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European Journal of Cancer 40 (2004) 1199–1207

European Journal of Cancer

www.ejconline.com

Factors influencing haematological recovery following high-dose chemotherapy and peripheral stem-cell transplantation for haematological malignancies: 1-year analysis

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Received 15 January 2004; accepted 19 January 2004

Abstract

Peripheral blood counts and factors influencing haematological recovery in 98 patients with a relapse-free survival of $\geqslant 1$ year treated with high-dose chemotherapy (HDC) and peripheral stem-cell transplantation (PSCT) for haematological malignancies were analysed. One year after PSCT full haematological recovery was demonstrated for haemoglobin (Hb) in 47% of patients, for the white blood cell count (WBC) in 94%, and for platelets in 64%; 39% had a trilineage recovery. In the multivariate analysis, recovery was influenced by age ($P=0.002$), number of reinfused CD34+ cells ($P=0.016$), Hb at start of HDC ($P=0.001$), and platelets at start of HDC ($P=0.008$). One year following PSCT, 61% of patients still have subnormal values in one or more haematopoietic cell lineage, suggesting a limited bone-marrow reserve. Long-term recovery is highly dependent on age, blood counts at start of HDC and number of reinfused CD34+ cells without a threshold, all reflecting the residual function of bone marrow before HDC. Reinfusing more CD34+ cells can accelerate long-term haematological recovery.

Keywords: Long-term; Haematological recovery; Haematopoiesis; Peripheral stem-cell transplantation; High-dose chemotherapy

1. Introduction

High-dose chemotherapy (HDC) followed by peripheral stem-cell transplantation (PSCT) has proved to be beneficial in selected patients with Hodgkin's disease and non-Hodgkin's lymphoma [1]. The consequence might be a defect in long-term haematopoiesis, which is reflected by a reduced number of bone-marrow progenitors for as long as 4–5 years after transplantation [2–5]. Most investigators state that peripheral blood counts are normal in most patients at 1 year after autologous transplantation [4,6–10]. Recently, however, we showed that haematological recovery in patients with solid tumours was incomplete in most at 1 year after autologous transplantation and in a significant proportion years thereafter [11].

Factors influencing short-term haematological recovery (granulocytes $\geqslant 0.5\times10^9$/l and untransfused platelets $\geqslant 20\times10^9$/l) after autologous transplantation have been studied extensively, but factors influencing long-term recovery (white blood cell count (WBC) $\geqslant 4\times10^9$/l, platelets $\geqslant 150\times10^9$/l and haemoglobin (Hb) $\geqslant 7.45$ mmol/l for females and $\geqslant 8.7$ mmol/l for males) are largely unknown. The available data suggest that long-term recovery is dependent on the number of CD34+ cells reinfused and the age of the patient [4,6,7,10,12]. Whether delayed or incomplete haematological reconstitution has functional consequences has not been systematically studied. Although rarely described explicitly, it is well known that many patients who relapse after autologous stem-cell transplantation display decreased haematological tolerance to reinduction chemotherapy [13]. In

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0959-8049/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.ejca.2004.01.029

addition, radiotherapy after transplantation and infections during follow up might result in haematopoietic stress and temporary cytopenia [9]. The observed abnormalities in haematopoiesis could therefore lead to significant clinical problems in a selected group of patients.

The present study analysed peripheral blood counts and mean corpuscular volume (MCV) at 1 year after HDC and PSCT, and sought to define factors that determine long-term haematological reconstitution after these two procedures.

2. Patients and methods

2.1. Patient characteristics

All patients treated with HDC followed by PSCT at the Department of Haematology, University Hospital Groningen, The Netherlands between June 1993 and June 2001 were analysed. 98 out of a total of 162 patients survived relapse free for at least 1 year after HDC and PSCT and were evaluated for the present study.

2.2. Mobilisation procedure and peripheral stem-cell harvest

Peripheral stem cells were collected following a disease-orientated course of chemotherapy and granulocyte-colony stimulating growth factor (G-CSF). Harvesting was performed via a dual-lumen catheter using a Hemonethics MCS+ pheresis machine. CD34+ cells were stained using a monoclonal anti-CD34 (anti HPCA-2) and quantified by flow cytometry (FACS Calibur; Becton Dickinson Woerden, The Netherlands). A target quantity of CD34+ cells of $\geqslant 2\times10^6$/kg body weight was envisaged.

2.3. Supportive measures

None of the patients received blood or platelet transfusions in the 4 weeks preceding PSCT. All patients were treated with selective gut decontamination during neutropenia. Neither G-CSF nor erythropoietin was administered after PSCT. Platelets were transfused if the platelet count fell below 10×10^9/l or if bleeding occurred. Erythrocytes were transfused if the Hb dropped below 5 mmol/l or if the patient had symptomatic anaemia. All blood products were irradiated.

2.4. Stem-cell cryopreservation

The leukapheresis product was mixed with minimal essential medium (MEM) containing 20% dimethyl sulphoxide. The final cell suspension was transferred into freezing bags and frozen to −40 °C with a computer-controlled cryopreservation device. The frozen cells were then transferred into the liquid phase of nitrogen and stored at −196 °C.

2.5. Conventional chemotherapy and high-dose regimens

Conventional chemotherapy was defined as a chemotherapy regimen not followed by reinfusion of stem cells. HDC was defined as a regimen that was followed by reinfusion of stem cells. The high-dose regimens were dependent on diagnosis. Patients ($n=12$) with Hodgkin's disease received BEAM (carmustine 300 mg/m^2 day 1, etoposide 200 mg/m^2 day 2–5, cytarabine 100 mg/m^2 day 2–5 and melphalan 140 mg/m^2 day 6) [14]. Patients with non-Hodgkin's lymphoma (NHL) received BEAM ($n=36$) or cyclophosphamide + TBI (total body irradiation) ($n=2$, cyclophosphamide 60 mg/kg for 2 days and TBI 9 Gy) [14]. Patients with multiple myeloma (MM) received high-dose melphalan ($n=37$, melphalan 100 mg/m^2) or cyclophosphamide + TBI ($n=8$) [15]. Patients with acute leukaemia received BEAM ($n=1$) or busulphan + cyclophosphamide ($n=2$, busulphan 4 mg/kg day 1–4, cyclophosphamide 60 mg/kg day 1–2) [16].

2.6. Radiotherapy

24 patients received local radiotherapy because of bulky disease or painful bone lesions before HDC or in the year following HDC for pre-existent lesions.

2.7. Stem-cell reinfusion

Immediately before infusion, the cryopreserved peripheral stem cells were rapidly thawed in a 40 °C waterbath, aspirated in a laminar-flow cabinet and reinfused through a double-lumen Hickman catheter. Premedication consisted of steroids and antihistamines.

2.8. Haematological determinations

Hb, WBC, platelets and MCV were determined by standard techniques using an automated Coulter particle counter (Coulter Electronics Nederland, Mijdrecht, The Netherlands). Patients were considered to have reached short-term recovery when granulocytes were $\geqslant 0.5\times10^9$/l and untransfused platelets $\geqslant 20\times10^9$/l. Long-term haematological recovery was defined as WBC $\geqslant 4\times10^9$/l, platelets $\geqslant 150\times10^9$/l and Hb $\geqslant$ 7.45 mmol/l for females and $\geqslant$ 8.7 mmol/l for males [4,6,7,11]. In the statistical analyses Hb was recalculated to a z-score because of the different normal Hb for males and females (z-score = $\mathrm{Hb}_{\mathrm{measured}}$–$\mathrm{Hb}_{\mathrm{mean\ for\ normals}}$/SD for normal Hb). Normal MCV was defined as 80-98 fl [11,17]. Following recovery from transplantation,

patients were seen in our hospital as outpatients at weekly to monthly intervals. Haematological recovery was examined in every blood count during the first year after PSCT.

2.9. Statistical analysis

Many variables showed an asymmetrical distribution; therefore medians are presented. Haematological recovery was assessed using Kaplan–Meier probability curves and statistical comparison of curves was performed by the log-rank test. The prognostic value of different variables for probability of haematological recovery was assessed by univariate and multivariate analysis using the Cox multiple-regression model. A $P<0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

Median age at transplantation was 46.5 years (range 17–64 years). 68 males and 30 females had been treated with HDC and PSCT. Patients had been diagnosed as follows: 12 Hodgkin's lymphoma, 38 NHL, 45 MM and three acute leukaemia. Patients had received a median of eight cycles (range 2–31) of conventional-dose chemotherapy before HDC. Patients received a median 8.4 (range 1.57–51)$\times 10^6$ CD34+ cells/kg body wt. Stem cells were harvested in 1–5 days (median 1). Median 11.5×10^6 CD34+ cells/kg body wt were harvested during a pheresis day. Radiotherapy was given to 24 patients just before or in the year following PSCT.

3.2. Peripheral blood counts and MCV

It appears that Hb and platelet recovery continued to improve over time. Six months after PSCT the median Hb was 7.7 mmol/l (range 3.7–9.3), median WBC was 5.3×10^9/l (range 1.8–14.1), median platelets were 136×10^9/l (range 7–338) and median MCV was 98.5 fl (range 79–113) (Figs. 1–4). One year after PSCT these values were 8.1 mmol/l (range 5.5–9.7) for Hb, 5.8×10^9/l (range 1.7–12.7) for WBC, 163×10^9/l (range 15–420) for platelets and 96 fl (range 79–116) for MCV. Approximately 25% of patients showed an elevated MCV from 3 months following transplantation.

3.3. Haematological recovery

Short-term recovery of granulocytes was observed after a median of 15 days (range 11–90) and of platelets after a median of 18 days (range 8–365). One year following PSCT 47% of patients had a normal Hb, 94% of patients had normal WBC, 64% had normal platelets and 39% had trilineage recovery. Recovery of WBC occurred first, followed by platelets and Hb (Fig. 5). No dependency on blood or platelet transfusion was seen beyond 6 months of follow up. No secondary myelodysplasia or leukaemia was encountered during the 1-year follow up.

3.4. Univariate analysis of variables influencing engraftment (Table 1)

The results of a univariate analysis of variables affecting long-term recovery of Hb, WBC recovery, platelet recovery and trilineage recovery are shown in Table 1. Younger age, female sex, higher number of reinfused CD34+ cells and higher Hb at start of HDC were favourable factors that predicted quicker long-term recovery of Hb. Diagnosis, higher number of CD34+ cells harvested per day, platelets and WBC at start of HDC influenced long-term recovery of WBC. Furthermore it was demonstrated that female sex, higher number of reinfused CD34+ cells, higher number of CD34+ cells harvested per day, higher Hb and platelets at start of HDC are favourable factors predicting quicker long-term recovery of platelets. Trilineage recovery was faster in younger age, female sex, higher number of reinfused CD34+ cells and higher Hb and platelets at start of HDC.

3.5. Multivariate analysis of variables influencing long-term engraftment (Table 2)

To investigate independent factors with respect to haematological recovery, a multiple linear-regression analysis was performed. All variables with $P<0.10$ in the univariate analysis were included in the model. Stepwise backward elimination of variables from the regression model resulted in selection of variables significantly influencing long-term engraftment. Younger age, melphalan as HDC, higher number of reinfused CD34+ cells, and higher Hb at start of HDC were favourable factors predicting more rapid long-term recovery of Hb. Recovery of WBC was influenced by diagnosis (patients with MM had quicker recovery than patients with NHL and Hodgkin's disease) and WBC at start of HDC. Higher number of reinfused CD34+ cells, higher number of CD34+ cells harvested per day, higher Hb and platelets at start of HDC were favourable factors predicting long-term recovery of platelets. Trilineage recovery was more rapid in younger patients, patients with the higher number of reinfused CD34+ cells, and higher Hb and platelets at the start of HDC. In the multivariate analysis, long-term recovery was not influenced by sex (male versus female) or radiotherapy (yes/no).

Fig. 6 shows the differences in the proportions of patients reaching complete trilineage recovery in the

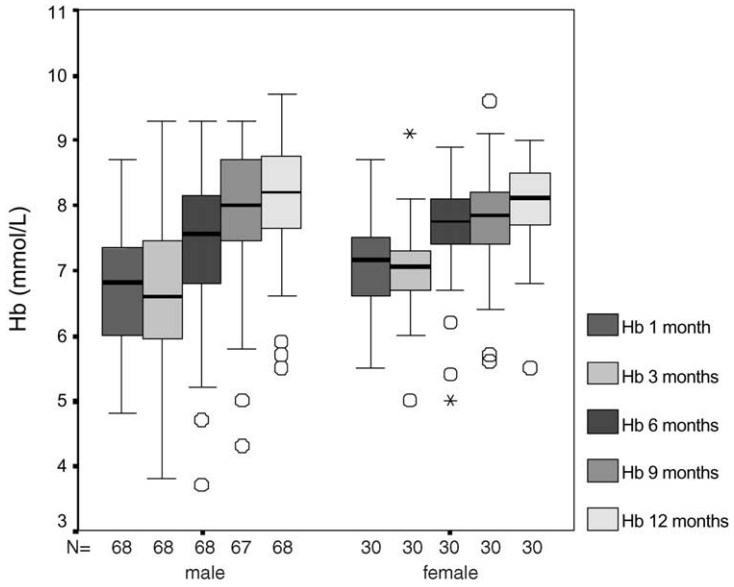

Fig. 1. Haemoglobin (Hb). Box and whisker plots of Hb for males and females during the 12 months following high-dose chemotherapy (HDC) and peripheral stem-cell transplantation (PSCT). The boxes on either side of the median (horizontal lines) indicate lower and upper quartiles. The whiskers indicate the closer of the 1.5×interquartile range of the minimum/maximum data points. Outlying points are plotted individually.

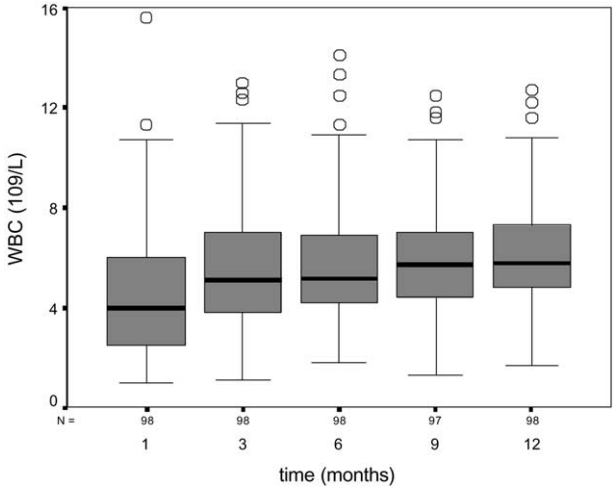

Fig. 2. White blood cell counts (WBC). Box and whisker plots of WBC during the 12 months following high-dose chemotherapy (HDC) and peripheral stem-cell transplantation (PSCT). The boxes on either side of the median (horizontal lines) indicate lower and upper quartiles. The whiskers indicate the closer of the 1.5× interquartile range of the minimum/maximum data points. Outlying points are plotted individually.

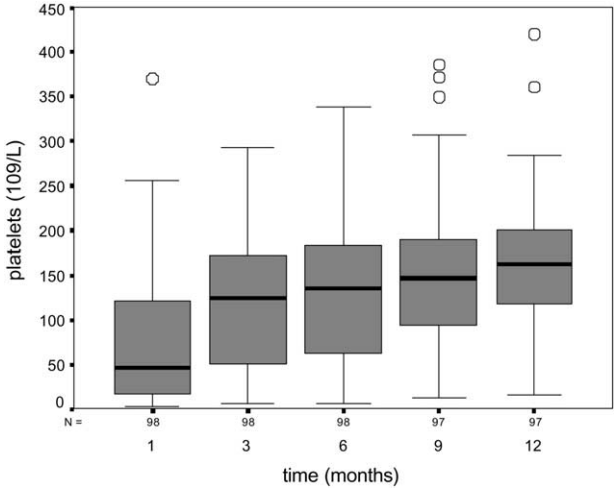

Fig. 3. Platelets. Box and whisker plots of platelets during the12 months following high-dose chemotherapy (HDC) and peripheral stem-cell transplantation (PSCT). The boxes on either side of the median (horizontal lines) indicate lower and upper quartiles. The whiskers indicate the closer of the 1.5× interquartile range of the minimum/maximum data points. Outlying points are plotted individually.

first year after transplantation, according to the number of reinfused CD34+ cells ($<5\times10^6$/kg body wt versus 5–10×10^6/kg body wt, log-rank $P=0.08$; 5–10×10^6/kg body wt versus $>10\times10^6$/kg body wt, log-rank $P=0.22$; $<5\times10^6$/kg body wt versus $>10\times10^6$/kg body wt, log-rank $P=0.01$).

4. Discussion

HDC followed by the infusion of autologous stem cells has increasingly been applied in the last decade for patients with high-risk or relapsed haematological malignancies [1]. The long-term (haematological) side-

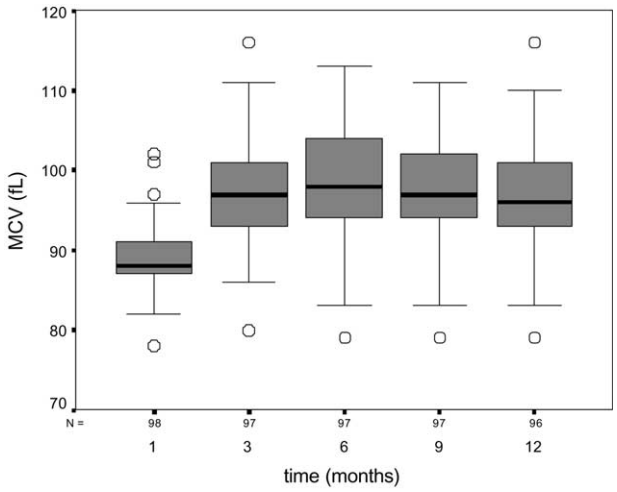

Fig. 4. Mean corpuscular volume (MCV). Box and whisker plots of MCV during the 12 months following high-dose chemotherapy (HDC) and peripheral stem-cell transplantation (PSCT). The boxes on either side of the median (horizontal lines) indicate lower and upper quartiles. The whiskers indicate the closer of the 1.5× interquartile range of the minimum/maximum data points. Outlying points are plotted individually.

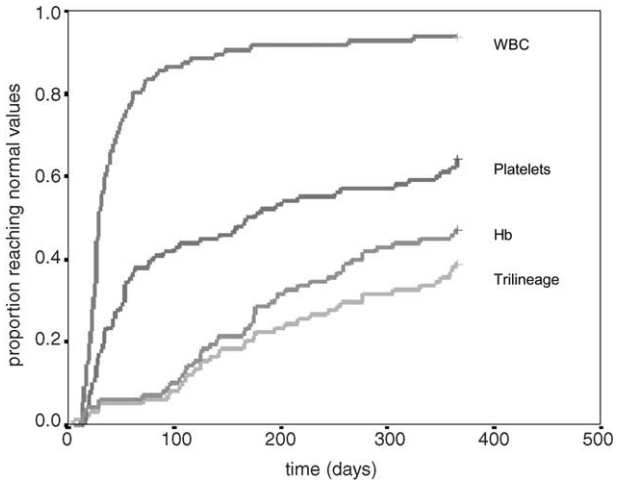

Fig. 5. Haematological recovery. Cumulative proportion of patients reaching normal haemoglobin (Hb), white cell count (WBC), platelets and trilineage recovery in 12 months following high-dose chemotherapy (HDC) and peripheral stem-cell transplantation (PSCT).

effects of this treatment are largely unknown, and indeed as a significant proportion of treated patients will require second-line chemotherapy, these long-term sequelae are worth studying.

In the present study of 98 patients with haematological malignancies, we investigated the factors that influence long-term haematological reconstitution after PSCT. The same criteria were used for normal haematological recovery as in a number of other studies that analysed long-term haematological recovery [4,6,7,11,18].

In the present study, short-term haematological recovery following HDC and PSCT was reached in approximately 2 weeks, which is in accord with other studies. In contrast to short-term recovery, long-term haematological recovery was slow. Nearly all patients had a normal WBC 1 year after PSCT, but at that time 36% still had low platelets, 53% had low Hb and only 39% of patients had full trilineage recovery. Few data exist concerning long-term haematological recovery. Most investigators suggest there can be complete haematological recovery at 1 year after transplantation [4,6,10]. However, more detailed study of the available data shows that in many patients recovery is slower. In a study by Haas and colleagues in 93 patients with haematological malignancies, it was estimated from the given data that no more than 70% of patients had reached normal platelet count after a follow up of 10 months [4]. In a study by Barbui and colleagues in 57 patients with NHL, trilineage long-term recovery was reached in 33 patients (58%) after a median follow up of 117 days. The WBC was the first measure to recover, Hb being the last [6]. In a study of Rossi and colleagues in 63 patients with NHL, approximately 80% of patients treated in first line reached trilineage recovery in 1 year compared to 60% of patients treated in relapse/resistance [7]. In a study by Schwartzberg and colleagues in 52 patients with haematological and solid malignancies, it was shown that for the 26 patients alive 1 year after reinfusion the mean peripheral blood counts were normal [8], but the range demonstrates that some patients had abnormally low counts after 1 year. Siena and colleagues describe that all patients reached 'normal haematopoiesis' after approximately 1 year [9]. In accordance with the results of the current study and an earlier study in patients with solid tumours [11], however, Amigo and colleagues found, that among 79 patients 42.4% had one or more abnormal peripheral cell lineages after 1 year [10]. Considerable problems arise from the assessment of these data. Most studies contain small numbers of patients from whom long-term data are available, not all studies use the same criteria for long-term engraftment and sometimes data from patients with active disease and data from those receiving active treatment are included. In contrast, all of the 98 patients presented in the current study were in complete remission after PSCT. Radiotherapy was given to 32 patients just before or in the year following PSCT.

In our study, roughly 25% of patients displayed an elevated MCV throughout the follow-up period, in accord with our earlier results [11]. Although not routinely determined in all patients with elevated MCV, we never found deficiencies of folate or vitamin B_{12}, nor did we encounter patients with thyroid dysfunction that could explain the elevated MCV. The elevated MCV could be part of some smouldering form of myelodysplasia. None of the patients, however, developed manifest myelodysplasia or secondary acute myeloid leukaemia in the year following PSCT, the risk of which is described to be increased following HDC with PSCT [19–24]. It is

Table 1
Univariate analysis of factors influencing haematological recovery (*P*-values)

	Hb normal	WBC normal	Platelets normal	Trilineage normal
Age (years)	<**0.001**	0.051	0.333	**0.013**
Sex (male/female)	<**0.001**	0.159	**0.002**	<**0.001**
Cycles of chemotherapy (number)	0.553	0.934	0.893	0.611
High-dose chemotherapy (type)	0.088	0.067	0.068	0.312
Radiotherapy (yes/no)	0.604	0.645	0.942	0.816
Diagnosis (type)	0.278	**0.012**	0.165	0.401
CD34+ cells reinfused (number)	**0.009**	0.346	**0.001**	**0.003**
Pheresis (CD34+ cells/day)	0.247	**0.024**	**0.002**	0.133
Hb at start of HDC (z-score)	<**0.001**	0.051	**0.001**	<**0.001**
Platelets at start of HDC (number)	0.064	**0.008**	<**0.001**	**0.020**
WBC at start of HDC (number)	0.378	**0.001**	0.701	0.697

Numbers in bold type are statistically significant at the chosen *P*-value. Hb, haemoglobin; WBC, white blood cell count; HDC, high-dose chemotherapy.

Table 2
Multivariate analysis of factors influencing haematological recovery (*P*-values)

	Hb normal	WBC normal	Platelets normal	Trilineage normal
Age (years)	<**0.001**	0.895		**0.002**
Sex (male/female)	0.108		0.811	0.064
High-dose chemotherapy (type)	**0.003**	0.442	0.619	
Diagnosis (type)		**0.026**		
CD34+ cells reinfused (number)	**0.006**		**0.040**	**0.016**
Pheresis (CD34+ cells/day)		0.176	**0.040**	
Hb at start of HDC (*z*-score)	<**0.001**	0.308	**0.006**	**0.001**
Platelets at start of HDC (number)	0.087	0.092	<**0.001**	**0.008**
WBC at start of HDC (number)		**0.011**		

Numbers in bold type are statistically significant at the chosen *P*-value. Hb, haemoglobin; WBC, white blood cell count; HDC, high-dose chemotherapy.

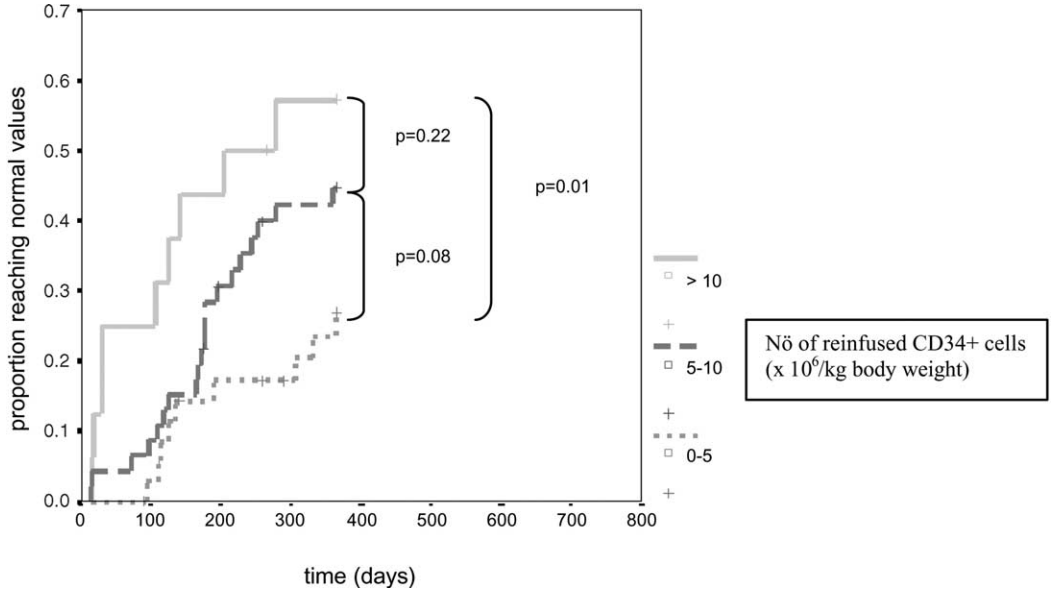

Fig. 6. CD34+. Influence of number of reinfused CD34+ cells on long-term (1 year) trilineage recovery.

suggested that prolonged dysfunction of the haematopoietic system is a risk factor for the emergence of these secondary diseases [21,22].

We have studied several factors that could influence long-term haematological recovery following HDC and PSCT. In the multivariate analysis we found a clear correlation between long-term recovery and age, number of reinfused CD34+ cells and the blood count at the start of HDC. Recovery of Hb was also relatively accelerated by melphalan used as HDC and recovery of WBC by a diagnosis of MM. Other factors such as radiotherapy, number of preceding conventional-dose chemotherapy cycles and sex did not influence haematological recovery in the multivariate analysis. It is difficult to compare these results with published data. Most studies on haematological recovery contain data on short-term recovery only [3,7,25–29]. Most of these studies found a correlation with stem-cell source (with bone marrow delayed recovery versus peripheral stem cells), number of reinfused stem cells and use of haematopoietic growth factors, but factors such as age, use of radiotherapy, type of high-dose regimen and number of preceding conventional-dose chemotherapy cycles also influenced short-term recovery. A relation between long-term haematological recovery and the number of reinfused stem cells has been suggested for doses up to 8×10^6 CD34+ cells/kg body wt [4,6,10,12]. Also, a relation has been observed with age and number of days to reach short-term recovery [6,7]. Our finding of a relation between long-term haematological recovery and haematological status at the start of HDC has not been described before. This probably reflects the residual function of bone-marrow progenitors preceding therapy.

The number of stem cells required for optimal short-term recovery is considered to be $2.5–5\times10^6$ CD34+ cells/kg body wt [4,29–31]. Reinfusion of more stem cells does not result in more rapid recovery. We showed, however, that for long-term recovery this threshold of $2.5–5\times10^6$ CD34+ cells/kg body wt does not apply. When more than 10×10^6 CD34+ cells/kg body wt were reinfused, long-term recovery was still accelerated. It is likely that the explanation is related to the type and function of the progenitor measured with the assay. The number of CD34+ cells reflects the committed stem cell that is critical for short-term engraftment [32]. While more mature stem cells are necessary for the short-term recovery with a clear threshold, long-term recovery is more dependent on more immature stem cells. Apparently $2.5–5\times10^6$ CD34+ cells/kg body wt contain enough stem cells for optimal short term, but not enough immature stem cells for optimal and fast long-term haematological recovery.

These results could have important implications for clinical practice in HDC and PSCT. Most factors shown to influence long-term haematological recovery, such as diagnosis, age and blood counts at the start of HDC, are not under the control of the transplant physician. However, it is possible to harvest and subsequently reinfuse more stem cells in those patients with the most negative risk factors for delayed long-term haematological recovery. Accelerating recovery could facilitate optimal dosing for new chemotherapy and radiotherapy in recurrent disease. Prolonged dysfunction of the haematopoietic system could lead to poor tolerance to subsequent myelotoxic treatments. Few clinical data are available on this subject. Brice and colleagues showed in 150 patients with Hodgkin's disease or NHL, that chemotherapy for relapsing lymphoma following autologous transplantation could be instituted without an increase in haematological toxicity [13]. However, they also demonstrated that it was more difficult to give additional chemotherapy after transplantation to the subgroup of patients with delayed platelet recovery. The impairment of haematological reconstitution that we observed might thus have clinical implications in planning full-dose chemotherapy or radiotherapy in relapse after transplantation.

On the other hand, the risk of tumour relapse might be increased when more stem cells are reinfused. Data on this subject are conflicting. Peripheral blood can contain tumour cells. The clinical value of the presence of these tumour cells in the stem-cell harvest is not yet clear. It is shown in gene-marking studies that recurrent disease can originate from cells reinfused during autologous transplantation [33,34]. However, there are no data showing a direct relation between the number of reinfused stem cells and the chance of recurrent disease. Reinfusing more stem cells might also have positive effects on immune reconstitution that might have a positive effect in deleting malignant cells after transplantation [35].

In conclusion, in the present study long-term haematological recovery following HDC and PSCT was slow. One year after PSCT, 61% of patients still have subnormal values in one or more cell lineages, suggesting a limited residual bone-marrow reserve. Long-term recovery is highly dependent on age, number of reinfused CD34+ cells without a threshold and blood counts at the start of HDC, all reflecting residual bone-marrow function before HDC. These data give further support to the concept of dual haematological recovery associated with progenitors at different stages of maturation following PSCT. Furthermore, they show that reinfusing more CD34+ cells can accelerate long-term haematological recovery.

5. Conflict of interest statement

There are no financial and personal relationships with other people or organisations that could inappropriately influence (bias) our work.

Acknowledgements

Supported in part by a grant from the Dutch College for Health Care Assurances, The Netherlands (CVZ).

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