0.05$) [74,75].

At the VIIIth International Myeloma Workshop held in 2001, two other randomised studies were presented which showed no improvement of OS with double transplantation. In an Italian study, patients were randomised to receive either HDM200 ($n = 81$) or HDM200 for the first transplantation and melphalan 120 mg/m^2 and busulphan for the second transplantation ($n = 97$). The CR rate was higher in the double transplantation group (26 versus 22%, non significant (NS)). At a follow-up of 30 months, the PFS was significantly longer in the double transplantation group (31.5 versus 20.5, $P = 0.03$). However, EFS and OS were not different (29.5 months and 71% probability at 4 years in the double transplantation group versus 21.5 months and 74%) [76].

Preliminary results of the French 'Myelome Autogreffe' group also did not show any benefit from double over single transplantation [66]. Longer follow-up is required to draw definite conclusions.

4. Conclusions

High-dose therapy has become the treatment of choice in patients with multiple myeloma up to the age of 65–70 years. Both the response rate and the survival are significantly better than with conventional chemotherapy. Moreover, the relapse-free interval is longer, which permits the patient to continue a normal life when possible. In the more fragile elderly population, however, conventional chemotherapy remains the treatment of choice and there the challenge is to find more effective, less toxic treatments. This is especially important since a better disease eradication also prohibits the gradual worsening of invalidating symptoms such as bone lesions and immune deficiency. It is clear that the presently available conventional or even high-dose therapy alone will not lead to cure, since most patients continue to relapse. New strategies are needed to eliminate minimal residual disease. Promising treatment options to be explored are non-myeloablative allogeneic transplantation and novel anti-myeloma drugs such as proteasome inhibitors, thalidomide and immunomodulatory agents (imid's). There is a gradual shift to using these approaches at higher ages. It may be expected that in the coming decade the role of conventional chemotherapy will be further replaced by tumour debulking using high-dose therapy, combined with new drugs that are specific for malignant myeloma cells.

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