CD34+ cell mobilization, blood graft composition, and posttransplant recovery in myeloma patients compared to non-Hodgkin's lymphoma patients: results of the prospective multicenter GOA study

Antti Turunen,[1,2] *Anu Partanen*,[1] *Jaakko Valtola*,[1] *Antti Ropponen*,[3] *Timo Siitonen*,[4] *Outi Kuittinen*,[2,5] *Hanne Kuitunen*,[6] *Mervi Putkonen*,[7] *Marja Sankelo*,[8] *Leena Keskinen*,[9] *Eeva-Riitta Savolainen*,[10] *Marja Pyörälä*,[1] *Taru Kuittinen*,[1] *Raija Silvennoinen*,[11] *Karri Penttilä*,[12,13] *Anu Sikiö*,[14] *Kaija Vasala*,[15] *Pentti Mäntymaa*,[16] *Jukka Pelkonen*,[3,16] *Ville Varmavuo*,[17] *and Esa Jantunen*[1,2,18]

BACKGROUND: Autologous stem cell transplantation is an established treatment option for patients with multiple myeloma (MM) or non-Hodgkin's lymphoma (NHL).

STUDY DESIGN AND METHODS: In this prospective multicenter study, 147 patients with MM were compared with 136 patients with NHL regarding the mobilization and apheresis of blood CD34+ cells, cellular composition of infused blood grafts, posttransplant recovery, and outcome.

RESULTS: Multiple myeloma patients mobilized CD34+ cells more effectively (6.3×10^6/kg vs. 3.9×10^6/kg, $p = 0.001$). The proportion of poor mobilizers (peak blood CD34+ cell count $<20 \times 10^6$/L) was higher in NHL patients (15% vs. 3%, $p < 0.001$). Plerixafor was added to rescue the mobilization failure in 17 MM patients (12%) and in 35 NHL patients (26%; $p = 0.002$). The infused grafts contained more natural killer (NK) and CD19+ cells in MM patients. Blood platelet and NK-cell counts were higher in MM patients posttransplant. Early treatment-related mortality was low in both groups, but NHL patients had a higher late (>100 days) nonrelapse mortality (NRM; 6% vs. 0%, $p = 0.003$).

CONCLUSIONS: Non-Hodgkin's lymphoma and MM patients differ in terms of mobilization of CD34+ cells, graft cellular composition, and posttransplant recovery. Thus, the optimal graft characteristics may also be different.

ABBREVIATIONS: 7-AAD = 7-aminoactinomycin; auto-SCT(s) = autologous stem cell transplantation(s); B-CD34+ = blood CD34+ (count); GOA Study = Graft and Outcome in Autologous Stem Cell Transplantation Study; HDT = high-dose therapy; ICU = intensive care unit; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma; NRM = nonrelapse mortality; OS = overall survival; PFS = progression-free survival; TRM = treatment-related mortality.

From the [1]Department of Medicine and [5]Department of Oncology, Kuopio University Hospital; the [2]Institute of Clinical Medicine, and the [3]Department of Clinical Microbiology, University of Eastern Finland; the [12]Finnish Medicines Agency; the [16]Laboratory Centre of Eastern Finland, Kuopio; [4]Department of Medicine, the [6]Department of Oncology, and the [10]Nordlab, Medical Research Center Oulu, Oulu University Hospital, Oulu; [7]Department of Medicine, Turku University Hospital, Turku; [8]Department of Internal Medicine, and the [9]Department of Oncology, Tampere University Hospital, Tampere; [11]Hematology, Comprehensive Cancer Center, Helsinki University Hospital, Helsinki; [13]Department of Medicine, Savonlinna Central Hospital, Savonlinna; [14]Department of Medicine, and the [15]Department of Oncology, Central Hospital of Central Finland, Jyväskylä; [17]Department of Medicine, Kymenlaakso Central Hospital, Kotka and [18]Department of Medicine, North Carelia Hospital District, Joensuu, Finland.

Address reprint requests to: Antti Turunen, Department of Medicine, Kuopio University Hospital, PO Box 100, Kuopio 70029 KYS, Finland; e-mail: antti.turunen@fimnet.fi.

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Multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL) are the most common indications for autologous stem cell transplantation (auto-SCT).[1] The majority of transplant-eligible MM patients receive auto-SCT after induction therapy, whereas in NHL patients auto-SCT might be considered after first-line therapy for patients with mantle cell lymphoma or those with aggressive peripheral T-cell lymphoma. In patients with diffuse large B-cell lymphoma auto-SCT is usually considered after a relapse, except in those patients not achieving complete remission after first-line chemoimmunotherapy.[2]

Approximately 99% of all auto-SCTs are performed with blood grafts.[1] Granulocyte–colony-stimulating factor (G-CSF) alone or combined with chemotherapy are commonly used as mobilizing agents. More recently plerixafor has become available especially in case of insufficient mobilization. Besides the mobilization method used, also several patient-related factors (e.g., age, disease, previous therapy, marrow infiltration) affect both the capacity to mobilize CD34+ cells for transplant purposes and the cellular composition of the grafts collected.[3–7] A significant proportion of patients fail to mobilize stem cells sufficiently to support high-dose therapy (HDT). In general, NHL patients carry a higher risk of poor mobilization than MM patients,[8,9] but in some studies this difference has not been detected.[10]

An adequate number of CD34+ cells has remained the most important marker of graft quality in the autologous setting. Higher graft CD34+ cell content has been linked with faster platelet (PLT) and neutrophil recovery after HDT.[11,12] In some retrospective studies higher graft CD34+ cell count has also been associated with improved progression-free survival (PFS) and even overall survival (OS).[13–16] A minimum collection target of 2.0×10^6/kg CD34+ cells has been proposed,[17] but the optimal graft CD34+ count for hematologic recovery and posttransplant outcome is still debatable.[5,18]

Higher total lymphocyte and natural killer (NK)-cell counts in the grafts have been linked with faster immune recovery and also better PFS and OS in both MM and NHL patients.[19,20] An antitumor effect mediated by NK cells or T lymphocytes has been proposed as a possible reason for the observed survival benefit.[18,21,22] MM and NHLs have different biologic features and treatments. In practice, there are also some differences in the mobilization of the blood grafts according to the diagnosis. There is a lack of data comparing graft cellular composition and hematologic and immune recovery posttransplant between MM and NHL patients. Limited comparative data are also available on posttransplant complications, including nonrelapse mortality (NRM).

The aim of the prospective multicenter Graft and Outcome in Autologous Stem Cell Transplantation (GOA) study was to investigate the effects of different mobilization methods on collected blood graft cellular composition and to evaluate the effects of infused graft cellular composition on hematologic and immunologic recovery as well as PFS and OS posttransplant. In this analysis based on the patients of the GOA study we compared MM patients with NHL patients regarding mobilization and apheresis of CD34+ cells, cellular composition of infused blood grafts, recovery of blood counts, and complications posttransplant.

PATIENTS AND METHODS

Patients

Between May 2012 and December 2016, altogether 283 patients receiving their first auto-SCT at the university hospitals of Kuopio, Oulu, Tampere, and Turku in Finland were included in the prospective observational GOA study. The population consisted of 147 patients with MM and 136 patients with NHL. A proportion of the MM patients (n = 40, 29%) also participated in the randomized MM-02 study by the Finnish Myeloma Group, in which the patients received mobilization with either low-dose cyclophosphamide (CY) plus G-CSF or G-CSF alone in a randomized fashion after three cycles of induction treatment with lenalidomide, bortezomib, and dexamethasone followed by a single auto-SCT and lenalidomide maintenance[23,24] (NCT01790737). The characteristics of MM and NHL patients included in the GOA study are presented in Table 1.

Mobilization and collection of blood grafts

All NHL patients were mobilized with chemotherapy plus G-CSF, whereas MM patients received either low-dose CY (2 g/m^2) plus G-CSF (n = 90, 61%) or G-CSF alone (n = 57, 39%) as mobilization therapy. The G-CSF used after mobilizing chemotherapy in NHL patients was a single injection with either 6 mg (n = 54, 40%) or 12 mg (n = 26, 19%) pegfilgrastim, 10 μg/kg filgrastim daily until the completion of apheresis (n = 41, 30%), or a single 6-mg dose of lipegfilgrastim (n = 15, 11%) depending on institutional preferences. In MM patients, the G-CSF used in chemomobilization was either 5 μg/kg/day filgrastim until the completion of graft collection (n = 70, 47%) or a single 6-mg dose of pegfilgrastim (n = 20, 14%). A higher filgrastim dose of 10 μg/kg was used in G-CSF alone mobilized MM patients (n = 57, 39%). The blood CD34+ count (B-CD34+) was analyzed in each university laboratory center daily during the stem cell collection period. A minimum collection target of at least 2×10^6/kg CD34+ cells per transplant was used in all transplant centers. For the subgroup of patients participating in the MM-02 study, a higher collection target of 3×10^6/kg CD34+ cells for a single transplant was used. If a second transplant was an option, the collection target was 4×10^6/kg CD34+ cells, and for the MM-02 patients, 6×10^6/kg CD34+ cells. Plerixafor was added to the mobilization preemptively in case of insufficient mobilization

TABLE 1. Patient, disease, and mobilization characteristics in the GOA study*

Variable	MM n = 147	NHL n = 137	Significance
Sex (male/female)	78/69	85/52	0.126
Age (years), median (range)	64 (49-73)	62 (19-73)	<0.001
MM patients			
Paraprotein type			
IgG	85 (58)		
IgA	34 (23)		
IgM	1 (0.4)		
Light chain	27 (18)		
NHL patients			
Histology			
DLBCL†		68 (50)	
MCL		37 (27)	
PTCL		18 (13)	
FL		13 (10)	
Burkitt lymphoma		1 (1)	
Mobilization			
CT + G-CSF	90 (61)	137 (100)	<0.001
G-CSF alone	57 (39)		<0.001
Use of plerixafor	17 (12)	35 (26)	0.002
Mobilization chemotherapy‡			
HD-AraC		57 (41)	
DHAP		44 (32)	
ICE		11 (5)	
CY§	90 (61)	4 (3)	
Other		21 (15)	

* Data are reported as number (%), unless otherwise specified.
† Including 12 patients with primary CNS lymphoma.
‡ Given to at least 10 patients.
§ 2 g/m^2 low-dose CY for MM patients and 4 g/m^2 for NHL patients.
DLBCL = diffuse large B-cell lymphoma; MCL = mantle cell lymphoma; PTCL = peripheral T-cell lymphoma; FL = follicular lymphoma; CT + G-CSF = chemotherapy + G-CSF; HD-AraC = high-dose cytarabine; DHAP = dexamethasone, high-dose cytarabine, cisplatin; ICE = ifosfamide, carboplatin, etoposide.

(B-CD34+ < 10×10^6/L despite increasing white blood cell [WBC] count >5×10^9/L, n = 38). If the previous apheresis yields were considered inadequate and the B-CD34+ counts were declining, plerixafor was also given (n = 14).

Kuopio University Hospital used initially a COBE Spectra AutoPBSC apheresis device (Terumo BCT), but from April 2013 onward a different apheresis system was used (Spectra Optia, Software 7.2, Terumo BCT). In Oulu and Tampere University Hospitals the Spectra Optia apheresis system was used throughout the study. Turku University Hospital used a different apheresis system (COM.TEC Fresenius blood cell separator, Fresenius Hemo Care GmbH). The blood volume circulated per apheresis was 2.3 to 3.0 times the estimated blood volume of the patient. The number of collected CD34+ cells was analyzed after each apheresis with a flow cytometry using an ISHAGE protocol[25] at the stem cell laboratory of each university hospital.

Graft analysis

Two 0.5-mL tubes were taken from each apheresis product for subsequent graft analysis. The specimens were preserved the same way as the grafts. Dimethyl sulfoxide was added for final concentration of 10% to protect the cells from stress or death during cryopreservation. A freezer with controlled-rate freezing in liquid nitrogen was used. The cryopreserved graft specimens were sent overnight from Oulu, Tampere, and Turku University Hospitals to the Department of Clinical Microbiology, University of Eastern Finland, Kuopio, for the analysis of graft cellular composition.

A single experienced flow cytometrist (AR) analyzed the graft specimen after thawing using a flow cytometry system (FACSCanto, Becton Dickinson). The antibodies used for CD34+ cells and subclasses were CD34, CD38, CD133, and CD45. The antibodies were delivered by Becton Dickinson, except for CD133, which came from Miltenyi Biotech GmbH. 7-Aminoactinomycin (7-AAD) was used to distinguish the viable CD34+ cells. Total T-cell, B-cell, and NK-cell counts as well as the CD3+CD4+ and CD3+CD8+ lymphocyte subsets in the grafts were determined using both CD3/CD8/CD45/CD4 and CD3/CD16+CD56/CD45/CD19 reagents (BD Multitest, Becton Dickinson) with tubes (BD Trucount, Becton Dickinson).

In the majority of MM patients (100/147, 68%) a part of the collected graft was kept cryopreserved to support a possible second HDT in the future at relapse or disease progression. In five NHL patients (4%) with a large median 15.5×10^6/kg (range 7.2×10^6/kg-25.5×10^6/kg) CD34+ cell total apheresis yield only part of the collected graft was infused after HDT whereas all other NHL patients received the whole collected graft after HDT.

HDT and posttransplant follow-up

All MM patients received 200 mg/m^2 high-dose melphalan as HDT on Day –2 followed by graft infusion on Day 0. Most of the NHL patients (117/137, 85%) received BEAM (300 mg/m^2 carmustine on Day −6, 100 mg/m^2 etoposide b.i.d. from Day −5 to Day −2, 200 mg/m^2 cytarabine b.i.d. from Day −5 to Day −2, and 140 mg/m^2 melphalan on Day −2). Twelve NHL patients (9%) with primary central nervous system lymphoma were given a combination of carmustine (400 mg/m^2 on Day −6) and thiotepa (5 mg/kg b.i.d. on Day −5 and Day −4) as HDT and seven NHL patients (5%) received BEAC (300 mg/m^2 carmustine on Day −7, 100 mg/m^2 etoposide b.i.d. from Day −6 to Day −3, 100 mg/m^2 cytarabine b.i.d. from Day −6 to Day −3, and 1500 mg/m^2 CY from Day −6 to Day −3).

The G-CSF usage posttransplant was registered: 98% of the NHL patients received G-CSF after the graft infusion compared to 72% of the MM patients ($p < 0.001$). Depending on institutional preferences, MM patients were given either 5 μg/kg filgrastim daily (n = 63, 60%) or a single 6-mg dose of pegfilgrastim on Day +1 after graft infusion

(n = 42, 40%). Respectively, NHL patients received either 5 μg/kg filgrastim daily (n = 27, 20%), pegfilgrastim (n = 72, 54%), or a single 6-mg dose of lipegfilgrastim on Day +1 (n = 34, 26%).

Platelet engraftment was defined as the first of 3 consecutive days with PLT count of more than 20×10^9/L without PLT transfusions after the graft infusion (Day 0). Neutrophil engraftment was defined as the first of 3 consecutive days with neutrophil count of more than 0.5×10^9/L, respectively. Complete blood counts were evaluated on Day +15 and 1, 3, 6, and 12 months after auto-SCT. In addition, in a proportion of the patients, blood lymphocyte subsets were analyzed at 1, 3, and 6 months posttransplant by using both CD3/CD8/CD45/CD4 and CD3/CD16+CD56/CD45/CD19 reagents (BD Multitest, Becton Dickinson) with tubes (BD Trucount, Becton Dickinson). This analysis was performed in MM patients participating in the MM-02 study (n = 40) as well as in 48 consecutive NHL patients treated in the Kuopio University Hospital catchment area. In the case of a disease relapse or progression the follow-up of the hematologic and immune recovery was discontinued.

Non-Hodgkin's lymphoma patients treated at the Kuopio University Hospital (n = 106) were given oral ciprofloxacin as an antimicrobial prophylaxis (500 mg b.i.d.) starting 2 days before the graft infusion until the onset of febrile neutropenia and broad-spectrum antibiotics or until neutrophil recovery of at least 1.0×10^9/L. MM patients did not receive antibiotic prophylaxis. Cotrimoxazole was used for 4 months after auto-SCT as prophylaxis against *Pneumocystis jiroveci*. In the case of allergy or intolerance to sulfonamides, monthly inhalations of pentamidine were used instead.

Infections during the first year after auto-SCT were recorded. Episodes of febrile neutropenia early after auto-SCT with a definition of a temperature over 38.0°C and neutrophil count of less than 0.5×10^9/L were evaluated. Positive blood culture findings, pneumonias, and intensive care unit (ICU) admissions during the hospitalization period after HDT were recorded as well as data on later infections caused by *P. jirovecii*, varicella zoster, or other infections requiring readmission into hospital. Early treatment-related mortality (TRM) was defined as a death within 100 days after auto-SCT from other reasons than malignancy per se. NRM was defined as a death of any cause prior to disease progression or relapse.

Statistical analysis

Analyses were performed in all patients and between the groups. Statistical analysis and calculations were performed with computer software (SPSS Statistics Version 25, IBM Corp.). Continuous variables are presented as medians and ranges. The Mann-Whitney U test and Pearson's chi-square test were used. All p values were two-tailed. p values of less than 0.05 were considered as significant.

Ethics

The Research Ethics Committee of North Savo Hospital District approved the GOA study (13/2012) and the FMG MM-02 study (51/2012). All patients gave their written informed consent before enrollment to the study.

RESULTS

Mobilization and collection of CD34+ cells

The peak B-CD34+ count was higher in MM patients than in NHL patients (median, 64×10^6/L vs. 39×10^6/L, $p < 0.001$). The proportion of poor mobilizers (peak B-CD34+ count $<20 \times 10^6$/L) was significantly higher in NHL patients (15% vs. 3%, $p < 0.001$). In contrast, the proportion of "super mobilizers" (peak B-CD34+ count $>100 \times 10^6$/L) was higher in MM patients (28% vs. 16%, p = 0.02). Plerixafor was added to the mobilization in 17 MM patients (12%) and in 35 NHL patients (26%; p = 0.002). The median B-CD34+ was higher among MM patients before (8×10^6/L vs. 6×10^6/L, p = 0.001) as well as after plerixafor injection (19×10^6/L vs. 12×10^6/L, p = 0.01). The median (range) plerixafor dose was 0.26 (0.11-0.39) mg/kg in MM patients and 0.25 (0.15-0.32) mg/kg in NHL patients (p = 0.532). The median (range) number of plerixafor injections was 1 (1-2) in MM patients and 2 (1-4) in NHL patients (p = 0.043). The median number of CD34+ cells collected (6.3×10^6/L vs. 3.9×10^6/kg, $p < 0.001$) was higher in MM patients. The number of CD3+ lymphocytes, CD3+CD4+ cells, NK cells and CD19+ B lymphocytes were all significantly higher in MM patients. The detailed mobilization and apheresis data are presented in Table 2.

Cellular composition of infused grafts

The median amount of viable CD34+ cells (with 7-AAD) in the infused graft was 2.35×10^6/kg in the MM group and 2.5×10^6/kg in the NHL group (p = 0.02). In MM patients, the grafts contained more NK cells (10.1×10^6/L vs. 6.1×10^6/kg, p = 0.01) and CD19+ B lymphocytes (1.69×10^6/L vs. 0.00×10^6/kg, $p < 0.001$; Table 3). In the subgroup of patients mobilized with CY plus G-CSF, the blood grafts of MM patients contained fewer CD3+ cells, CD3+CD4+, CD3+CD8+, and NK cells (Table 3) than those of NHL patients.

Posttransplant follow-up

The neutrophil engraftment posttransplant was faster in NHL patients (9 days vs. 12 days, $p < 0.001$) but the median time to PLT engraftment was 12 days in the both groups (p = 0. 686). During the auto-SCT hospitalization period 88% (n = 119) of the NHL patients had febrile neutropenia compared to 79% (n = 116) in the MM group (p = 0.06). There was no difference between the groups regarding the incidence of bacteremia after auto-SCT (n = 23, 17% vs. n = 27, 18%, p = 0.748). In patients with bacteremia,

TABLE 2. Comparison of mobilization and graft collection data between all MM and NHL patients and between chemomobilized (CY + G-CSF) MM and NHL patients*

Variable	NHL	All MM patients†	p value‡ (vs. NHL)	MM† (CY + G-CSF)	p value‡ (vs. NHL)
WBC count at the time of first apheresis ($\times 10^9$/L)	12 (0.9-116.2); 136	17.4 (1.1-82.4); 143	0.007§	10.0 (1.1-79.6); 90	0.029§
B-CD34+ cells at the time of first apheresis ($\times 10^6$/L)	30 (5-538); 136	57 (10-415); 143	<0.001§	75 (11-415); 89	<0.001§
CD34+ cell yield with first apheresis ($\times 10^6$/kg)	2.3 (0.1-25.5); 136	3.7 (0.2-17.9); 147	<0.001§	4.5 (0.7-17.8); 90	<0.001§
Peak B-CD34+ count ($\times 10^6$/L)	39 (6-538); 136	64 (12-415); 147	<0.001§	93 (12-415); 90	<0.001§
Peak B-CD34+ count <20 × 10^6/L	20 (15)	4 (3)	<0.001§	2 (2)	0.002§
Peak B-CD34+ count >100 × 10^6/L	22 (16)	41 (28)	0.018§	38 (42)	<0.001§
Total collected CD34+ cell yield ($\times 10^6$/kg)‖	3.9 (1.6-25.5); 136	6.3 (2.0-17.9); 147	<0.001§	7.4 (2.0-17.9); 90	<0.001§
Total collected CD3+ yield ($\times 10^6$/kg)¶	88.8 (0.7-1022.5); 128	123.9 (5.5-1576.2); 124	0.001§	71.1 (5.5-354.2); 72	0.374
Total collected CD3+CD4+ yield ($\times 10^6$/kg)¶	44.2 (0.5-365.3); 128	71.2 (3.4-608.9); 124	<0.001§	45.1 (3.4-290.3); 72	0.490
Total collected CD3+CD8+ yield ($\times 10^6$/kg)¶	35.1 (0.4-644.9); 128	44.9 (1.5-1213); 124	0.084	24.2 (1.5-133.9); 72	0.025§
Total collected NK-cell yield ($\times 10^6$/kg)¶	6.1 (0.1-56.9); 128	15.6 (0.5-748.9); 124	<0.001§	6.2 (0.5-70.9); 72	0.860
Total collected CD19+ cell yield ($\times 10^6$/kg)¶	0.0 (0.0-100.2); 128	2.6 (0.0-97.0); 124	<0.001§	1.6 (0.0-66.6); 72	<0.001§
Number of apheresis procedures	2 (1-4); 136	2 (1-4); 147	0.080	2 (1-4); 90	0.717

* Data are presented as median (range); number of observations or number (%).
† Most MM patients had a higher minimum CD34+ cell collection target (4.0 × 10^6/kg).
‡ Compared to the NHL patient group.
§ Statistically significant ($p < 0.05$)
‖ Measured before cryopreservation by flow cytometry.
¶ Measured after thawing by flow cytometry.

TABLE 3. Comparison of cellular composition of the infused grafts between all MM and NHL patients and between chemomobilized (CY + G-CSF) MM patients and NHL patients

Blood graft content ($\times 10^6$ cells/kg)§	NHL*	All MM patients*	p value†	MM (CY + G-CSF)*	p value†
CD34+ cells without 7-AAD	3.2 (0.8-16.5); 128	3.1 (0.6-8.7); 127	0.182	3.5 (1.6-8.7); 73	0.519
CD34+ cells with 7-AAD	2.5 (0.6-14.3); 129	2.4 (0.2-7.2); 127	0.020‡	2.8 (0.7-7.2); 73	0.795
CD34+CD133+CD38– cells	0.07 (0.006-0.3); 129	0.06 (0.005-0.6); 127	0.099	0.07 (0.007-0.6); 73	0.955
CD3+ cells	88.8 (0.7-1022.5); 128	78.8 (2.8-1576.2); 125	0.947	41.3 (2.8-354.2); 72	<0.001‡
CD3+CD4+ cells	44.2 (0.5-365.3); 128	48.5 (2.1-474.7); 125	0.279	25.6 (2.1-290.3); 72	0.004‡
CD3+CD8+ cells	34.3 (0.4-644.9); 128	25.5 (0.8-1213.9); 125	0.344	13.8 (0.8-90.7); 72	<0.001‡
CD19+ cells	0.0 (0.0-100.2); 128	1.7 (0.0-66.6); 125	<0.001‡	0.9 (0.0-66.6); 72	<0.001‡
NK cells	6.1 (0.05-56.9); 128	10.1 (0.24-748.9); 125	0.011‡	3.3 (0.2-35.5); 72	0.005‡

* Data are presented as median (range); number of observations.
† Compared to the NHL patient group.
‡ Statistically significant ($p < 0.05$).
§ Measured after thawing by flow cytometry.

Gram-positive predominance in blood culture findings was observed in both NHL (n = 18/23, 78%) and MM patients (n = 15/27, 56%, p = 0.083). NHL patients had more ICU admissions (n = 5, 4% vs. n = 0, 0%, p = 0.02) and a longer median duration of hospitalization(22 days vs. 18 days, p < 0.001).

During the first year after auto-SCT the readmission rate due to infections did not differ between the groups (22% vs. 24%, p = 0.768). There were five verified *Pneumocystis* infections in the NHL group (4%) compared to one in the MM group (1%, p = 0.08). Varicella zoster was reported in 10% of the patients in the both groups (p = 0.940). Early TRM was low in the both groups with two deaths in the NHL group (1.5%) and no deaths at all among the MM patients (p = 0.14). Late (>100 days) NRM was significantly higher in NHL patients (n = 8, 6%) than in MM patients (n = 0, 0%; p = 0.003). Infections were the leading cause of NRM (4/10, 40%).

TABLE 4. Comparison of hematologic recovery after auto-SCT between MM and NHL patients

Variable	MM*	NHL*	p value
Neutrophil engraftment (days)	12 (9-30); 147	9 (0-30); 136	<0.001†
PLT engraftment (days)	12 (0-55); 145	12 (0-201); 133	0.605
Hb (g/L)			
+1 month	116 (80-143); 141	112 (64-140); 112	0.002†
+3 months	123 (89-156); 143	122 (86-158); 118	0.252
+6 months	126 (91-159); 132	129 (70-160); 110	0.729
+12 months	131 (102-161); 114	134 (96-176); 96	0.058
WBCs ($\times 10^9$/L)			
+15 days	3.0 (0.3-126.0); 144	5.0 (0.3-26.9); 135	<0.001†
+1 month	4.9 (2.1-26.8); 141	5.0 (1.6-12.0); 132	0.781
+3 months	4.5 (1.7-13.7); 143	4.2 (1.9-40.0); 118	0.065
+6 months	4.4 (1.7-13.4); 132	4.4 (1.3-10.2); 110	0.894
+12 months	4.8 (0.7-9.0); 113	5.2 (2.4-11.1); 96	0.170
Neutrophils ($\times 10^9$/L)			
+15 days	1.6 (0.06-9.0); 132	3.4 (0.2-20.7); 127	<0.001†
+1 month	2.1 (0.4-23.7); 127	2.1 (0.07-9.7); 130	0.798
+3 months	2.1 (0.5-7.6); 136	1.5 (0.1-11.2); 116	<0.001†
+6 months	2.0 (0.2-9.8); 122	2.0 (0.4-10.7); 101	0.610
+12 months	2.4 (0.7-5.8); 98	2.4 (0.6-9.7); 88	0.189
Lymphocytes ($\times 10^9$/L)			
+15 days	0.6 (0.07-3.7); 111	0.6 (0.04-4.2); 117	0.596
+1 month	1.6 (0.5-6.1); 108	1.8 (0.4-8.1); 120	0.593
+3 months	1.6 (0.4-6.5); 125	1.8 (0.4-5.5); 108	0.263
+6 months	1.5 (0.4-3.8); 107	1.8 (0.4-4.8); 97	0.063
+12 months	1.6 (0.6-4.7); 88	1.8 (0.4-5.4); 82	0.418
PLT count ($\times 10^9$/L)			
+15 days	57 (9-431); 144	54 (4-296); 135	0.897
+1 month	184 (12-633); 140	133 (10-343); 131	<0.001†
+3 months	184 (27-362); 143	143 (10-357); 117	<0.001†
+6 months	192 (66-385); 132	164 (14-328); 109	0.002†
+12 months	196 (62-417); 114	177 (23-326); 95	0.023†

* Data are reported as median (range); number of observations.
† Statistically significant ($p < 0.05$).

TABLE 5. Comparison of immune recovery after auto-SCT between MM and NHL patients

Variable	MM*	NHL*	p value
CD3+ cell count ($\times 10^9$/L)			
+1 month	1.1 (0.3-5.9); 27	1.2 (0.2-4.4); 48	0.77
+3 months	1.2 (0.2-2.6); 39	1.5 (0.3-4.8); 32	0.04†
+6 months	1.0 (0.4-1.9); 34	1.3 (0.3-4.0); 29	0.06
CD4+ cell count ($\times 10^9$/L)			
+1 month	0.3 (0.1-2.0); 27	0.3 (0.05-1.5); 48	0.43
+3 months	0.3 (0.1-0.8); 39	0.4 (0.1-0.9); 32	0.09
+6 months	0.3 (0.1-0.7); 34	0.3 (0.1-0.7); 30	0.77
CD8+ cell count ($\times 10^9$/L)			
+1 month	0.8 (0.2-5.4); 27	0.9 (0.1-3.9); 48	0.38
+3 months	0.9 (0.2-2.2); 39	1.1 (0.1-4.2); 32	0.06
+6 months	0.6 (0.2-1.6); 34	0.9 (0.2-3.4); 29	0.03†
CD19+ cell count ($\times 10^9$/L)			
+1 month	0.0 (0.0-0.1); 27	0.0 (0.0-0.0); 47	<0.001†
+3 months	0.1 (0.0-0.4); 39	0.0 (0.0-0.3); 32	<0.001†
+6 months	0.1 (0.0-0.5); 34	0.0 (0.0-0.3); 29	<0.001†
NK-cell count ($\times 10^9$/L)			
+1 month	0.4 (0.1-0.8); 27	0.2 (0.02-0.7); 48	0.03†
+3 months	0.2 (0.1-0.9); 39	0.2 (0.05-0.9); 32	0.15
+6 months	0.23 (0.10-0.75); 34	0.17 (0.03-1.14); 29	0.02†
CD4+/CD8+ ratio			
+1 month	0.4 (0.0-1.2); 27	0.3 (0.1-1.1); 48	0.34
+3 months	0.3 (0.0-1.3); 39	0.3 (0.1-1.1); 32	1.0
+6 months	0.4 (0.0-1.3); 34	0.4 (0.1-1.3); 29	0.59

* Data are presented as median (range); number of observations. Reference values of blood flow cytometry reported by the Laboratory Center of Eastern Finland: B-T-CD3, 0.85×10^9 to 2.28×10^9/L; B-CD19, 0.12×10^9 to 0.43×10^9/L; B-T-CD4, 0.458×10^9 to 1.406×10^9/L; B-T-CD8, 0.24×10^9 to 0.98×10^9/L; B-NK, 0.08×10^9 to 0.57×10^9/L.
† Statistically significant ($p < 0.05$).

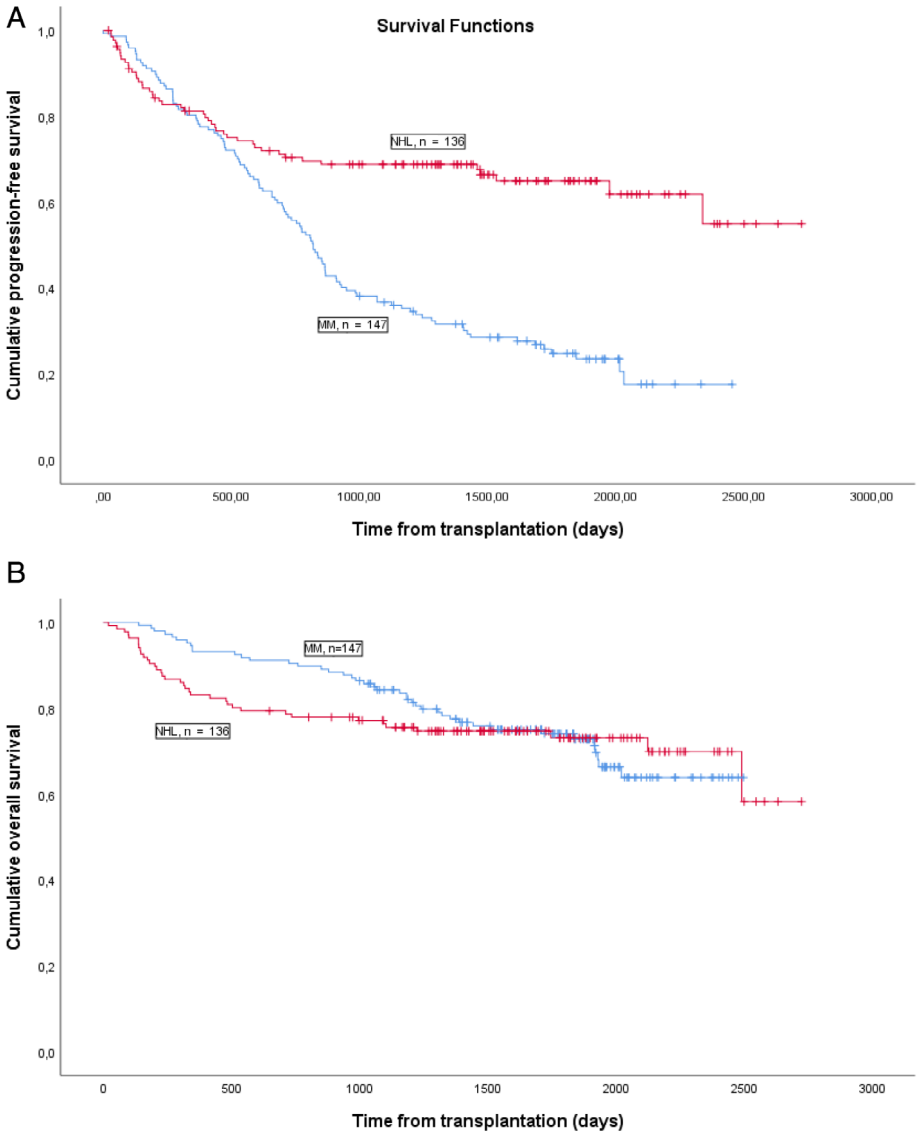

Fig. 1. PFS (A) and OS (B) of the MM and NHL patients. [Color figure can be viewed at wileyonlinelibrary.com]

Hematologic and immune recovery after auto-SCT

The median hemoglobin (Hb) level at 1 month after auto-SCT was higher among MM patients (116 vs. 112 g/L, p = 0.001). The pace of WBC and neutrophil recovery was faster in NHL patients on Day +15 after the graft infusion. Later the neutrophil level decreased in the NHL group and was significantly lower at 3 months posttransplant. The lymphocyte recovery was comparable between the groups. The PLT count was higher in the MM group from 1 month until 1 year after auto-SCT. Data on posttransplant hematologic recovery are shown in Table 4.

The immune recovery also somewhat differed between the groups. The NK-cell count was higher in the MM group, reaching significance at 1 month and at 6 months after auto-SCT. The CD19+ B-lymphocyte count was higher among MM patients during the whole posttransplant follow-up period. The immune recovery data are presented in Table 5.

Long-term follow-up

The median (range) follow-up for patients remaining alive was 55 (22-91) months in the NHL group and 61 (33-83) months in the MM group in October 2019. In the MM group 111 patients (76%) had experienced a relapse or disease progression and 42 patients (29%) had died. Disease relapse had occurred in 46 NHL patients (34%) and 37 patients (27%) had died, respectively (Fig. 1). All nonrelapse deaths in our study were observed in patients older than 60 years of age.

DISCUSSION

In this analysis based on the patient population of the prospective multicenter GOA study, MM patients were compared with NHL patients in regard to mobilization and apheresis of CD34+ cells, cellular composition of blood grafts infused after HDT, posttransplant recovery, and outcome. MM patients mobilized CD34+ cells better and thus needed less plerixafor. In addition, the blood grafts given to MM patients contained more NK and CD19+ cells. Furthermore, some differences in the hematologic and immune recovery after auto-SCT were noted according to the diagnosis. NHL patients carried a significantly higher risk of late NRM.

In this study 15% of the NHL patients were categorized as poor mobilizers whereas only 3% of MM patients had a peak B-CD34+ count of less than 20×10^6/L after mobilization. The results are in line with a prior Finnish single-center retrospective analysis[9] in which 1.5% of the MM patients and 17% of the NHL patients mobilized poorly. In a large US retrospective study[8] the mobilization failure rates were 5% for MM and 26% for NHL patients; the majority of the patients were mobilized with G-CSF alone. In a more recent retrospective study,[26] mobilization failed in 22% of the lymphoma patients compared to 9% of the MM patients. In contrast, in a German retrospective study[10] the proportion of poor mobilizers did not differ between chemomobilized MM and NHL patients. In our study the plerixafor usage was more common among NHL patients (26% vs. 12%). The preemptive use of plerixafor[27] may contribute to the lower number of poor mobilizers in this study than in previous reports.

In an Austrian prospective study the median CD34+ yield per apheresis procedure was 4.4×10^6/kg CD34+ cells for MM patients and 3.5×10^6/kg for lymphoma patients[28] and thus somewhat higher than in our study. In a Swedish retrospective analysis the chemomobilized MM patients recorded a median total yield of 11.2×10^6/kg compared to significantly lower yields in different NHL subgroups.[29] In our study the apheresis yields were lower than those in the Swedish study obviously due to the differences in mobilization regimens used but also due to lower collection targets. Chemomobilization has been shown to result in higher graft CD34+ content in MM patients with fewer apheresis procedures than G-CSF mobilization;[23] this was also evident in the whole GOA Study population. The more intense chemotherapy in the pretransplant phase may account for the decreased ability to mobilize CD34+ cells in NHL. In addition, the use of large-volume leukapheresis may improve CD34+ cell collection efficiency especially in poorly mobilizing patients.[30] Data regarding the effect of large-volume leukapheresis on more detailed graft cellular composition are limited.[31,32] In this study the apheresis procedures were performed with standard-volume leukapheresis.

In our study with a roughly comparable infused graft CD34+ content, the blood grafts contained a significantly higher number of NK cells and CD19+ B cells in MM patients. The number of CD19+ B lymphocytes in the grafts was very low in both groups. The use of rituximab as a part of the therapy in most NHL patients accounts for the observed difference as rituximab kills B lymphocytes effectively. However, when the grafts of chemomobilized (CY plus G-CSF) MM patients and NHL patients were compared, the CD3+, CD3+CD4+, CD3+CD8+, and NK-cell counts were in fact lower among MM patients, reflecting effective lymphocyte killing capacity of CY even with a moderate dose. The differences in mobilizing therapy mainly explain the observed differences. Previously we have found that grafts mobilized with G-CSF alone contain significantly more lymphocytes and NK cells than those mobilized with low-dose CY plus G-CSF.[33]

Although there was no difference in the PLT count on Day +15 after auto-SCT between the groups, the MM patients recorded significantly higher PLT counts within a year after auto-SCT. These observations suggest better graft function in MM patients. An apparent reason is the more intense chemotherapy given to the NHL patients before mobilization and auto-SCT. The neutrophil engraftment was faster among NHL patients in our study. The differences in G-CSF use after the graft infusion mainly explain the difference.

The blood NK-cell counts after auto-SCT were higher among MM patients, reaching a significance at 1 and 6 months posttransplant. The CD3+ and CD3+CD8+ levels were somewhat lower among NHL patients during the follow-up, while there was no difference in the recovery of blood CD3+CD4+ cells. Previously it has been shown that graft CD3+, CD3+CD4+, and NK-cell counts correlate with early NK-cell recovery in NHL patients.[34] Since only the NK-cell counts differed in the blood grafts in our study, this cell population in the grafts might be responsible for the observed difference in NK-cell recovery. The long-term CD3+ and CD3+CD4+ cell recovery has been previously shown to be slower among MM patients,[35] corroborating our findings of slower CD3+CD4+ and CD3+CD8+ lymphocyte recovery. All MM patients with analysis of immune recovery belonged to MM-02 study, in which 10 mg/day lenalidomide maintenance was started on Day + 100. This treatment might have some effect on both immune recovery and on neutrophil and PLT counts later.

The incidence of febrile neutropenia and bloodstream infections during hospitalization following auto-SCT was comparable between the groups, but NHL patients had more ICU admissions. These results are in line with a previous prospective study from our institute in which 7.2% of the NHL patients with febrile neutropenia and none of the MM patients were treated at the ICU after auto-SCT.[36] Severe sepsis was observed in 14% of the NHL patients compared to only 2.8% of the MM patients. The predominance of Gram-positive bloodstream infections after auto-SCT has also been observed previously.[36,37] In our study the

early NRM was absent among MM patients and was 1.5% in the NHL group. Previous studies have shown slightly higher rates of early mortality.[38,39] Late (>100 days) NRM has been shown to comprise mainly of secondary malignancies, infections, and cardiovascular disease in previous reports.[40] In a large Argentinian cohort[39] the NRM was 2.9% in MM patients and 8.1% in NHL patients at 3 years after auto-SCT, corroborating our observations. With a relatively long follow-up, we observed significantly higher risk of NRM in NHL patients.

This is to the best of our knowledge the largest study in an autologous setting evaluating blood graft cellular composition in detail. Thus, it allows comparison of mobilization characteristics, graft composition, posttransplant recovery, and complications in two major disease categories, where auto-SCT is commonly applied. Furthermore, this study represents a multicenter real-life situation at the present time (2012-2016) as the study was observational.

There are differences in graft cellular composition, hematologic and immune recovery posttransplant, risk of nonrelapse death, and outcome between NHL and MM patients. Further analyses are needed to evaluate the potential effects of different graft cellular components on posttransplant recovery and outcome. These analyses should be carried out separately for MM and NHL patients.

CONFLICT OF INTEREST

Dr. Partanen reports honoraria from Behring and has participated in the Scientific Advisory Board meetings organized by Abbvie. Dr. Valtola has participated Medical Advisory Boards organized by Amgen and Janssen-Cilag and has also received consultancy fees from Amgen, Sanofi and Janssen-Cilag. Dr. Siitonen has participated in the Scientific Advisory Boards of Roche, Amgen and Pfizer and received consultancy fees from Amgen. Dr. Taru Kuittinen has received consultancy fees from Sanofi-Genzyme, BMS, Sanofi, Celgene, Roche, Amgen, Janssen, Pfizer, Leo-Pharma, Sobi, MSD, Takeda, Bayer, Novo Nordisk and Boehringer-Ingelheim. Dr. Silvennoinen has received Celgene Research Funding for FMG-MM02 study, Amgen, BMS and Takeda Research funding, compensation as a member of the Scientific Advisory Board of Celgene, Amgen, Janssen-Cilag, Takeda and consultancy fees from Amgen, Sanofi. Dr. Varmavuo reports consultancy fees from Abbvie, Amgen, Celgene, Janssen-Cilag, Roche, and Sanofi. Dr. Jantunen has participated in the Scientific Advisory Boards of Amgen, Takeda, TEVA and Sanofi. The other authors have disclosed no conflicts of interest.

REFERENCES

1. Passweg JR, Baldomero H, Basak GW, et al. The EBMT activity survey report 2017: a focus on allogeneic HCT for non-malignant indications and on the use of non-HCT cell therapies. Bone Marrow Transplant 2019;54:1575-85.
2. Jantunen E, Sureda A. The evolving role of stem cell transplants in lymphomas. Biol Blood Marrow Transplant 2012;18: 660-73.
3. Kuittinen T, Nousiainen T, Halonen P, et al. Prediction of mobilisation failure in patients with non-Hodgkin's lymphoma. Bone Marrow Transplant 2004;33:907-12.
4. Kumar S, Dispenzieri A, Lacy MQ, et al. Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma. Leukemia 2007;21:2035-42.
5. Jantunen E, Fruehauf S. Importance of blood graft characteristics in auto-SCT: implications for optimizing mobilization regimens. Bone Marrow Transplant 2011;46:627-35.
6. Rossi G, Skert C, Morello E, et al. PBSC mobilization in lymphoma patients: analysis of risk factors for collection failure and development of a predictive score based on the kinetics of circulating CD34+ cells and WBC after chemotherapy and G-CSF mobilization. Hematol Oncol 2015;33:125-32.
7. Giebel S, Sadus-Wojciechowska M, Halaburda K, et al. Increased efficacy of intermediate-dose cytarabine + G-CSF compared to DHAP + G-CSF for stem cell mobilization in patients with lymphoma: an analysis by the polish lymphoma research group. Ann Hematol 2016;95:263-9.
8. Pusic I, Jiang SY, Landua S, et al. Impact of mobilization and remobilization strategies on achieving sufficient stem cell yields for autologous transplantation. Biol Blood Marrow Transplant 2008;14:1045-56.
9. Jantunen E, Varmavuo V, Juutilainen A, et al. Kinetics of blood CD34+ cells after chemotherapy plus G-CSF in poor mobilizers: implications for pre-emptive plerixafor use. Ann Hematol 2012; 91:1073-9.
10. Wuchter P, Ran D, Bruckner T, et al. Poor mobilization of hematopoietic stem cells-definitions, incidence, risk factors, and impact on outcome of autologous transplantation. Biol Blood Marrow Transplant 2010;16:490-9.
11. Ketterer N, Salles G, Raba M, et al. High CD34(+) cell counts decrease hematologic toxicity of autologous peripheral blood progenitor cell transplantation. Blood 1998;91:3148-55.
12. Stiff PJ, Micallef I, Nademanee AP, et al. Transplanted CD34(+) cell dose is associated with long-term platelet count recovery following autologous peripheral blood stem cell transplant in patients with non-Hodgkin lymphoma or multiple myeloma. Biol Blood Marrow Transplant 2011;17:1146-53.
13. Gordan LN, Sugrue MW, Lynch JW, et al. Poor mobilization of peripheral blood stem cells is a risk factor for worse outcome in lymphoma patients undergoing autologous stem cell transplantation. Leuk Lymphoma 2003;44:815-20.
14. Toor AA, Ayers J, Strupeck J, et al. Favourable results with a single autologous stem cell transplant following conditioning with busulphan and cyclophosphamide in patients with multiple myeloma. Br J Haematol 2004;124:769-76.
15. Pavone V, Gaudio F, Console G, et al. Poor mobilization is an independent prognostic factor in patients with malignant lymphomas treated by peripheral blood stem cell transplantation. Bone Marrow Transplant 2006;37:719-24.

16. Yoon DH, Sohn BS, Jang G, et al. Higher infused CD34+ hematopoietic stem cell dose correlates with earlier lymphocyte recovery and better clinical outcome after autologous stem cell transplantation in non-Hodgkin's lymphoma. Transfusion 2009;49:1890-900.
17. Giralt S, Costa L, Schriber J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. Biol Blood Marrow Transplant 2014;20:295-308.
18. Saraceni F, Shem-Tov N, Olivieri A, et al. Mobilized peripheral blood grafts include more than hematopoietic stem cells: the immunological perspective. Bone Marrow Transplant 2015;50: 886-91.
19. Porrata LF, Litzow MR, Inwards DJ, et al. Infused peripheral blood autograft absolute lymphocyte count correlates with day 15 absolute lymphocyte count and clinical outcome after autologous peripheral hematopoietic stem cell transplantation in non-Hodgkin's lymphoma. Bone Marrow Transplant 2004;33:291-8.
20. Porrata LF, Gertz MA, Geyer SM, et al. The dose of infused lymphocytes in the autograft directly correlates with clinical outcome after autologous peripheral blood hematopoietic stem cell transplantation in multiple myeloma. Leukemia 2004;18: 1085-92.
21. Chung DJ, Pronschinske KB, Shyer JA, et al. T-cell exhaustion in multiple myeloma relapse after autotransplant: optimal timing of immunotherapy. Cancer Immunol Res 2016;4:61-71.
22. Porrata LF. Autologous graft-versus-tumor effect: reality or fiction? Adv Hematol 2016;2016:5385972.
23. Silvennoinen R, Anttila P, Säily M, et al. A randomized phase II study of stem cell mobilization with cyclophosphamide+G-CSF or G-CSF alone after lenalidomide-based induction in multiple myeloma. Bone Marrow Transplant 2016;51:372-6.
24. Luoma S, Anttila P, Säily M, et al. RVD induction and autologous stem cell transplantation followed by lenalidomide maintenance in newly diagnosed multiple myeloma: a phase 2 study of the Finnish Myeloma Group. Ann Hematol 2019;98: 2781-91.
25. Gratama JW, Kraan J, Keeney M, et al. Validation of the single-platform ISHAGE method for CD34(+) hematopoietic stem and progenitor cell enumeration in an international multicenter study. Cytotherapy 2003;5:55-65.
26. Lee KH, Jung SK, Kim SJ, et al. Incidence and risk factors of poor mobilization in adult autologous peripheral blood stem cell transplantation: a single-centre experience. Vox Sang 2014; 107:407-15.
27. Jantunen E, Lemoli RM. Preemptive use of plerixafor in difficult-to-mobilize patients: an emerging concept. Transfusion 2012;52:906-14.
28. Worel N, Fritsch G, Agis H, et al. Plerixafor as preemptive strategy results in high success rates in autologous stem cell mobilization failure. J Clin Apher 2017;32:224-34.
29. Ungerstedt JS, Watz E, Uttervall K, et al. Autologous hematopoietic stem cell transplantation in multiple myeloma and lymphoma: an analysis of factors influencing stem cell collection and hematological recovery. Med Oncol 2012;29:2191-9.
30. Abrahamsen JF, Stamnesfet S, Liseth K, et al. Large-volume leukapheresis yields more viable CD34+ cells and colony-forming units than normal-volume leukapheresis, especially in patients who mobilize low numbers of CD34+ cells. Transfusion 2005;45:248-53.
31. Smolowicz AG, Villman K, Tidefelt U. Large-volume apheresis for the harvest of peripheral blood progenitor cells for autologous transplantation. Transfusion 1997;37:188-92.
32. Bojko P, Scharifi M, Stössel K, et al. Comparison of processing four and five times the patients' blood volume during peripheral blood stem cell collection and analysis of CD34+38- and CD34+49d+ subsets during apheresis. J Cancer Res Clin Oncol 2002;128:19-28.
33. Valtola J, Silvennoinen R, Ropponen A, et al. Blood graft cellular composition and posttransplant outcomes in myeloma patients mobilized with or without low-dose cyclophosphamide: a randomized comparison. Transfusion 2016;56: 1394-401.
34. Valtola J, Varmavuo V, Ropponen A, et al. Blood graft cellular composition and posttransplant recovery in non-Hodgkin's lymphoma patients mobilized with or without plerixafor: a prospective comparison. Transfusion 2015;55:2358-68.
35. Laurenti L, Piccioni P, Piccirillo N, et al. Immune recovery of lymphocyte subsets 6 years after autologous peripheral blood stem cell transplantation (PBSCT) for lymphoproliferative diseases. A comparison between NHL, HD and MM in group of 149 patients. Leuk Lymphoma 2004;45:2063-70.
36. Rönkkö R, Juutilainen A, Koivula I, et al. Changes in the microbiological epidemiology of febrile neutropenia in autologous stem cell transplant recipients. Infect Dis (Lond) 2018;50: 436-42.
37. Piñana JL, Montesinos P, Martino R, et al. Incidence, risk factors, and outcome of bacteremia following autologous hematopoietic stem cell transplantation in 720 adult patients. Ann Hematol 2014;93:299-307.
38. Jantunen E, Itälä M, Lehtinen T, et al. Early treatment-related mortality in adult autologous stem cell transplant recipients: a nation-wide survey of 1482 transplanted patients. Eur J Haematol 2006;76:245-50.
39. Berro M, Arbelbide JA, Rivas MM, et al. Hematopoietic cell transplantation–specific comorbidity index predicts morbidity and mortality in autologous stem cell transplantation. Biol Blood Marrow Transplant 2017;23:1646-50.
40. Jantunen E, Itälä M, Siitonen T, et al. Late non-relapse mortality among adult autologous stem cell transplant recipients: a nation-wide analysis of 1,482 patients transplanted in 1990-2003. Eur J Haematol 2006;77:114-9.