Simple variables predict survival after autologous transplantation: a single centre experience in 181 multiple myeloma patients

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Autologous stem cell transplantation (ASCT) has an important role in the treatment of multiple myeloma (MM) patients. The aim of our study was to analyse retrospectively the impact of selected simple parameters on the survival of patients with MM after ASCT, including age, type of M-protein, stage of MM, treatment response, and presence of renal impairment. A total of 181 MM patients were transplanted in our centre between 1995 and 2004. The median follow-up from transplant was 59 months. Following ASCT, 29% of patients were in complete remission (CR) and 62% in partial remission (PR); 35% of patients had very good partial response (VGPR). Median time to progression (TTP) and overall survival (OS) from start of therapy were 33.0 and 78.3 months, respectively. Significant prognostic parameters for poor survival after ASCT were: age at transplant > 60 years ($P < 0.001$), TTP < 20 months ($P < 0.001$), IgA type of monoclonal immunoglobulin ($P = 0.045$), renal impairment with serum creatinine > 177 μmol/l (> 2 mg/dl; $P = 0.004$), clinical stage III according to ISS ($P = 0.002$) and no achievement of CR and/or VGPR after ASCT ($P < 0.001$). The stage of the disease before ASCT did not significantly affect OS after ASCT.

Key words: multiple myeloma; autologous transplantation; age; complete response; prognostic factors

Multiple myeloma (MM) is a clonal plasma cell proliferative disorder, it accounts for 10% of all hematologic malignancies [1, 2].

When compared with standard-dose chemotherapy for MM, high-dose chemotherapy with autologous stem cell transplantation (ASCT) has been found to be significantly superior in terms of complete remission (CR), CR duration, progression-free survival (PFS) and overall survival (OS) [3–6].

Complete response is a major goal of transplantation, and there are efforts to improve the CR rate by choosing more aggressive induction therapy or performing tandem transplantation, or both [7]. Many other variables were evaluated in an effort to identify those that influence survival after ASCT in MM [8–11].

Reliable and simple staging of MM is important for accurate prognostic evaluation. The new International Staging System (ISS) for MM has been presented recently [12]. It is based on a simple combination of serum β_2-microglobulin and albumin values.

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We have retrospectively analysed 181 patients with MM undergoing ASCT in our centre. The aims of our analysis were to evaluate the influence of selected clinically important and easily measured parameters, including age, type of M-protein, stage of MM according to ISS and Durie-Salmon [13], response before and after ASCT, presence or absence of renal impairment, and the type of maintenance therapy on time to progression (TTP) and OS after transplant.

Patients and methods

Patient characteristics, staging and response criteria. From January 1995 to December 2004, 181 patients with newly diagnosed symptomatic MM with stage I-III according to the Durie-Salmon (DS) staging system underwent ASCT at our centre.

All patients met the eligibility criteria for the ASCT (age up to 70 years, good performance status before transplant with Karnofsky > 70%, no presence of other significant diseases). Median time from diagnosis of MM to transplant was 8 months. Patients with stage I according to DS had two or three risk factors of early progression as described by Facon [14]

Table 1 Patient characteristics

	No	*Percent*
Patients	181	100
Age at transplant (median, range)	56 (31–69)	
Clinical stage according to DS	181	100
I	17	9
II	28	16
III	136	75
Clinical stage according to ISS	166	100
I	71	43
II	70	42
III	25	15
Type of M-protein		
IgG	113	61
IgA	41	23
IgD	3	2
BJ	21	12
Nonsecretory	3	2
Pretransplant response status		
Complete response	12	7
Partial response/Very good partial response	114/41	62/23
Minimal response	32	18
No response	21	12
Progression	2	1

and some of them had a single symptomatic bone lesion. Patients' characteristics are shown in Table I. The median age at transplant was 56 years.

Staging was carried out according to the DS staging system and the ISS (ISS: stage I = β_2-microglobulin < 3.5 mg/l and albumin ≥ 35 g/l; stage II = β_2-microglobulin < 3.5 mg/l and albumin < 35 g/l, or β_2-microglobulin ≥ 3.5 mg/l to < 5.5 mg/l; stage III = β_2-microglobulin ≥ 5.5 mg/l) [12, 13]. Standard EBMT criteria were used for the evaluation of disease response [15]. Within the PR group, patients with very good partial response (VGPR), i.e. at least 90% reduction of the initial M-protein level, were evaluated separately. VGPR is not included in the EBMT criteria.

Clinical stages at the start of chemotherapy according to DS were as follows: stage I in 17 patients (9%), stage II in 28 patients (16%), and stage III in 136 patients (75%).

Initial values of albumin and β_2-microglobulin were not available for 15 patients. Clinical stages according to ISS were the following: stage I in 71 cases (43%), stage II in 70 cases (42%), and stage III in 25 cases (15%). Pretransplant response status is shown on Table 1. Serum creatinine ≥ 177 μmol/l (≥ 2 mg/dl) at start of treatment was observed in 18 (10%) patients.

Treatment. Patients were treated by four cycles of VAD (vincristine, doxorubicin, dexamethasone).

Peripheral blood stem cells (PBSC) were mobilised by high-dose cyclophosphamide 2.5 or 5g/m^2, with subsequent G-CSF at 5 or 10 μg/kg/day from day 3 to the last day of leukapheresis and collected during one to three consecutive leukaphereses.

The conditioning regimen consisted of melphalan 200 mg/m^2 in most cases (172 patients, 95%). The dose of melphalan was reduced to 140 mg/m^2 in patients with renal impairment at the time of transplant and in patients with serious complications during previous treatment (9 cases, 5 %).

Three types of maintenance therapy were used in 165 patients after transplant until progression/relapse of MM: interferon alpha (IFN) alone (IFN group); IFN alternating with dexamethasone (IFN/DEX group); CED chemotherapy (cyclophosphamide, etoposide, dexamethasone) followed by IFN (CED/IFN group). The IFN group (91 patients) received IFN 3 x 10^6 units three times weekly subcutaneously. The IFN/DEX group (48 patients) was treated using IFN 3 x 10^6 units three times weekly alternating with dexamethasone 40 mg per os on days 1–4, 10–13, 20–23 in three month intervals. The CED/IFN group (26 patients) received 4 cycles of chemotherapy CED in four-month intervals and then IFN 3 x 10^6 units three times weekly subcutaneously.

Statistical analysis. Computations for the statistical analysis were performed using the STATISTICA(version 6.1) software package and SAS version 7. The Kaplan-Meier method was used to estimate TTP and OS probabilities, with differences compared by the log-rank test. All statistical analyses were two-sided and performed at the 5% significance level. Time to progression (TTP) was measured from start of therapy to disease progression, with deaths due to causes other than progression not counted as an event but censored at that time-point. Overall survival was measured from start of therapy to death or most recent follow-up.

Results

Engraftment and transplant-related mortality. The median number of CD34+ cells infused was 4.5 x 10^6/kg (range: 0.9–22.7 x 10^6/kg). The median time to platelet recovery (>50 x 10^9/l) was 13 days (range: 10–56 days), while the neutrophil engraftment (>0.5 x 10^9/l) was achieved at a median time of 13 days (range: 10–27 days).

The transplant-related mortality (TRM) at day +100 was 2% (4/181 patients). The causes of death were septicaemia (2 patients), heart failure (1 patient) and haemorrhage (1 patient).

Postransplant responses and survival. The best response according to EBMT criteria was evaluated in the first 6 months after transplantation. Among 176 patients suitable for treatment response after transplant, 52 patients (30%) were in complete remission (CR), 113 patients (65%) were in partial remission (PR), 7 patients (4%) had minimal response (MR), and 2 patients (1%) had no response (NR – not meeting the criteria of MR or progressive disease). Of the 113 patients who achieved PR, 62 patients had very good partial response (VGPR is ≥ 90% reduction of the initial level of M-protein).

The median follow-up from transplant was 59 months. The median TTP was 33.0 months and the median OS was 78.3 months.

Overall survival was significantly affected by TTP (P< 0.001). Fifty patients with TTP < 20 months had significantly

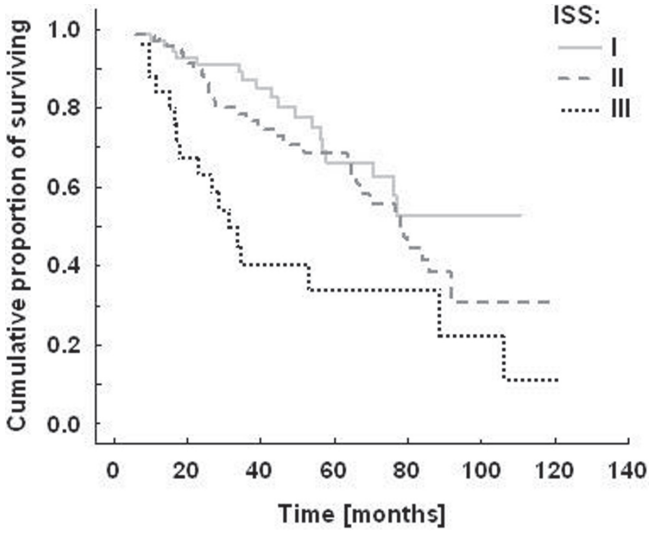

Fig. 1 Survival by stage according to the International Staging System

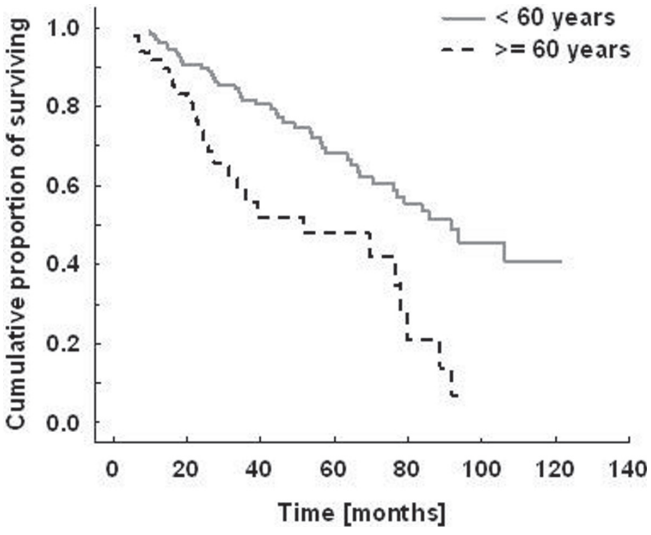

Fig. 2 Survival by age

shorter median OS than 126 patients with TTP ≥ 20 months (median OS 24.6 months versus 90.2 months).

Factors associated with TTP and OS after ASCT. The results of the univariate analysis are summarised in Table 2. Variables associated with better TTP were non-IgA type of M-protein, achievement of CR or VGPR after transplant and age < 60 years at transplant.

Negative prognostic factors influencing OS at significant level in the univariate analysis (P < 0.05) were: IgA type of M-protein, stage III according to ISS, renal impairment at diagnosis, age at transplant ≥ 60 years, no CR and VGPR after transplant.

1) Clinical stage according to DS and ISS. Survival after transplant was influenced by clinical stage according to ISS (Fig. 1). Median OS of patients with ISS stage III was 31.2 months, with ISS stage II 77.9 months, and with ISS stage I median OS has not been reached yet. Patients with ISS stage III had significantly shorter OS than other patients (median OS 31.2 months versus 78.9 months, P =0.002). Median TTP of patients with ISS stage III had 22.4 months, median TTP of patients with ISS stage II was 33.9 months and with ISS stage I 41.1 months.

Differences in TTP and OS between patients with clinical stages according to the DS staging system were not statistically significant (P = 0.612, P = 0.055).

2) Age. Patients with age at transplant < 60 years (133/181) had significantly better survival after ASCT than patients with age ≥ 60 years (median OS 88.9 months versus 45.6 months, P < 0.001) (Fig. 2). Differences in TTP in patients with age at transplant < 60 years and with age ≥ 60 years were not statistically significant, but there was a trend to longer TTP in the younger patients (median TTP 35.7 months versus 24.5 months, P = 0.394).

Transplant-related mortality was higher in patients ≥ 60 years (2/48, 4%) in comparison with patients < 60 years (2/133, 1.5%). No other differences in the causes of death between these two age groups were observed, with deaths in both groups mostly related to the progression of MM.

3) Responses before and after transplant. We compared the group achieving CR (12/181) prior to transplant with others. There were no significant differences in TTP (median TTP 33.1 months versus 32.7 months, P = 0.294) or in OS (median OS 82.3 months versus 76.8 months, P = 0.866).

No significant differences were found between the groups with CR+PR (124/181) before transplant and MR+NR before transplant in TTP (median TTP 32.2 versus 40.6 months, P = 0.376) and in OS (median OS 76.5 versus 84.5 months, P = 0.415).

Patients who achieved CR after transplant (52 cases) had significantly longer TTP (P < 0.001) and OS than others

Table 2 Univariate analysis

	TTP (P value)	OS (P value)
Type of M-protein (IgA vs others)	**0.027**	**0.045**
Stage according to ISS (III vs others)	0.070	**0.002**
Stage according to DS (III vs others)	0.612	0.055
Renal impairment at start of treatment	0.086	**0.004**
Age at transplant (> 60 vs others)	0.394	**< 0.001**
Response prior to transplant (CR vs others)	0.294	0.866
Response prior to transplant (MR+NR vs CR+PR)	0.376	0.415
Response after transplant (CR vs others)	**< 0.001**	**< 0.001**
Response after transplant (CR+VGPR vs others)	**< 0.001**	**0.033**
Type of maintenance therapy (CED/IFN vs others)	0.422	0.792

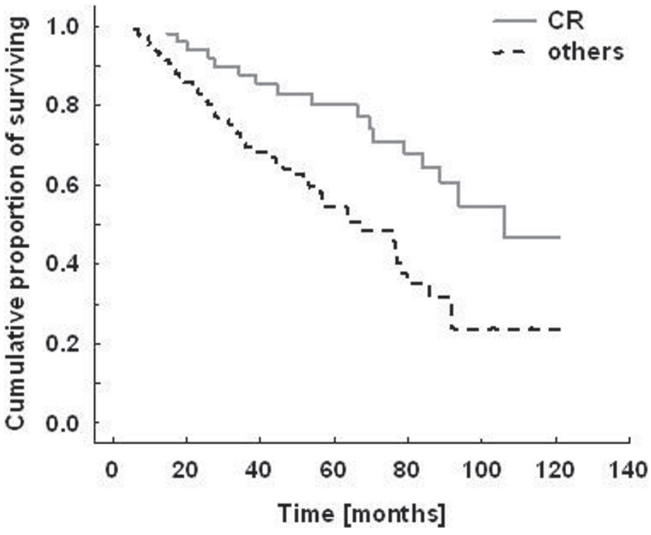

Fig. 3 Survival by response after transplantation

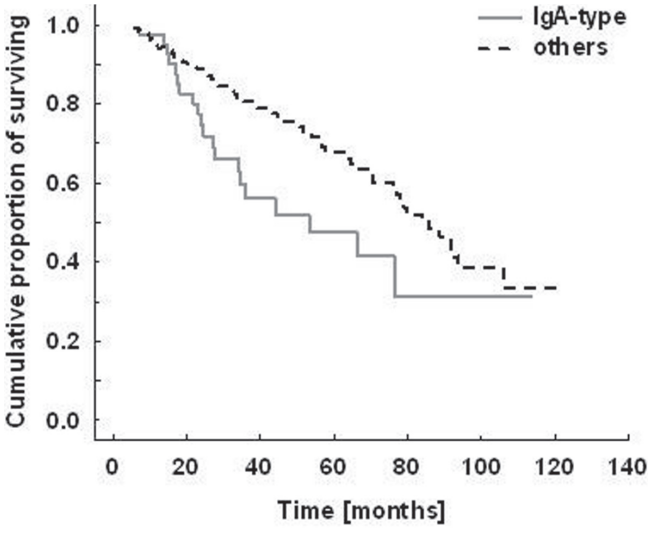

Fig. 4 Survival by IgA type of M-protein

(median OS 100.8 versus 65.1 months, P < 0.001) (Fig. 3). Also the group of patients who achieved CR+VGPR after transplant (113 cases), had significantly longer TTP and OS than others (median TTP 44.6 versus 23.8 months, P < 0.001; median OS 87.0 months versus 66.1 months, P = 0.033).

4) Type of monoclonal immunoglobulin. We also evaluated correlation between the type of M-protein and TTP and OS. The patients with IgA type of M-protein (41/181) had shorter TTP (median TTP 22.0 months versus 40.6 months, P = 0.027) and shorter OS (median OS 47.9 versus 84.0 months, P = 0.045) than patients with other types (Fig. 4).

5) *Renal impairment*. Patients with renal impairment (18/181) at start of therapy of MM (creatinine > 177 μmol/l) had significantly shorter OS than patients without renal impairment (median OS 25.7 versus 81.4 months, P = 0.004). There was also a trend to shorter TTP but the difference was not statistically significant (median TTP 20.2 versus 34.6 months, P = 0.086).

6) *Maintenance therapy after transplant*. Three types of maintenance therapy after transplant were compared (IFN, IFN/DEX, CED/IFN). No significant differences in TTP (P = 0.422) or OS (P = 0.792) were found between the group with consolidation chemotherapy (CED/IFN) and other groups. However, the number of patients in the CED/IFN group was lower in comparison with other post-transplant therapy groups.

Discussion

The objectives of our study were to analyse the prognostic significance of several simple variables to TTP and OS after ASCT.

Advanced age has been shown to be a poor prognostic factor in several trials using conventional chemotherapy [16, 17] or ASCT [18–20]. On the other hand, some reports using the cut-off value of 65 years or even 70 years have suggested that age is not an exclusion criterion for ASCT [8, 21]. In our analysis, patients with age ≥ 60 years had significantly shorter OS (P < 0.001) than younger patients.

The combination of two simple but significant prognostic variables for MM, i.e. albumin and b_2-microglobulin, is the principle of the new International Staging System [12]. We tested ISS in our group of patients and our findings confirm the validity and reproducibility of this staging system. Our patients with stage III according to ISS had significantly shorter survival after ASCT (P = 0.002) than others.

High-dose chemotherapy with ASCT can be feasible in MM patients with renal failure [10, 22, 23]. Some authors found no significant influence of renal failure on TTP or OS after ASCT [22]. However, according to other reports [23], overall survival in patients with renal impairment was significantly shorter. Higher TRM and higher number of non-haematological toxicities were reported in these patients [10, 22, 23], therefore a reduction of the melphalan dose has been recommended. We compared the survival after transplant of patients with renal impairment at diagnosis with patients having normal renal function. The survival of our patients with renal impairment was significantly shorter (P = 0.004).

The possible influence of the type of M-protein on the survival after ASCT is unclear. According to some authors [24], IgA type is a marker of poor prognosis, with both shorter TTP and OS after transplant. Other authors presented no influence of IgA type of M-protein on TTP and OS [25]. In our set of patients, IgA type of M-protein was a negative prognostic factor for both TTP and OS after ASCT.

Achievement of CR after transplant is a strong prognostic factor, which is associated with significantly longer TTP and OS after transplant [26–28]. Our data confirm these results.

Based on the results of IFM trials [29] criteria for response have been modified to incorporate the VGPR category as a helpful tool identifying a subgroup of patients with superior outcome as compared to patients who achieved standard PR. We have been able to confirm that the group of patients with CR+VGPR after transplant had significantly better OS than others.

Duration of response is an important end point and can predict ultimate overall survival [30]. Several different methods are used to calculate response duration and the impact of treatment. Time to progression is a helpful method to discretely assess the durability of treatment benefit. We confirm significant relation between length of TTP and OS in our group of patients ($P < 0.001$).

The role of maintenance therapy after ASCT remains unclear. Regarding the use of post-transplant IFN as maintenance treatment, some reports suggest that this agent may be beneficial in prolonging TTP and OS after ASCT [19, 25]. Some patients benefited from post-transplant consolidation chemotherapy with improved OS [26]. On the other hand, the major limitation of this approach can be the inability to deliver all planned treatments [31]. In our cohort of patients, we used three types of post-transplant therapy, i.e. IFN alone, alternating IFN and dexamethasone, and consolidation chemotherapy CED followed by IFN. We found no significant differences in TTP or OS between these three types of post-transplant therapy in our patients. These results are preliminary, the group of patients with consolidation chemotherapy is still small and was analysed retrospectively with shorter follow-up in comparison with other groups (the median follow-up from transplant was 24 months). A randomized study comparing consolidation chemotherapy after transplant with IFN maintenance therapy has been underway in some transplant centres of Czech and Slovak Republic since 2002.

In conclusion, ASCT is an effective procedure for MM patients, associated with low TRM. In our group of patients, both TTP and OS after ASCT were influenced by IgA type of M-protein, and the achievement of CR and VGPR after transplant. Survival after ASCT correlated with TTP, the presence of initial renal impairment, age and stage according to ISS.

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