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Original contributions

Treatment of multiple myeloma with high-dose chemotherapy and autologous haematopoietic progenitor cell transplantation – a single centre experience

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Introduction. Patients suffering from multiple myeloma treated with melphalan and prednizone survive three years on average. Recently a higher survival rate has been associated with high-dose chemotherapy followed by transplantation of haematopoietic progenitor cells. This paper presents our experience with high-dose chemotherapy in the treatment of patients suffering from multiple myeloma.
Patients and methods. 31 patients with multiple myeloma were treated with autologous transplantation of progenitor cells from peripheral blood: 24 patients underwent a single transplantation, whereas 7 underwent double transplantation. During conditioning regimen melphalan was administered for the first transplantation, and melphalan or BEAM regimen for the second one.
Results. 29 patients achieved complete haematological recovery, the regeneration of megakaryopoiesis being statistically delayed after the second transplantation. There were 12 CR, 2 PR and 15 NR. Three year EFS was 31%, OS was 85%. The risk factor for EFS was late versus early transplant, and for OS it was renal failure.
Conclusions. Results show that high-dose chemotherapy, followed by autologous transplantation of progenitor cells, is a relatively low risk procedure (4%). and allows achieving long term remission.

Leczenie szpiczaka mnogiego za pomocą wysoko dawkowanej chemioterapii oraz autologicznego przeszczepu szpiku – doświadczenia własne

Wstęp. Pacjenci chorujący na szpiczaka mnogiego, leczeni przy pomocy melfalanu w konwencjonalnych dawkach w skojarzeniu z prednizonem, przeżywają średnio trzy lata. Wydłużenie długości życia można uzyskać poprzez zastosowanie chemioterapii w wysokich dawkach, skojarzonej z autologicznym przeszczepem szpiku. Prezentowana praca przedstawia własne doświadczenia, związane ze stosowaniem wysoko dawkowanej chemioterapii w leczeniu chorych ze szpiczakiem mnogim.
Pacjenci i metody. 31 chorych zostało poddanych przeszczepowi z krwi obwodowej: 24 z nich otrzymało przeszczep pojedynczy, u siedmiu zastosowano podwójny zabieg. W kondycjonowaniu do pierwszego przeszczepu stosowano melfalan, do drugiego melfalan lub BEAM.
Wyniki. U 29 chorych doszło do pełnej regeneracji szpiku, po drugim z zabiegów obserwowano przedłużony czas odtwarzania się megakariopoezy. Szacowane 3-letnie przeżycie bez choroby wynosi 31%, całkowite przeżycie 85%. Wykonanie przeszczepu w późnym okresie choroby stanowi czynnik ryzyka jej nawrotu, czynnikiem ryzyka dla całkowitego przeżycia jest niewydolność nerek w chwili przeszczepu.
Wnioski. Uzyskane rezultaty sugerują, że wysoko dawkowana chemioterapia, połączona z autologicznym przeszczepem szpiku, jest stosunkowo bezpieczną procedurą i pozwala na uzyskanie długotrwałych remisji.

Key words: multiple myeloma treatment, high-dose chemotherapy, autologous bone marrow transplantation
Słowa kluczowe: leczenie szpiczaka mnogiego, chemioterapia w wysokich dawkach, autologiczny przeszczep szpiku

Introduction

Patients suffering from multiple myeloma treated with Melphalan in a standard dose and Prednizone, survive, on average, no more than four years [1]. 3% of the patients survive ten years, whereas complete remission has not been observed [2, 3]. The introduction of multi-drug chemotherapy has not improved the above figures [4]. Higher

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expectations concerning the survival rate have recently been associated with high-dose chemotherapy followed by transplantation of haematopoietic progenitor stem cells (HDC/HSCT). In a randomised clinical trial conducted in France (IFM 90), on a group of patients who underwent autologous transplantation, prolonged event free survival (EFS) and overall survival (OS) were observed [5]. The introduction of high-dose chemotherapy was also demonstrated in a case-matched study conducted by Southwest Oncology Group and a in a population-base study preformed by Nordic Myeloma Study Group [6, 7]. The results of the above investigations have prompted the European Bone Marrow Transplant registry (EBMT) to recommend autologous transplantations of progenitor cells to be routinely employed in clinical practice [8]. This paper presents our experience concerned with the employment of HDC/HSCT in treatment of patients with multiple myeloma.

Patients and methods

Since 1996 31 patients with myeloma underwent HDC/HSCT at the Department of Haematology of the Medical University of Gdańsk. The characteristics of patients at the first and second transplant are detailed in Tables I and II. Only patients responding to previous treatment, with ≤30% plasmocytes in bone marrow were qualified for the HDC/HSCT.

In order to achieve mobilisation of progenitor stem cells, a cycle of Cyclophosphamide was administered once at a dose of 6 g/m^2 (31 transplantations), 4 g/m^2 (two transplantations) or 3 g/m^2 (5 transplantations). Beginning with the next day rhG-CSF (Neupogen, Roche Polska) was administered subcutaneously on a daily basis. G-CSF was administered at a dose of 300 μg in patients weighing less than 60 kg, and, 480 μg in the remaining. Progenitor stem cells were collected at the growth stage of leukocytosis, following a nadir induced by the employment of the above presented chemotherapy, on exceeding a level of 1,0 G/l. During conditioning regimen Melphalan was administered at a dose of 200 mg/m^2 (day -2), followed by an autologous transplantation of progenitor cells (details in Table III). In seven cases the procedure was repeated (Table II).

Conditioning regimen preceding the second transplantation depended on the effects achieved during the first one. In the event of complete or partial remission Melphalan was administered again in the initial dose. If no effect was achieved the BEAM (BCNU 300 mg/m^2, Etoposide 150 mg/m^2, ARA-C 200 mg/m^2, Melphalan 140 mg/m^2) regimen was introduced (Table III). Complete remission was defined according to Blade et al [9] as the lack of monoclonal protein in serum and urine in immunoelectrophoresis and immunofixation studies, and a percentage count of plasmocytes in bone marrow lower than 5%. Partial remission was defined as the normalisation of the total percentage of plasmocytes in bone marrow (<5%), and a reduction of the amount of monoclonal protein by 50% or to a value of 0.2g/l in 24-hour urine in the case of Bence-Jones disease. In the period following transplantation antibacterial (fluorochinolones), antimycotic (fluconazole) and antiviral (Acyclovir used up to day +30) prophylaxis were introduced. At a later stage antibacterial prophylaxis was discontinued, the administration of Acyclovir was extended to day +100, and the administration of anti-HBS serum (Hepatect) was employed due to a high risk of hepatitis type B. Routinely, following transplantation, haematopoietic growth factors were not administered. In six patients Interferon alpha, was administered at a dose of 3 mln. UI three times a week, from the time of the completion of the grafting criteria until one year after transplantation. In the second half of 1997 the above procedure was discontinued; supportive therapy following transplantation not being employed.

Table I. Characteristics of patients at the first transplant

	No. of evaluated patients	No	(%)
Myeloma type:	31		
IgG		21	(68)
Bence-Jones		6	(19)
IgA		2	(6)
IgD		1	(3)
Non-secreting		1	(3)
Light chain type:	31		
Kappa		23	(74)
Lambda		7	(23)
Non-secreting		1	(3)
Sex:	31		
females		16	(52)
males		15	(48)
Disease stage at diagnosis (Durie-Salmon):	31		
I		4	(13)
II		4	(13)
III		23	(75)
Renal function:	31		
A		27	(87)
B		4	(13)
Number of previous chemotherapy regimens:	31		
1		14	(58)
2		3	(13)
3-4		5	(21)
6-7		2	(8)
median	1		
range	1-7		
β2-mikroglobulin level:	30		
<6/.0		24	(80)
≥6.0		6	(20)
Indications for transplant:	31		
early transplant		21	(68)
late transplant		10	(32)
Type of transplant	31		
single		24	(77)
double		7	(23)
Age of patients (median, range)	49		(34-66)

Statistical methods

Survival probabilities were calculated employing the Kaplan-Meier method and comparisons made using the log-rank test. The following variables were included in a model of prognostic factors for OS and EFS: Sex, number of transplants, heavy and light chain type, stage according to the Durie-Salmon classification, time of transplant (early/late), renal sufficiency, β2-microglobulin level >6.0 mg/ml. When comparing the rate of haematological recovery after every transplantation, the Wilcoxon test was utilised.

Results

From among 31 patients who underwent transplantation of hematopoietic progenitor cells, 29 achieved complete haematological recovery. One patient, treated during a period of renal insufficiency, with a creatinine level of

Table II. Characteristic of patients at the second transplant

	No. of evaluated patients	No / %
Myeloma type:	7	
IgG		4 (57)
Bence-Jones		3 (43)
Light chain type:	7	
Kappa		2 (28)
Lambda		5 (71)
Sex:	7	
females		4 (57)
males		3 (43)
Disease stage at diagnosis (Durie-Salmon):	7	
II		1 (14)
III		6 (86)
Renal function	7	
A		7 (100)
B		0 (0)
Indications for transplant:	7	
early transplant		6 (86)
late transplant		1 (14)
Age of patients: median, range	7	44 (36-50)
Time between the first and the second transplant: median, range (days)	7	179 (134-242)

>5mg/dl, died due to septic complications. In another patient reconstitution of megakaryopoiesis was not achieved in a period of two years following the second transplantation. The patient has symptoms of active myeloma and is at present treated with Thalidomide. Among other observed complications oral mucositis and neutropenic fever were most often, usually mild or moderate.

In the majority of patients the process of recovery of haematopoiesis was satisfactory. The level of leukocytes exceeded the value of 1.0 G/l usually on day 15 (11-24) following the first transplantation, and on day 19 (13-29) after the second one. Granulocytes achieved a level of 0.5 G/l on day 17 (10-28) following the first transplantation, and on day 20 (13-29) after the second one. The rate of recovery of leukocytes and granulocytes after the first and second transplantations did not differ significantly. Platelets presented a value higher than 50 G/l on day 21 (10-32) after the first transplantation, and on day 38 (18-53) after the second one, the difference being statistically significant (p=0.04) (Table III).

As a result of the transplants 12 patients achieved complete (CR) and 2 partial remission (PR), according to the criteria presented in the Patients and Methods section. In the remaining 16 patients the reduction of monoclonal protein was less than 50% or the count of plasmocytes following treatment exceeded 5%. Presently, at a median time of observation of +643 days, 26 of the 31 patients, who underwent transplantation are alive, 7 of them still in CR. The three year OS is 85% (Figure 1), and the three year EFS is 31% (Figure 2). The only risk

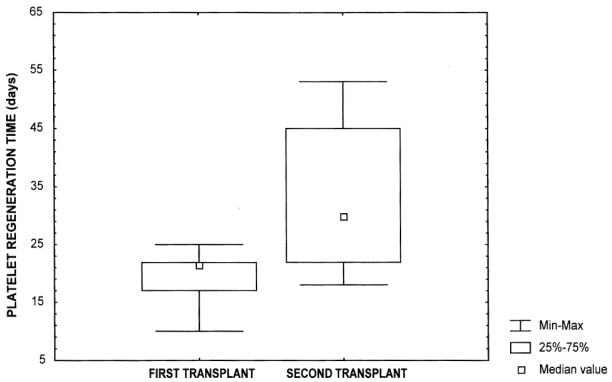

Figure 1. Platelet regeneration after each transplant

Table III. Characteristics of the transplants

	First transplant	Second transplant
Conditioning regimen:		
Melphalan 200	31 (100%)	5 (71%)
BEAM		2 (29%)
(No, %)		
Characteristics of transplanted material:		
MNC ($x10^8$)	4.8 (1.7–10.2)	4.4 (1.9–6.4)
CD34 ($x10^6$)	6.4 (1.2–93.2)	2.1 (0.6–6.1)
CFU-GM ($x10^4$)	39.2 (12.6–192.2)	23.8 (7.1–82.1)
(median, range)		
Regeneration time:		
leukocyte >1.0 G/l	15 (11–24)	19 (13–29)
granulocyte >0.5 G/l	17 (10–28)	20 (13–29)
platelets > 50 G/l	21 (10–NR)	38 (18–NR)
(median, range)		
Results:		
CR	8 (33%)	4 (57%)
PR	1 (4%)	1 (14%)
<PR	14 (58%)	2 (29%)
toxic death	1 (4%)	0
(No, %)		

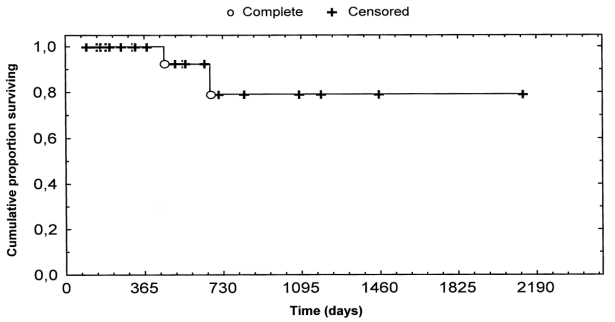

Figure 2. Overall survival of patients with multiple myeloma after autologous haematopoietic cell transplantation

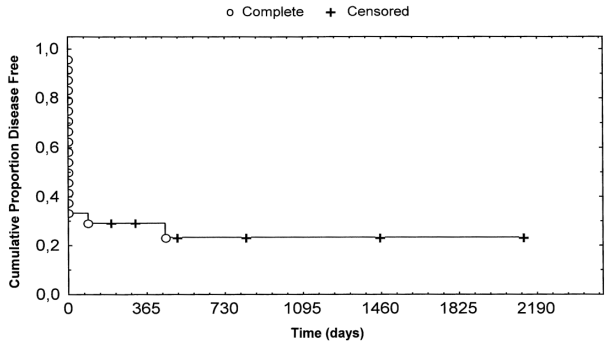

Figure 3. Disease free survival of patients with multiple myeloma after autologous haematopoietic cell transplantation

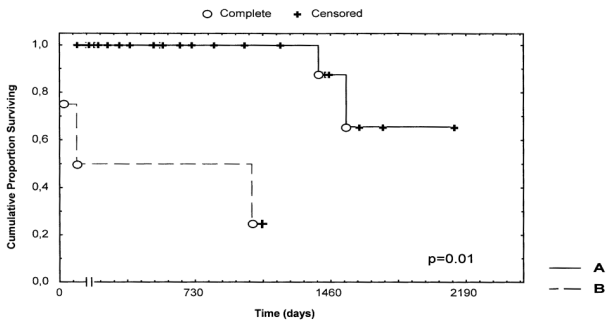

Figure 4. Survival according to renal status at transplantation:
A-creatinine ≤ 2.0 mg/dl
B-creatinine > 2.0 mg/dl

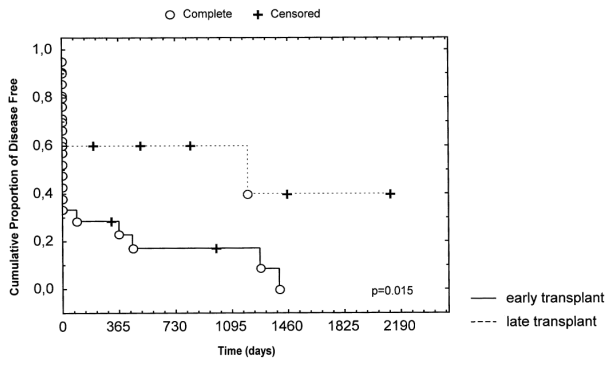

Figure 5. Disease free survival according to time of transplantation

factor for OS was renal insufficiency (p>0.01) (Figure 4), and for EFS the time of transplant (early versus late) (p=0.015).

Discussion

Multiple myeloma is the second most common indication for conducting autologous transplantations of bone marrow in Europe, following non-Hodgkin lymphoma according to the European Bone Marrow Transplantation Registry (EBMT) [8]. Administration of autologous haematopoietic cells following high-dose chemotherapy is relatively well tolerated by patients, but entails a risk of contamination. As a result, the complete remission rate is relatively high but relapses are common. Our experience in this respect is similar. In the group of patients who underwent treatment, 12 (39%) achieved complete remission and another 2 (6%) achieved partial remission. The results are very close to 44% of CR reported by Desikan et al among 1000 patients with myeloma treated by HCD/ASCT in one centre, similar results being reported by other groups [10-13]. Unfortunately, molecular data indicates only sporadic occurrence of complete remission following autologous transplantation [14, 15]. Some data suggest that a higher CR rate and prolonged DFS and OS can be achieved by double transplants [16--18]. The issue of one versus two autotransplants for myeloma patients at diagnosis is currently being addressed in two randomised studies [19, 20]. We have not observed better survival in patients who received double transplantation, but only seven patients were enrolled in the tandem transplant program.

A large proportion of patients relapse after HDC/ASCT. As a result 3 year EFS in our group is 31%. Better EFS was observed in patients who received HDC/ASCT as first line treatment than in patients with advanced or resistant myeloma (p=0.015). Some authors question the value of high-dose therapy in the treatment of late myeloma [21]. Currently most centres perform HDC/ASCT as a part of initial treatment [5-7, 16-19].

Only one early death observed among the 31 treated patients is a clear indication of minor risks associated with transplantations. The only death was observed in a patient with renal insufficiency. Renal failure is a well established risk factor for HDC/ASCT [16]. In one study transplant related mortality in such a group of patients was as high as 29% [22]. Unfortunately, in cases treated with standard therapy, median survival is around four months and any attempt to overcome this would be more than welcome [23]. Despite high transplant-related mortality in some patients, stem cell transplantation contributes to the reversal of renal failure. In published studies almost half of the patients showed improvement in renal functioning after HDC/ASCT [22, 24]. A query remains as to what is the optimal conditioning regimen. Despite results of the study of Tricot et al. suggesting that high-dose melphalan pharmacokinetics is not affected by renal functioning, some authors prefer to use conditioning regimens without melphalan [25, 26].

Our results indicate that high-dose chemotherapy followed by autologous transplantation of bone marrow is a low risk procedure. It allows to achieve long term remission even in some patients suffering from an advanced and treatment – resistant type of the disease. It must be emphasised that autologous transplantation allows achieving long term remission rather than complete elimination of the disease. Nevertheless HDC/ASCT constitute progress in the treatment of patients with multiple myeloma.

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