Haematologica 2000; 85:832-838
original paper

Immune reconstitution after autologous hematopoietic stem cell transplantation in relation to underlying disease, type of high-dose therapy and infectious complications

HLIF STEINGRIMSDOTTIR,* ASTRID GRUBER,* MAGNUS BJÖRKHOLM,* ANNA SVENSSON,°
MONA HANSSON°
Department of Medicine, Division of Haematology; °Department of Clinical Immunology and Transfusion Medicine, Karolinska Hospital and Karolinska Institute, Stockholm, Sweden

ABSTRACT

Background and Objectives. **Autologous peripheral stem cell transplantation (APSCT) is increasingly used for various hematologic malignancies and solid tumors. The objective of this study was to analyze the immune reconstitution after APSCT and see if there was any correlation with diagnosis, age, type of high-dose therapy, CD34$^+$ selection of the autograft and double vs single APSCT.**

Design and Methods. **Lymphocyte subset recovery was studied in 46 consecutive patients with hematologic malignancies and breast cancer, who underwent APSCT. Eleven patients with multiple myeloma received tandem autografts. Thirty-one patients were given total body irradiation (TBI) as part of the high-dose treatment. Eighteen patients received a CD34$^+$ selected graft. The percentage and absolute numbers of lymphocyte populations, T-cells (CD2$^+$, CD3$^+$), B-cells (CD19$^+$), NK cells (CD56$^+$ CD3$^-$ and CD16$^+$CD3$^-$) and T-cell subpopulations (CD4$^+$, CD8$^+$, CD4$^+$CD45RA$^+$, CD4$^+$ CD45RO$^+$, CD4$^+$DR$^+$, CD8$^+$ CD45RO$^+$, CD8$^+$DR$^+$), were monitored with flow cytometry during the first year after APSCT.**

Results. **The total B-cell (CD19$^+$) and T-cell (CD3$^+$) counts were reconstituted to normal levels 2-4 months after APSCT. All patients had a low CD4/CD8 ratio during the observation period, related to both a low number of CD4$^+$ cells and elevated numbers of CD8$^+$ cells. The low number of CD4$^+$ cells was due to a persistently low level of naive CD4$^+$CD45RA$^+$ cells. A high proportion of the CD8+ cells displayed a phenotype compatible with activated T-cells (CD8$^+$DR$^+$) up to 10 months after autografting. The number of NK cells (CD56$^+$3$^-$ or CD16$^+$3$^-$) reached normal values within one month post-transplant. No single variable, such as diagnoses, age, TBI as part of the high-dose treatment, tandem autografting or CD34$^+$ selection of the graft, influenced the immune or hematopoietic reconstitution and no correlation with documented infectious complications was found.**

Interpretation and Conclusions. **Despite heterogeneity of diseases, age, initial treatment and high-dose regimens, lymphocyte subset analysis did not reveal any differences in hematopoietic or immune reconstitution. All patients had a low CD4$^+$/CD8$^+$ ratio during at least the first year post-transplant, caused by a persistent increase of CD8$^+$ lymphocytes and a constant reduction of CD4$^+$ lymphocytes, making the patients susceptible to infections for a prolonged period of time post-transplant.**
©2000, Ferrata Storti Foundation

Key words: autologous stem cell transplantation, immune reconstitution, hematopoietic reconstitution, infectious complication, lymphocyte subset recovery

Correspondence: Hlif Steingrimsdottir, M.D., Department of Medicine, Division of Hematology, Karolinska Hospital, SE-171 76 Stockholm, Sweden. Phone: international +46-8-51770000 – Fax: international +46-8-317303 – E-mail: hlif@hotmail.com

High-dose chemoradiotherapy followed by hematopoietic stem cell transplantation (HSCT) is increasingly used for various hematologic malignancies and solid tumors. Studies concerning the reconstitution of lymphocyte subsets have reported similar composition after allogeneic and autologous bone marrow /peripheral blood progenitor cell transplantation although many authors have observed differences in regard to reconstitution time[1-6] and lymphocyte function in favor of peripheral progenitor cell transplantation.[7] The B-cell recovery seems to parallel ontogeny in patients without chronic graft-versus-host disease as evidenced by the pattern of quantitative recovery of circulating B-cells, the increased B-cell size and the constellation of surface antigens on B-cells.[8] However, to date, it is not completely understood along which pathway the T-cells regenerate. In the present study we analyzed immune reconstitution in 46 patients after APSCT in relation to diagnosis, age, type of high-dose therapy, CD34$^+$ selection of the autograft and double vs single APSCT. We also related the recovery of lymphocyte subsets to incidence and type of infectious complications.

Design and Methods

Patients and treatment

Immune reconstitution was studied in 46 consecutive patients who lived within Stockholm county and were referred for APSCT. The monitoring started after

Table 1. Patient characteristics according to diagnosis.

	AML (n=10)	*ALL (n=3)*	*MM (n=15)*	*NHL (n=11)*	*HD (n=2)*	*BC (n=5)*
Age (yrs)						
median	49	46	55	51	26	51
range	(30-60)	(43-52)	(36-60)	(38-62)	(22-30)	(43-59)
TBI (%)	8 (80)	3 (100)	14 (94)	8 (73)	0	0
Tandem autograft (%)	0	0	11 (73)	0	0	0
Purified autograft (%)	0	0	10 (67)	7 (63)	1 (50)	0
Number of reinfused $CD34^+$ cells ($x10^6$/kg body wt)	5.4	8.7	3.8	3.9	5.8	6

AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; MM: multiple myeloma; NHL: non-Hodgkin's lymphoma; HD: Hodgkin's disease; BC = breast cancer.

the white blood cell (WBC) count reached 1×10^9/L post-transplantation. The patients' characteristics are shown in Table 1. Twenty-five females and 21 males, with a median age of 53 (range 22-62) years were included in this study. Diagnoses were non-Hodgkin's lymphoma (NHL) (n=11), Hodgkin's disease (HD) (n=2), multiple myeloma (MM) (n=15), acute myeloid leukemia (AML) (n=10), acute lymphoblastic leukemia (ALL) (n=3), and breast cancer (BC) (n=5). The patients with AML received APSCT in first complete remission (CR) and the majority (n=9) were treated according to the ICE protocol.[9] All patients with lymphoma received APSCT in second or third CR or partial remission (PR), except 2 patients with T-cell lymphoma who received high dose treatment in first CR. Four patients (3 NHL and 1 HD) received BEAM chemotherapy.[10] Etoposide and cyclophosphamide in combination with either total body irradiation (TBI) or busulfan as myelosuppression for APSCT was given to 17 (8 NHL, 1 HD , 3 ALL, 1 AML and 4 MM) and 3 (3 AML) patients respectively.[11,12] Eleven patients with MM received double APSCT.[13] Altogether 31 patients were given TBI as part of the high-dose treatment. Eighteen patients (10 MM, 7 NHL and 1 HD) received a $CD34^+$ selected graft and 28 patients received an unmanipulated graft, with a mean dose of $CD34^+$ cells at ABSCT of 3.4×10^6/kg and 5.8×10^6/kg respectively. Positive selection was performed with the Ceprate® SC biotin-avidin immunoadsorption method (CellPro Europe) achieving a mean purity of the $CD34^+$ selected fraction of 79±12% and a mean number of $CD3^+$ cells of 0.25×10^6/kg. Granulocyte colony-stimulating factor (G-CSF) was given to 36 patients after autografting.

All patients were in complete remission or had stable disease when included in this study. Nine patients relapsed or progressed during the observation period (3 ALL, 2 AML, 3 NHL and 1BC) and were at that time point excluded from further immunologic monitoring.

Analysis of surface markers by flow cytometry

The analysis of lymphocyte subsets was performed prior to high-dose therapy, post-transplantation when the WBC count exceeded 1×10^9/L and approximately on days 30, 60, 90 and every third month thereafter up to twelve months. Twenty-four patients were followed for 1 year and the median time of monitoring for all patients was 268 days (range: 90-365). Patients who received tandem APSCT were only followed after the second autografting. A venous blood sample was collected into EDTA and analyzed for surface markers within 24 hrs. WBC counts were determined using an automated cell counter (Coulter MD II, Coulter Corp., Hialeah, FL, USA). Leukocytes were analyzed for surface markers by direct addition of labeled monoclonal antibodies (Mabs) to 50-100 uL blood containing < 1×10^6 WBC. After 30 min incubation at +4°C with Mabs, RBC were lysed and fixed by Coulter Q-prep (Coulter Corp.) and analysis by multiparameter flow cytometry using a Coulter Epics Elite (Coulter Corp.) was performed. The total leukocyte population was analyzed, with gating for lymphocytes, monocytes and granulocytes according to their forward - (FS) and side scatter (SSC) properties and reactivity with anti CD14 and anti CD45 (Mo2 RD and KC56 FITC, respectively, from Coulter Corp.). The absolute number of lymphocytes was determined by multiplying the percentage of lymphocytes ($CD14^-/CD45^{++}$) by the total WBC count. For lymphocyte subsets the following Mabs labeled with FITC or phycoerythrin (RD) were used; anti-CD3 (clone UCHT1) anti CD4 (T4), anti CD8 (T8), anti CD2 (T11), anti CD19 (B4), anti CD56 (NKH1), anti CD45RA (2H4), anti HLA-DR (I3) all from Coulter Corp., anti CD45RO (UCHL1) were purchased from DAKO (Dakopatts) and anti CD16 (Leu11c) from Becton Dickinson.

The absolute number of cells in any given lymphocyte population was calculated by multiplying the percentage of positive cells in the lymphocyte gate by the absolute number of lymphocytes.

Reference values (10th -90th percentiles) given in the figures are derived from the analysis of 20-80 healthy adults.

Infections

Infectious complications from day 30 to 12 months post-transplant were registered from the medical records and the patients were classified according to the following variables: clinical signs of upper respiratory tract infection; clinical signs of lower respiratory tract infection with positive pulmonary X-ray; clinical signs of septicemia with fever and C-reactive protein elevation, positive culture results; herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections and clinical signs of CMV infection with positive polymerase chain reaction (PCR), indicating CMV reactivation or infection. Patients undergoing tandem autografting received trimethoprim-sulfa for 3 months after the treatment as prophylaxis against *Pneumocystis carinii* infection.

Statistical analysis

The clinical and laboratory data were analyzed according to standard statistical methods using an Excel computer program. Comparisons of groups regarding infectious complications were performed by the chi squared test. Linear regression curves were established for all the patients in the study to analyze the recovery of each lymphocyte subpopulation. The

Table 2. Hematopoietic recovery in relation to purification of the autograft vs not.

	Purified graft (n=18)	*Not purified graft (n=28)*	*p*
Diagnosis	10 MM 7 NHL 1 HD	13 AL 1 HD 5 MM 4 NHL 5 BC	
TBI (%)	14 (78)	19 (68)	
Tandem autograft (%)	10 (55)	1 (3)	
PMN < 0.5×10^9/L, days, median	10 (7-12)	12 (5-27)	NS
PMN < 1.0×10^9/L, days, median	13 (8-12)	13 (5-30)	NS
Platelets <20×10^9/L, days, median	13 (2-33)	15 (1-60)	NS
Platelets <50×10^9/L, days, median	23 (9-110)	62 (10-365)	NS

difference in recovery of total lymphocyte count, total T-cells and subsets, NK-cells and B-cells between groups was assessed by comparing the mean regression for each group with the ANOVA one-factor test. A standard significance level of $p<0.05$ was chosen.

Results

Hematopoietic reconstitution

All patients but two had complete, trilineage hematopoietic recovery after 2 months.

The median time to neutrophil recovery > 0.5×10^9/L was 10 days (n=46, range 5-27), platelet count > 20×10^9/L 11 days (range 1-30) and platelet count > 50×10^9/L 16 days (range 9-365).

$CD34^+$ selection of the autograft did not influence the time to hematopoietic recovery (Table 2). There was no significant difference in hematopoietic recovery related to diagnosis, type of high-dose therapy or tandem vs single autograft (data not shown).

The patients with MM who received TBI, tandem autografts and $CD34^+$ selected grafts showed a similar pattern in hematopoietic reconstitution as other patients, with a median time to neutrophil count > 0.5×10^9/L of 10 days (range 5-13) and platelet count > 20×10^9/L of 11 days (range 2-60).

Primary graft failure was observed in two patients with AML. In one patient a second autograft was performed 200 days post-transplantation.

Immune reconstitution

All patients had B-cell ($CD19^+$) counts below normal levels during the first 2-3 months. The T-cell ($CD3^+$) count reached normal levels within 2 months after high-dose therapy. However, all patients had a low CD4/CD8 ratio during the 12 months of observation. This was related to both a relative decrease in $CD4^+$ cells and an increase in $CD8^+$ cells. A large proportion, up to 80%, of the $CD8^+$ cells expressed HLA DR, a phenotype associated with activated T-cells. By 12 months post-transplant the $CD8^+$ cell count tended to decrease to normal adult values. The low number of $CD4^+$ T-cells was due to a persistently low level of immature naive $CD4^+CD45RA^+$ cells during the observation period. NK-cell counts ($CD56^+CD3^-$ or $CD16^+CD3^-$) reached normal values within one month after APSCT. Two patients with MM had T-helper cells ($CD4^+$) that were double positive for CD45RO and CD45RA, whereas all other patients had no overlap between the $CD4^+$ CD45RA and CD45RO populations.

The lymphocyte reconstitution was analyzed in relation to diagnosis, age, type of high-dose treatment and $CD34^+$ selection of the graft. No difference in immune reconstitution was found in relation to diagnoses (Figure 1). Although the majority of the MM patients received TBI as part of the high-dose treatment, tandem autografting and CD34 selected grafts, the pattern of immune reconstitution did not differ from that of the other patient groups. The MM patients showed a trend towards a slower B-cell reconstitution and a higher number of $CD8^+DR^+$ cells compared to the remaining patients but these differences did not reach statistical significance. Age did not have any impact on the recovery of lymphocyte subsets (data not shown). Eighteen patients (10 MM, 7 NHL, 1 HD) received a $CD34^+$ selected graft and 28 patients (10 AML, 3 ALL, 1 HD, 5 MM, 4 NHL, 5 BC) received unmanipulated grafts. The mean number of $CD34^+$ cells at APSCT was 3.4×10^6/kg in the *selected* group and 5.8×10^6/kg in the *non-selected* group. The reconstitution pattern of lymphocytes after APSCT did not differ between these two groups (Figure 2). The influence of TBI on immune reconstitution was analyzed in 26 patients who received *non-selected* and single autografts. In this group 17 patients (8 AML, 3 ALL, 3 MM, 3 NHL) received TBI and 9 (2 AML, 1 HD, 1 MM, 5 BC) only chemotherapy. There was no difference in lymphocyte regeneration between these two groups (data not shown).

Infectious complications

Of the 15 MM patients, 14 received TBI, 10 purified grafts and 11 double APSCT. These patients showed a tendency, although not statistically signif-

Table 3. Infectious complications in relation to diagnosis.

	AL (n=13)	*MM (n=15)*	*Lymphoma (n=13)*	*BC (n=5)*	*p*
Number of patients infected (%)	4 (31)	9 (60)	3 (31)	2 (40)	0.383
Herpes zoster (%)	3 (23)	4 (31)	1 (8)	0	NS
Generalized varicella-zoster (%)	0	1 (6.7)	0	0	NS
CMV (%)	0	0	0	0	NS
Upper resp. tract infection (%)	3 (23)	5 (33)	1 (8)	1 (20)	0.257
Bacteremia (%)	0	2 (13)	0	1 (20)	NS
Pneumonia (%)	0	4 (27)	1 (8)	0	NS
Urinary tract infection (%)	0	1 (6.7)	0	0	NS
Other bact. infection (%)	0	2 (13)	0	0	NS

The p value describes the heterogeneity between the groups

©Ferrata Storti Foundation

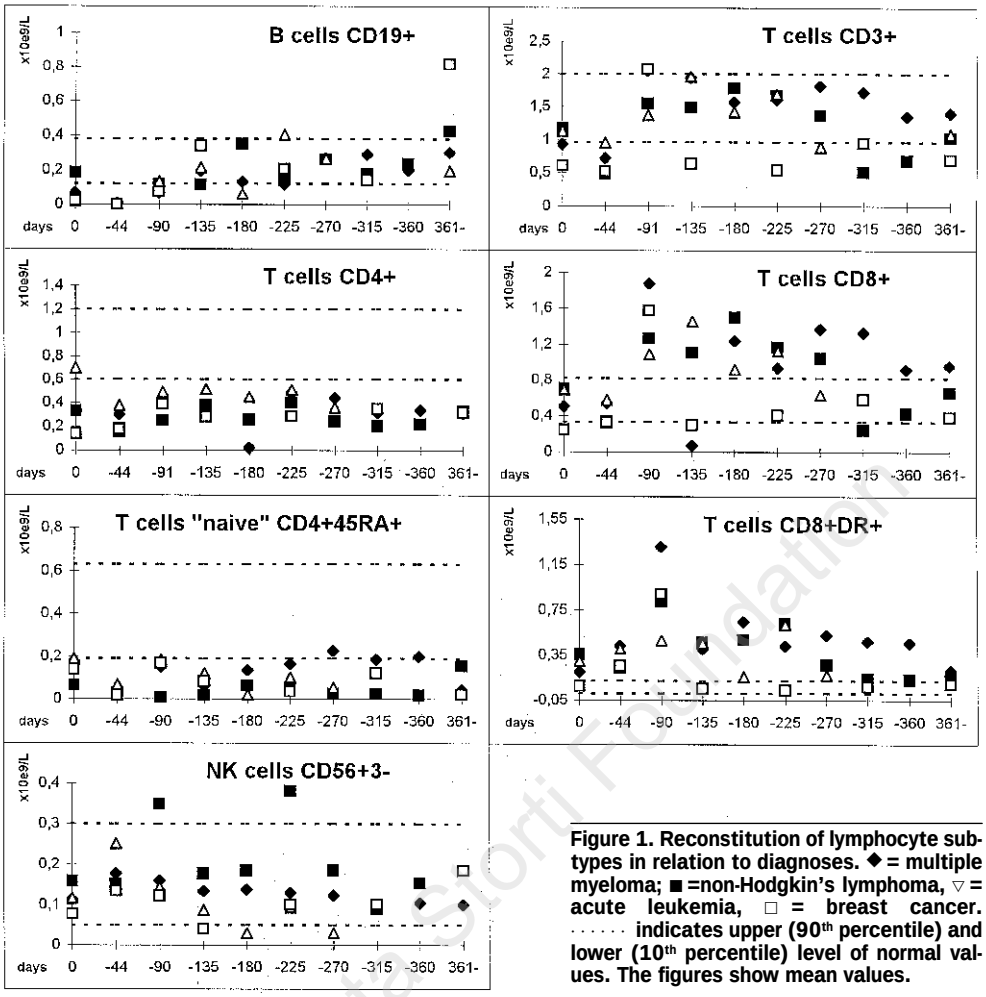

Figure 1. Reconstitution of lymphocyte subtypes in relation to diagnoses. ◆ = multiple myeloma; ■ =non-Hodgkin's lymphoma, ▽ = acute leukemia, □ = breast cancer. ····· indicates upper (90th percentile) and lower (10th percentile) level of normal values. The figures show mean values.

©Ferrata Storti Foundation

icant, to develop more infectious complications during the first year post-transplantation compared to the other patients, not taking into account the 30 days immediately after high-dose treatment. Nine of the 15 patients with MM developed infections during the observation period. Herpes virus infections, respiratory tract infections and bacteremia were more frequent in this group of patients (Table 3). The risk of infectious complications was not predicted by the immune reconstitution (Figure 3). No deaths caused by infectious complication were observed during the first year post-transplantation.

Discussion

This study describes hematopoietic and immune reconstitution during 12 months following APSCT in 46 patients. The patients form a heterogeneous group with regards to diagnoses, extent of previous treatment and type of high-dose regimen. Despite this variability, hematopoietic recovery was remarkably uniform and did not correlate with the underlying disease, TBI as part of the high-dose regimen, single vs double APSCT or $CD34^+$ selection of the graft. It has been shown that the time to neutrophil and platelet recovery is inversely related to the number of reinfused $CD34^+$ cells[14,15] with a threshold number of 2.5×10^6 $CD34^+$ cells/kg.[16] All patients in this study were autografted with more than 2.5×10^6/kg $CD34^+$ cells, except three who received between 1.5 and 2×10^6/kg $CD34^+$ cells and they did not differ, with regard to hematopoietic and immune reconstitution, from the remaining patients.

The total number of B-cells reached the normal range approximately 2 months post-transplantation in all patients, irrespective of diagnosis, age or high-dose regimen (Figure 1). In studies of B-cell development after HSCT, the B-cell reconstitution seems to parallel ontogeny and derive from the stem cells rather than from grafted mature B-cells.[8] This is compatible with our results in APSCT, in which intensification of the high-dose treatment and $CD34^+$ selection of the graft did not influence the B-cell recovery. Other investigators have shown that serum Ig levels

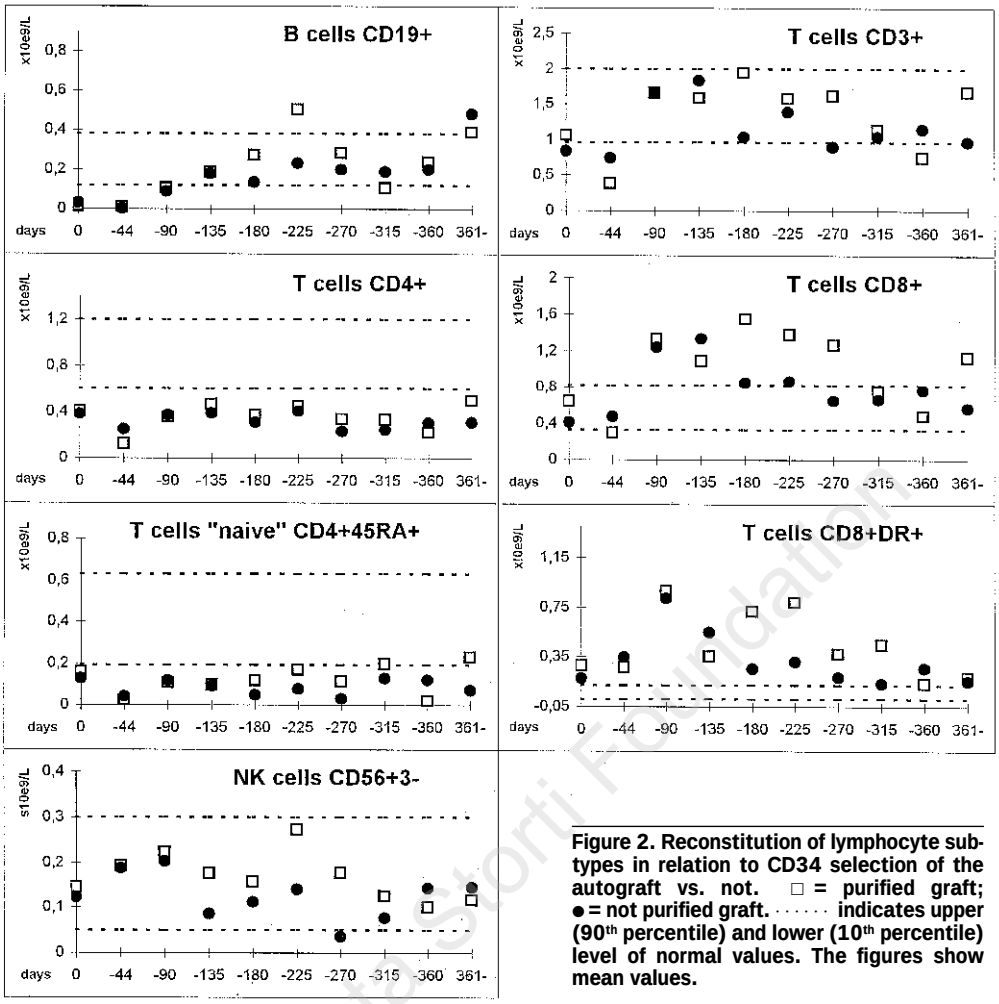

Figure 2. Reconstitution of lymphocyte subtypes in relation to CD34 selection of the autograft vs. not. □ = purified graft; ● = not purified graft. ····· indicates upper (90th percentile) and lower (10th percentile) level of normal values. The figures show mean values.

©Ferrata Storti Foundation

remain low during the first 3 months after allogeneic bone marrow transplantation and that proliferative responses to T-cell independent antigen are blunted, probably due to inadequate B-cell function.[17,18]

NK-cells were observed among the first cells to recover, reaching normal levels within one month post-APSCT which is in line with other reports.[6] The activity of NK cells also returns to normal shortly following transplantation, which may be relevant for anti-tumor immune responses post-transplantation.[19] The maturation of NK-cells is not dependent on residual thymus tissue and this may account for the rapid recovery.

Both $CD4^+$ and $CD8^+$ lymphocyte populations comprise functionally distinct subsets, based on the expression of different isoforms of the CD45 antigen. At birth most T-cells express CD45RA which are considered to be immature and naive. T-cells may convert to $CD45RO^+$ after stimulation and become mature cells of the memory type. Previous reports show that the regenerating $CD4^+$ T-cells after HSCT in adult life are mainly $CD45RO^+$ as the generation of $CD4+CD45RA^+$ T-lymphocytes is thymus-dependent.[3,6,20,21,22] In this series of patients CD45RO was consistently expressed on essentially all $CD4^+$ T-lymphocytes during the first year post-transplant. The $CD8^+$ T-lymphocytes, however, appear to regenerate by a thymus-independent pathway,[23] explaining the rapid $CD8^+$ cell reconstitution and absolute number exceeding the normal values for the first 8 months post-transplant. A large proportion of the $CD8^+$ cells, up to 80%, expressed HLA-DR, a phenotype associated with activated T-cells (Figure 1). This was observed in all patients, post-APSCT, regardless of diagnosis or type of high-dose regimen. Interestingly, the MM patients showed a similar pattern of immune reconstitution to that of the other groups of patients. However, there was a trend to more infectious complications during the first year post-transplant in this group of patients. It is possible that functional analysis of the lymphocyte subpopulations might have detected some differences in the immunologic recovery.

A potential objective of stem cell selection in the autologous transplant setting is to deplete the graft of

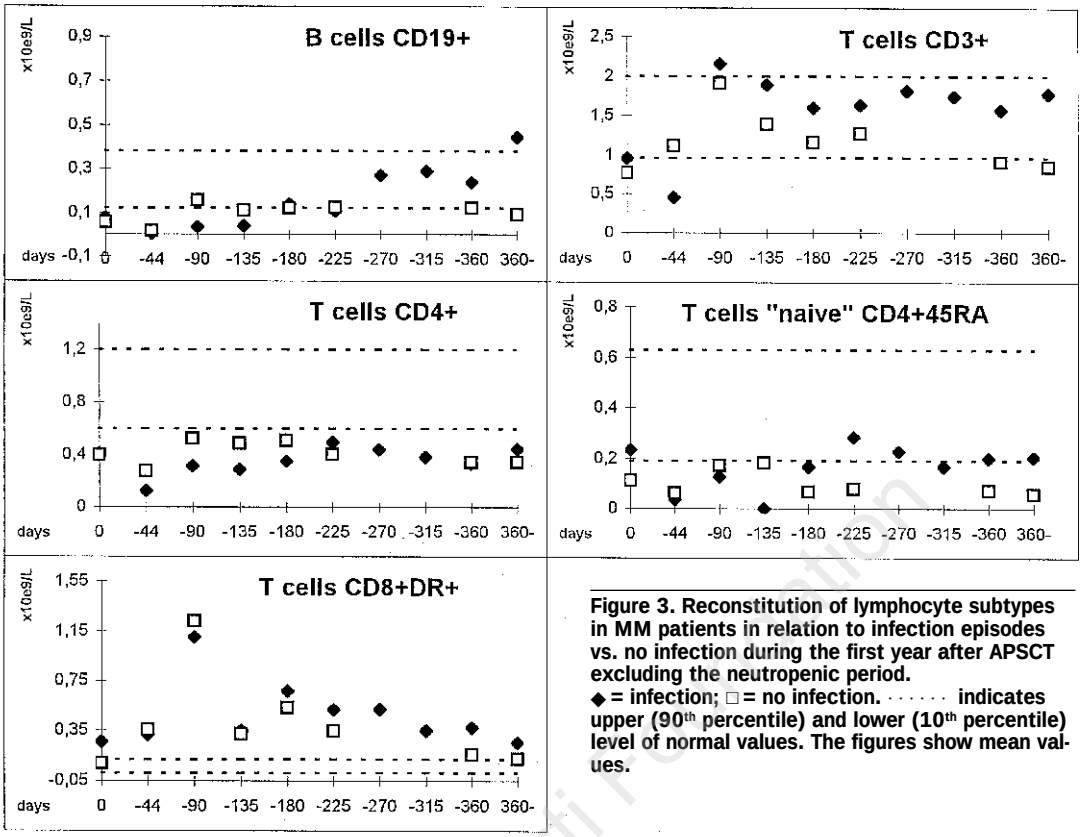

Figure 3. Reconstitution of lymphocyte subtypes in MM patients in relation to infection episodes vs. no infection during the first year after APSCT excluding the neutropenic period.
◆ = infection; □ = no infection. ····· indicates upper (90th percentile) and lower (10th percentile) level of normal values. The figures show mean values.

non-CD34+ tumor cells, perhaps limiting the risk of post-transplant relapse. However, it has been postulated that purification of the autograft delays immune reconstitution, which might result in higher infectious morbidity and relapse rate post-transplantation, potentially neutralizing the beneficial effects of stem cell selection.[24,25] In this study there was no correlation between purification of the autograft and delayed immune reconstitution or increased risk of infectious complications post-transplantation. These results and the observation that the CD4+/CD8+ ratio is normal in the graft,[19] indicate that persisting mature T-cells in the graft have a minor impact on T-cell regeneration. It might be expected that intensification of the high-dose treatment with TBI and/or tandem autografting would delay the T-cell recovery post-transplantation. However, in this study, TBI and/or tandem autografting did not influence immune reconstitution. In the light of the above observations, we suggest that progenitors in the graft account for the post-transplant T-cell reconstitution along a non-thymic dependant pathway, resulting in an inverted CD4+/CD8+ ratio and low numbers of CD4+ CD45RA+ cells for at least one year following APSCT.

In conclusion, despite the heterogeneity of diseases, age, initial treatment and high-dose regimens, lymphocyte subset analysis did not reveal any differences in hematopoietic or immune reconstitution. As in previous studies low CD4+/CD8+ ratios were observed during at least the first year post-transplant. This is caused by a persistent increase of CD8+ lymphocytes and a constant reduction of CD4+ lymphocytes. The slow reconstitution of certain lymphocyte subsets following intensive treatment makes the patients susceptible to infections, in particular viral infections, for a prolonged period of time and might affect the course of the underlying disease.

Funding
This study was supported by the Swedish Cancer Foundation.

Contributions and Acknowledgments
HS: Clinical data, analyzed data, wrote the manuscript. AG: Clinical data, contributed to writing of the manuscript. MB: Analysis of data, contributed to writing the manuscript. AS: Laboratory work. MH: formulated the questions asked and designed the study and analyzed data.

Disclosures
Conflict of interest: none.
Redundant publications: no substantial overlapping with previous papers.

Manuscript processing
Manuscript received March 9, 2000; accepted May 19, 2000.

Potential implications for clinical practice

- Patients receiving tandem autaografting and TBI could be prone to more severe infectious complications post-transplant. Low CD4/CD8 ratios were observed during at least the first year post-transplant. This slow reconstitution of certain lymphocyte subsets following intensive treatment makes the patients susceptible to infection, in particular viral infections, for a prolonged period of time and might affect the course of the underlying disease. These observations may have important implications for approaches considering vaccine strategies post-transplant as well as strategies for immunotherapeutic models.

References

1. Henon PR, Liang H, Beck-Wirth G, et al. Comparison of hematopoietic and immune recovery after autologous bone marrow or stem cell transplantation. Bone Marrow Transplant 1992; 9:285-91.
2. Roberts MM, To LB, Gillis D, et al. Immune reconstitution following peripheral blood stem cell transplantation, autologous bone marrow transplantation and allogenic bone marrow transplantation. Bone Marrow Transplant 1993; 12:469-75.
3. Ashihara E, Shimazaki C, Yamagata N, et al. Reconstitution of lymphocyte subsets after peripheral blood stem cell transplantation: two-color flow cytometric analysis. Blood Marrow Transplant 1994; 13:377-81.
4. Ottiger HD, Beelen DW, Scheulen B, Schaefer UW, Grosse-Wilde H. Improved immune reconstitution after allotransplantation of peripheral blood stem cells instead of bone marrow. Blood 1996; 88:2775-9.
5. Charbonnier A, Sainty D, Faucher C, Arnoulet C, Chabannon C, Blase D. Immune reconstitution after blood cell transplantation. Hematol Cell Ther 1997; 39:261-4.
6. Koehne G, Zeller W, Stockschlaeder M, Zander AR. Phenotype of lymphocyte subsets after autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 1997; 19:149-56.
7. Talmadge JE, Reed E, Ino K, et al. Rapid immunologic reconstitution following transplantation with mobilized peripheral blood stem cells as compared to bone marrow. Bone Marrow Transplant 1997; 19:161-72.
8. Storek J, Ferrara S, Ku N, Giorgi JV, Champlin RE, Saxon A. B cell reconstitution after human bone marrow transplantation: recapitulation of ontogeny? Bone Marrow Transplant 1993; 12:387-98.
9. Rohatner R, Bassan M, Björkholm M, et al. High-dose treatment with peripheral blood progenitor cell support as consolidation of first remission in younger patients with acute myelogenous leukemia [abstract]. Blood 1998; 92(Suppl. 1):1198.
10. Caballero MD, Rubio J, Rifon J, et al. BEAM chemotherapy followed by autologous stem cell support in lymphoma patients: analysis of efficacy, toxicity and prognostic factors. Bone Marrow Transplant 1997; 20:451-8.
11. Blume K, Forman S, O'Donell MR, et al. Total body irradiation and high-dose etoposide: a new preparatory regimen for bone marrow transplantation in patients with advanced hematologic malignancies. Blood 1987; 69:1015-20.
12. Spitzer T, Peters C, Ortlieb M, et al. Etoposide in combination with cyclophosphamide and total body irradiation or busulfan as conditioning for marrow transplantation in adults and children. Int J Radiat Oncol Biol Phys 1994; 29:39-44.
13. Bjorkstrand B, Ljungman P, Bird JM, Samson D, Gahrton G. Double high-dose chemoradiotherapy with autologous stem cell transplantation can induce molecular remission in multiple myeloma. Bone Marrow Transplant 1995; 15:367-71.
14. Schwartzberg L, Birch R, Blanco R, et al. Rapid and sustained hematopoietic reconstitution by peripheral blood stem cell infusion alone following high-dose chemotherapy. Bone Marrow Transplant 1993; 11: 369-74.
15. Dercksen MW, Rodenhuis S, Dirkson MK, et al. Subsets of CD34+ cells and rapid hematopoietic recovery after peripheral-blood stem-cell transplantation. J Clin Oncol 1995; 13:1922-32.
16. Haas R, Witt B, Möhle R, et al. Sustained long-term hematopoiesis after myeloablative therapy with peripheral blood progenitor cell support. Blood 1995; 85:3754-61.
17. Bengtsson M, Smedmyr B, Festin R, Oberg G, Simonsson B, Totterman TH. B lymphocyte regeneration in marrow and blood after autologous bone marrow transplantation: increased numbers of B cells carrying activation and progression markers. Leuk Res 1989; 13:791-7.
18. Small TN, Keever CA, Weiner-Fedus S, Heller G, O'Reilly RJ, Flomenberg N. B-cell differentiation following autologous, conventional, or T-cell depleted bone marrow transplantation: a recapitulation of normal B-cell ontogeny. Blood 1990; 76:1647-56.
19. Talmadge JE, Reed EC, Kessinger A et al. Immunologic attributes of cytokine mobilized peripheral blood stem cells and recovery following transplantation. Bone Marrow Transplant 1996; 17:101-9.
20. Mackall CL, Granger L, Sheard MACepeda R, Gress RE. T-cell regeneration after bone marrow transplantation: differential CD45 isoform expression on thymic-derived versus thymic-independant progeny. Blood 1993; 82:2585-94.
21. Storek J, Witherspoon RP, Storb R. T cell reconstitution after bone marrow transplantation into adult patients does not resemble T cell development in early life. Bone Marrow Transplant 1995; 16:413-25.
22. Autran B, Malphettes M, Dhédin N, Gorochov G, Leblond V, Debre P. Studies of T cell reconstitution after HSCT. Hematol Cell Ther 1997; 39:252-6.
23. Mackall CL, Fleisher TA, Brown MR, et al. Distinctions between CD8+ and CD4+ T-cell regenerative pathways result in prolonged T-cell subset imbalance after intensive chemotherapy. Blood 1997; 89:3700-7.
24. Shpall E, Jones R, Bearman S, et al. Transplantation of enriched CD34-positive autologous marrow into breast cancer patients following high-dose chemotherapy: Influence of CD34-positive peripheral-blood progenitors and growth factors on engraftment. J Clin Oncol 1994; 12:28-36.
25. Bomberger C, Singh-Jairam M, Rodey G, et al. Lymphoid reconstitution after autologous PBSC transplantation with FACS-sorted CD34+ hematopoietic progenitors. Blood 1998; 91:2588-600.

©Ferrata Storti Foundation