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CD34$^+$ Cell Mobilization, Autograft Cellular Composition and Outcome in Mantle Cell Lymphoma Patients

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Keywords

Mantle cell lymphoma · Autologous · CD34$^+$ cells · Mobilization · CD4$^+$CD8$^+$ cells · Graft composition · Lymphocytes · Transplantation

Abstract

Backgound: Autologous stem cell transplantation (ASCT) is a standard treatment in transplant-eligible mantle cell lymphoma (MCL) patients after first-line chemoimmunotherapy. ***Study Design and Methods:*** This prospective multicenter study evaluated the impact of CD34$^+$ cell mobilization and graft cellular composition analyzed by flow cytometry on hematologic recovery and outcome in 42 MCL patients. ***Results:*** During CD34$^+$ cell mobilization, a higher blood CD34$^+$ cell count (>30 × 10^6/L) was associated with improved overall survival (median not reached [NR] vs. 57 months, p = 0.04). The use of plerixafor did not impact outcome. Higher number of viable cryopreserved graft CD34$^+$ cells (>3.0 × 10^6/kg) was associated with faster platelet (median 11 vs. 15 days, p = 0.03) and neutrophil (median 9 vs. 10 days, p = 0.02) recovery posttransplant. Very low graft CD3$^+$CD8$^+$ cell count (≤10 × 10^6/kg) correlated with worse progression-free survival (PFS) (HR 4.136, 95% CI 1.547–11.059, p = 0.005). On the other hand, higher absolute lymphocyte count >2.5 × 10^9/L at 30 days after ASCT (ALC-30) was linked with better PFS (median NR vs. 99 months, p = 0.045) and overall survival (median NR in either group, p = 0.05). ***Conclusions:*** Better mobilization capacity and higher graft CD3$^+$CD8$^+$ cell count had a positive prognostic impact in this study, in addition to earlier lymphocyte recovery (ALC-30>2.5 × 10^6/L). These results need to be validated in another study with a larger patient cohort.

Introduction

The current role of autologous stem cell transplantation (ASCT) following first-line chemoimmunotherapy in the treatment of transplant-eligible mantle cell lymphoma (MCL) patients is relatively strong [1]. Although the only randomized study demonstrating superior progression-free survival (PFS) in patients treated with high-dose therapy (HDT) and ASCT was conducted in

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Table 1. Patient characteristics

Variable	*n* = 42
Sex (male/female)	30/12
Age, median (range), years	64 (43–73)
Stage, *n* (%)	
II	5 (12)
III	7 (17)
IV	28 (67)
Missing	2 (5)
MIPI, *n* (%)	
Low	7 (17)
Intermediate	9 (21)
High	13 (31)
Missing	13 (31)
Bone marrow infiltration at diagnosis[a], *n* (%)	27 (64)
Bone marrow infiltration at mobilization[a], *n* (%)	2 (5)
First-line therapy, *n* (%)	
Nordic MCL2 protocol	39 (93)
R-hyper-CVAD – HD-MTX/HD-AraC	3 (7)
Mobilization chemotherapy, *n* (%)	
High-dose AraC	42 (100)
Use of plerixafor, *n* (%)	8 (19)
G-CSF used for mobilization, *n* (%)	
Filgrastim	12 (29)
Pegfilgrastim	18 (43)
Lipegfilgrastim	12 (29)
Disease status before ASCT, *n* (%)	
I CR	30 (71)
I PR	11 (26)
Progressive disease	1 (2)

MCL, mantle cell lymphoma; MIPI, mantle cell lymphoma prognostic index; R-hyper-CVAD – HD-MTX/HD-AraC, rituximab, hyperfractionated cyclophosphamide, doxorubicin, vincristine and dexamethasone (R-hyper-CVAD) alternating with high-dose methotrexate and high-dose cytarabine; AraC, cytarabine; CR, complete remission; PR, partial response; PR, partial remission. [a]Missing bone marrow infiltration data in 1 patient at diagnosis and in 6 patients before mobilization (of which 5 had bone marrow infiltration at diagnosis).

the pre-rituximab era [2], more recent retrospective data support the use of front-line ASCT in eligible patients also following induction therapy containing rituximab [3]. However, in high-risk patients with either TP53 mutations or high-risk MCL International Prognostic Index including Ki-67 proliferation index (MIPI-c), the outcome after chemoimmunotherapy followed by ASCT consolidation remains poor [4].

A higher graft $CD34^+$ cell count has been linked with more rapid platelet and neutrophil recovery early after ASCT and with improved survival in retrospective [5, 6] and also in prospective [7, 8] non-Hodgkin lymphoma (NHL) patient cohorts containing also MCL patients. However, the number of lymphocytes in the blood graft is about 10–20 fold higher than the number of $CD34^+$ cells [9]. Higher graft lymphocyte content has been associated with improved PFS and OS in NHL patients [10]. More data are needed to define the impact of more detailed autograft cellular composition on outcome in MCL patients after ASCT.

The prospective multicenter Graft and Outcome in Autologous stem cell transplantation (GOA) study aimed to evaluate the impact of different mobilization regimens on $CD34^+$ cell mobilization and graft composition as well as the effect of graft cellular composition on posttransplant outcome. This analysis covers these issues in MCL patients included in this prospective observational multicenter study.

Patients and Methods

Patients

The study population consists of 42 MCL patients who received ASCT after chemoimmunotherapy in the University Hospitals of Kuopio, Oulu, and Tampere between 2012 and 2018 and participated in the prospective non-interventional multicenter GOA study. The diagnosis was based on an evaluation by an experienced pathologist at the local hospital confirmed by a hematopathologist if necessary. The data on the histopathological subtype were missing in a considerable number of patients and, thus, not reported here. Most of the patients had a high-risk disease based on the MIPI score and were diagnosed with an advanced-stage disease (Table 1). Autograft cellular composition analyses were performed after cryopreservation in 34 patients transplanted between 2012 and 2016.

Monoclonal CD20 antibody rituximab (R) in combination with a dose-intensified cyclophosphamide, doxorubicin, vincristine, and prednisone (maxi-CHOP) regimen alternating with R + high-dose cytarabine (HD-AraC) according to the Nordic MCL2 protocol [11] was given as induction regimen to 39 patients (93%). Three patients (7%) received rituximab, hyperfractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone (R-hyper-CVAD) alternating with high-dose methotrexate and AraC (HD-MTX/HD-AraC) as induction therapy [12]. After ASCT, 3 patients (7%) received rituximab maintenance.

Mobilization and Collection of Blood Grafts

All patients received HD-AraC combined with a granulocyte colony-stimulating factor (G-CSF) as mobilizing therapy. The type of G-CSF used for mobilization was chosen according to local preferences. Plerixafor was added to the mobilization preemptively in case of low blood $CD34^+$ cell count $<10 \times 10^6$/L with a rising white blood cell count $>5 \times 10^9$/L or in case of decreasing B-$CD34^+$ counts with insufficient apheresis yields [13].

The blood $CD34^+$ cell counts and complete blood counts were analyzed daily during the collection period. The apheresis machine used was Spectra Optia (Terumo BCT) in Oulu and Tampere University Hospitals. Kuopio University Hospital also used Spectra Optia except for collections performed in the timeframe between May 2012 and March 2013, when COBE Spectra AutoPBSC (Terumo BCT) was used. The minimum collection target was 2.0×10^6/kg $CD34^+$ cells. All University Hospitals used standard volume leukaphereses with a daily circulated estimated total blood volume ranging from 2 to 3. The daily $CD34^+$ cell apheresis yield was analyzed in the stem cell laboratories of each participating university hospital.

Table 2. Blood graft cellular composition measured after thawing in 36 MCL patients

Blood graft content (× 10^6 cells/kg)	Patients mobilized without plerixafor (n = 27)	Patients mobilized with plerixafor (n = 7)	p value
$CD34^+$ cells without 7-AAD	4.4 (1.3–14.9)	2.7 (0.8–4.5)	**0.022**
$CD34^+$ cells with 7-AAD	3.6 (1.0–14.3)	1.9 (0.6–3.4)	**0.016**
$CD34^+CD133^+CD38^-$ cells	0.09 (0.006–0.35)	0.07 (0.009–0.18)	0.594
$CD3^+$ cells	50.5 (2.1–405.4)	112.3 (69.7–406.6)	**0.009**
$CD3^+CD4^+$ cells	34.4 (1.5–107.1)	65.9 (32.4–148.8)	**0.006**
$CD3^+CD8^+$ cells	23.4 (0.7–331.0)	71.0 (16.1–286.0)	**0.020**
$CD19^+$ cells	0.0 (0.0–0.5)	0.0 (0.0–100.2)	0.923
NK cells	3.6 (0.2–56.9)	7.0 (0.4–23.2)	0.277

Data are presented as median (range). 7-AAD, 7-aminoactinomycin.

Graft Processing and Analysis of Graft Cellular Composition

Dimethyl sulfoxide was added to a final concentration of 10% to the graft bags to protect the cells during cryopreservation. Two 0.5-mL samples were obtained from each apheresis product for subsequent graft cellular composition analyses. The grafts and samples were cryopreserved in vapor phase nitrogen (−170°C) using a freezer with a controlled-rate freezing program.

After thawing, the graft composition analyses were centrally performed by a single experienced flow cytometrist at the Department of Microbiology, University of Eastern Finland, Kuopio. FACSCanto flow cytometry system (Becton Dickinson; San Jose, CA, USA) was used for cell composition analyses. 7-aminoactinomycin was used to identify viable $CD34^+$ cells. CD34, CD38, CD133, and CD45 antibodies were used to distinguish $CD34^+$ cells and $CD34^+$ subclasses. The antibodies were delivered by Becton Dickinson except the CD133, which came from Miltenyi Biotech GmbH, Bergisch Gladbach, Germany. The T, B, and NK cell counts as well as the $CD3^+CD4^+$ and $CD3^+CD8^+$ T cell subpopulations were distinguished using both CD3/CD8/CD45/CD4 and CD3/CD16+CD56/CD45/CD19 reagents (BD Multitest; Becton Dickinson) with tubes (BD Trucount, Becton Dickinson).

HDT and Posttransplant Follow-Up

The HDT used in all patients was BEAM (carmustine 300 mg/m^2 on day −6, etoposide 100 mg/m^2 b.i.d. from day −5 to day −2, cytarabine 200 mg/m^2 b.i.d. from day −5 to day −2 and melphalan 140 mg/m^2 on day −2) followed by graft infusion on day 0. Thereafter, the patients were given either daily filgrastim 5 μg/kg (n = 8, 18%) or, on day +1 after graft infusion, a single 6 mg dose of pegfilgrastim (n = 17, 39%) or lipegfilgrastim (n = 19, 43%), as this was an institutional policy.

The definition of posttransplant neutrophil and platelet (PLT) recovery were the number of days from the graft infusion (day 0) to the first of three consecutive days with a neutrophil count >0.5 × 10^9/L and PLT count >20 × 10^9/L without PLT infusions. Complete blood counts were analyzed on day +15 and at 1, 3, 6, and 12 months after transplantation in the local central hospitals responsible for the follow-up of the patients in order to determine the long-term hematologic recovery. In case of a MCL relapse, the follow-up for hematologic recovery was discontinued. Non-relapse mortality was defined as a death of any cause without prior MCL relapse. The definition of PFS was time from ASCT to MCL relapse or death. Overall survival was defined as time from ASCT to death from any cause.

Statistical Analysis

The statistical analyses were performed using SPSS Statistics version 27 (IBM Corporation, Armonk, NY, USA). Continuous variables are presented as medians and ranges. The statistical tests used to assess statistical significance were Mann-Whitney U test for non-parametric continuous variables and Pearson's χ^2 test for categorical variables.

Receiver operating curve (ROC) analyses were performed to determine optimal count offs for continuous variables correlating with hematological recovery, PFS, and OS. The continuous hematological recovery parameters were transformed into categorical variables using median as a cutoff point to enable ROC analyses. Youden's index was applied to optimize the cutoffs in ROC analyses.

The survival analyses were performed with Kaplan-Meier method with log-rank test or with Cox regression model. The Cox regression model results are presented with hazard ratios and 95% confidence intervals (CIs). Two-tailed p values <0.05 were considered statistically significant.

Results

Mobilization and Collection of $CD34^+$ Cells

The median time from MCL diagnosis to HD-AraC mobilization was 122 days (range 54–203). The G-CSF used for mobilization purposes was a single subcutaneous pegfilgrastim injection with either 6 mg (n = 7, 17%) or 12 mg (n = 11, 26%) dose in 18 patients, a single 6 mg dose of lipegfilgrastim in 12 patients (29%), and a daily dose of filgrastim with either 5 μg/kg (n = 6, 14%) or 10 μg/kg (n = 6, 14%) dose until the completion of graft collection in 12 patients. Altogether 8 patients (19%) received plerixafor with a median dose 0.25 mg/kg (0.16–0.32) preemptively with a median of 4.6 × 10^6/L (1.0–9.0) blood $CD34^+$ cell count before the plerixafor injection.

The median number of aphereses was 1 (1–4), and total collected graft $CD34^+$ cell yield measured before cryopreservation was 4.6 × 10^6/kg (2.0–16.8). The median peak blood $CD34^+$ cell count during mobilization period was 58 × 10^6/L (8–389). There was no statistically significant difference in the peak blood $CD34^+$ cell count, in the median collected graft $CD34^+$ cell count, or

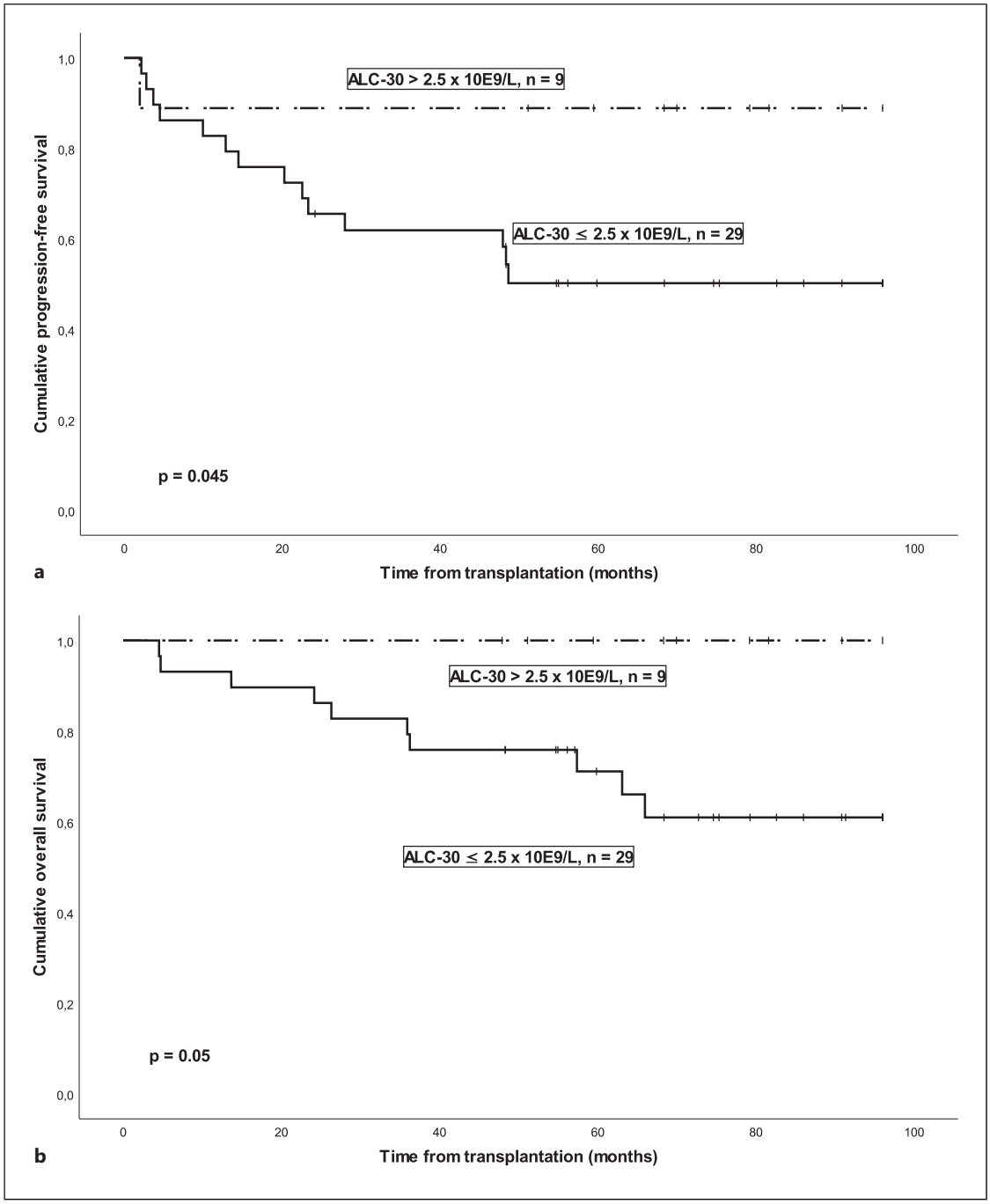

Fig. 1. Progression-free (**a**) and overall survival (**b**) of MCL patients according to the absolute lymphocyte count at 1 month after ASCT (ALC-30). The figures are truncated at 8 years.

in the number of aphereses needed in regard to the bone marrow infiltration at diagnosis, MIPI risk group, or the type of G-CSF used in mobilization.

Graft Cellular Composition

After thawing, the median viable (with 7-AAD) $CD34^+$ cell count in the graft was 3.3×10^6/kg (0.6–14.3). The median loss of viable $CD34^+$ cells during processing and cryopreservation was 23% (0–77). In patients who received plerixafor due to mobilization difficulties, the post-thaw viable $CD34^+$ cell count was lower (1.9 vs. 3.6×10^6/kg, $p = 0.016$), and the graft lymphocyte subset counts were higher (Table 2).

Hematologic and Immune Recovery

The median time to neutrophil recovery was 10 days (8–14) and time to platelet recovery was 12 days (6–49), respectively. A higher viable graft $CD34^+$ cell count (>3.0×10^6/kg, $n = 19$) was linked with faster neutrophil (9 vs. 10

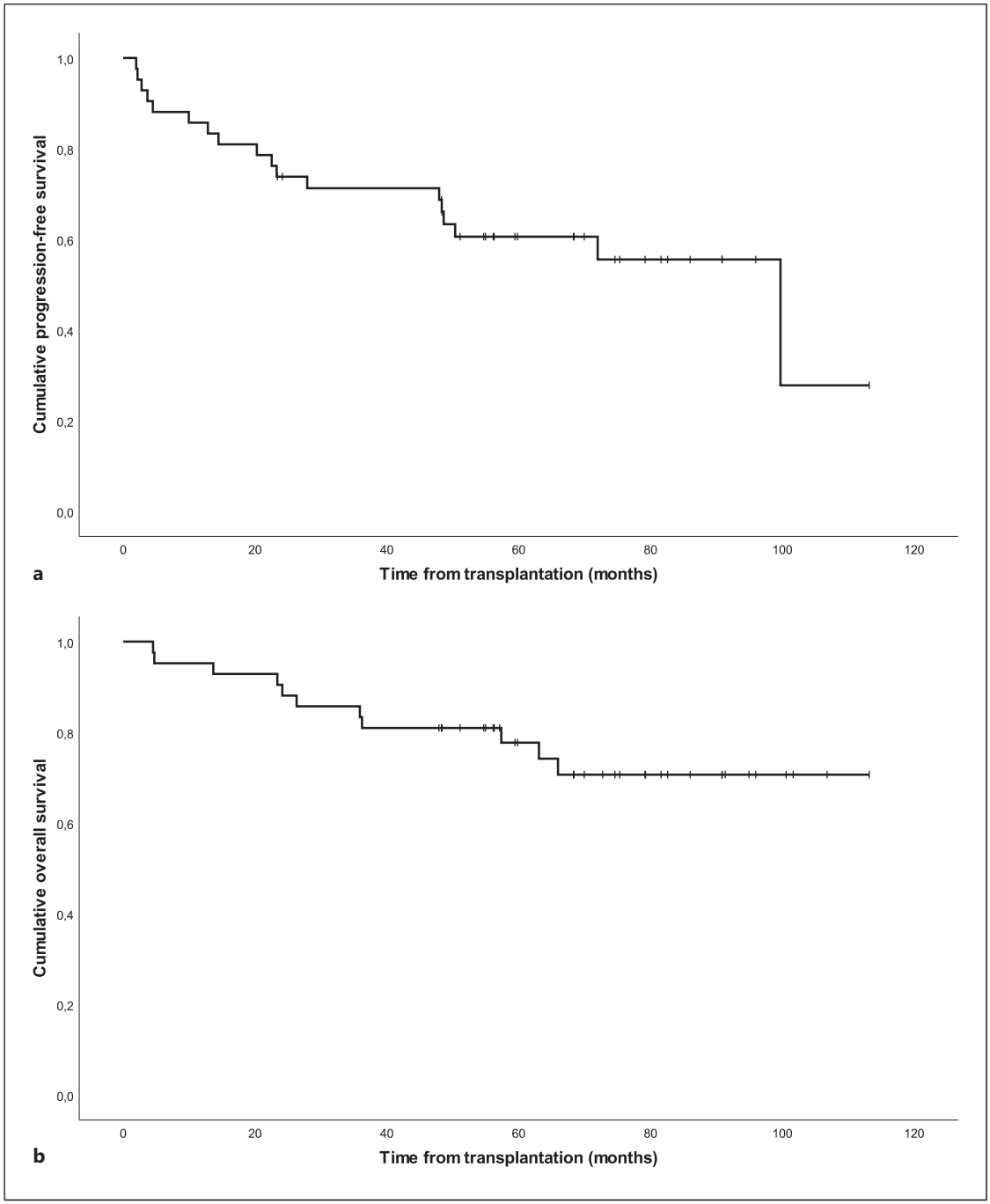

Fig. 2. Progression-free (**a**) and overall survival (**b**) after ASCT in MCL patients (n = 42).

days, $p = 0.02$) and platelet recovery (11 vs. 15 days, $p = 0.03$). The median platelet count was higher also at 1 month after ASCT (148 vs. 74 × 10^9/L, $p = 0.015$) in patients with >3.0 × 10^6/kg $CD34^+$ cell count in the infused graft. The graft $CD34^+CD133^+CD38^-$ cell count did not impact statistically significant platelet recovery in the short or long term (data not shown). The proportion of patients with PLT counts below 50 × 10^9/L declined over time, being 14.6% (n = 6/41) at 1 month, 8.3% (n = 3/36) at 3 months, 2.9% at six (n = 1/35), and 3.0% at 12 months (n = 1/33) after ASCT.

The median absolute lymphocyte count at day +15 after ASCT (ALC-15) was 0.6 × 10^9/L (0.04–3.7) and at day +30 (ALC-30) 1.9 × 10^9/L (0.5–8.1). While ALC-15 was not prognostic, ALC-30>2.5 × 10^9/L was associated with better PFS and OS (Fig. 1).

Posttransplant Outcome

After ASCT, febrile neutropenia was observed in 32 patients (76%), and culture-positive bloodstream infections were documented in 4 patients (9.5%). None of the

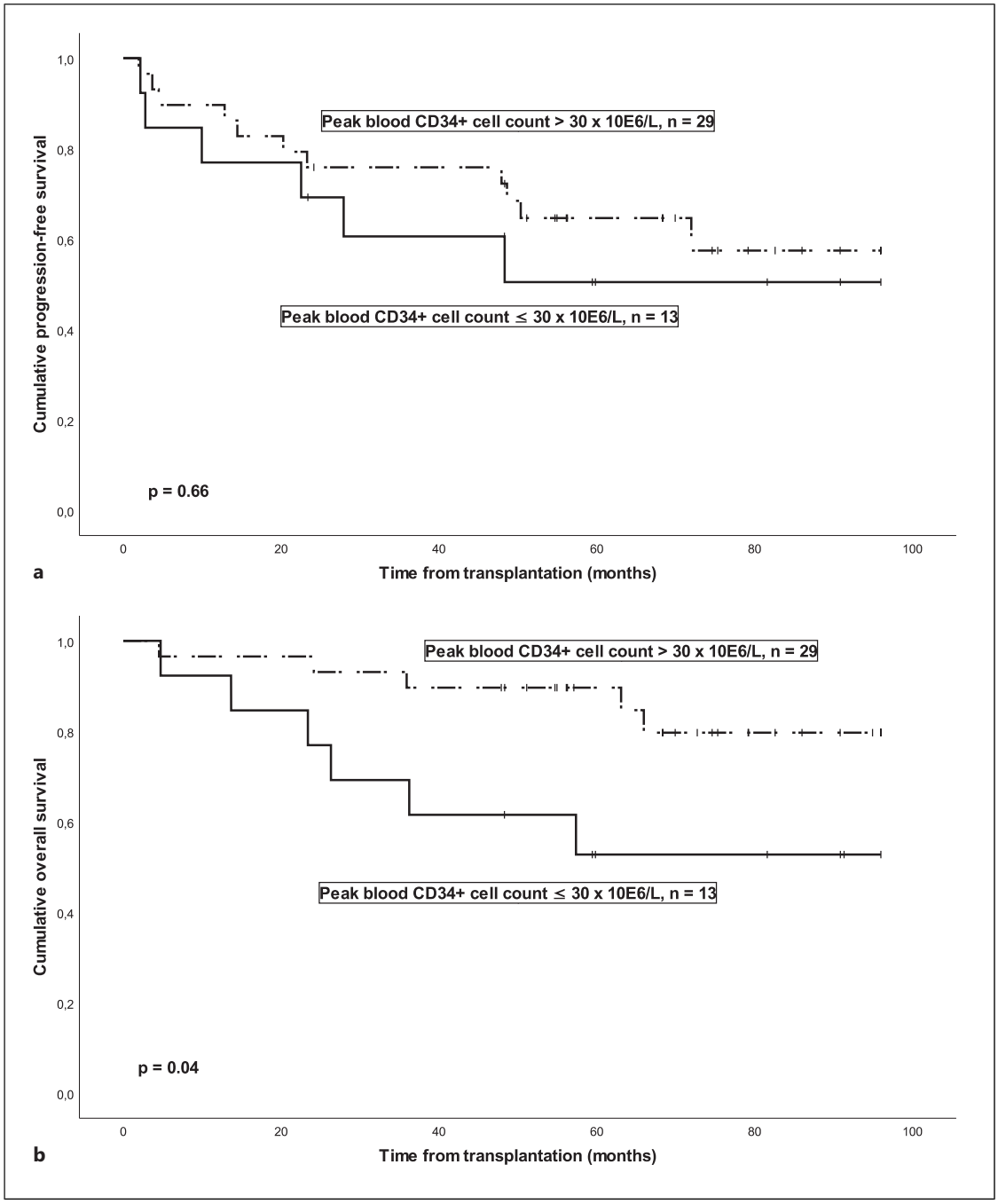

Fig. 3. Progression-free (**a**) and overall survival (**b**) of MCL patients according to the peak blood CD34$^+$ cell count. The figures are truncated at 8 years.

patients needed treatment in the intensive care unit. A higher graft CD34$^+$ cell count (>2.5 × 10^6/kg) was associated with shorter duration of hospitalization during ASCT period (20 vs. 22 days, $p = 0.006$). There were no early deaths within 100 days after ASCT.

After a median follow-up of 75 months (48–113), 18 patients (43%) had suffered a MCL relapse and 11 patients (26%) had died, respectively (Fig. 2). The leading cause of death was MCL ($n = 8/11$, 73%). One patient died of graft-versus-host disease following subsequent allogeneic stem cell transplantation, and 1 patient died due to lung cancer. A disease relapse within 2 years after ASCT ($n = 11$) was associated with a clearly worse OS (median 36 months vs. not reached [NR], $p < 0.001$).

In terms of mobilization parameters, a higher peak blood CD34$^+$ count (>30 × 10^6/L, $n = 23$) was associated with better OS (median NR vs. 57 months, $p = 0.04$) with no impact on PFS (median NR in either group, $p = 0.66$,

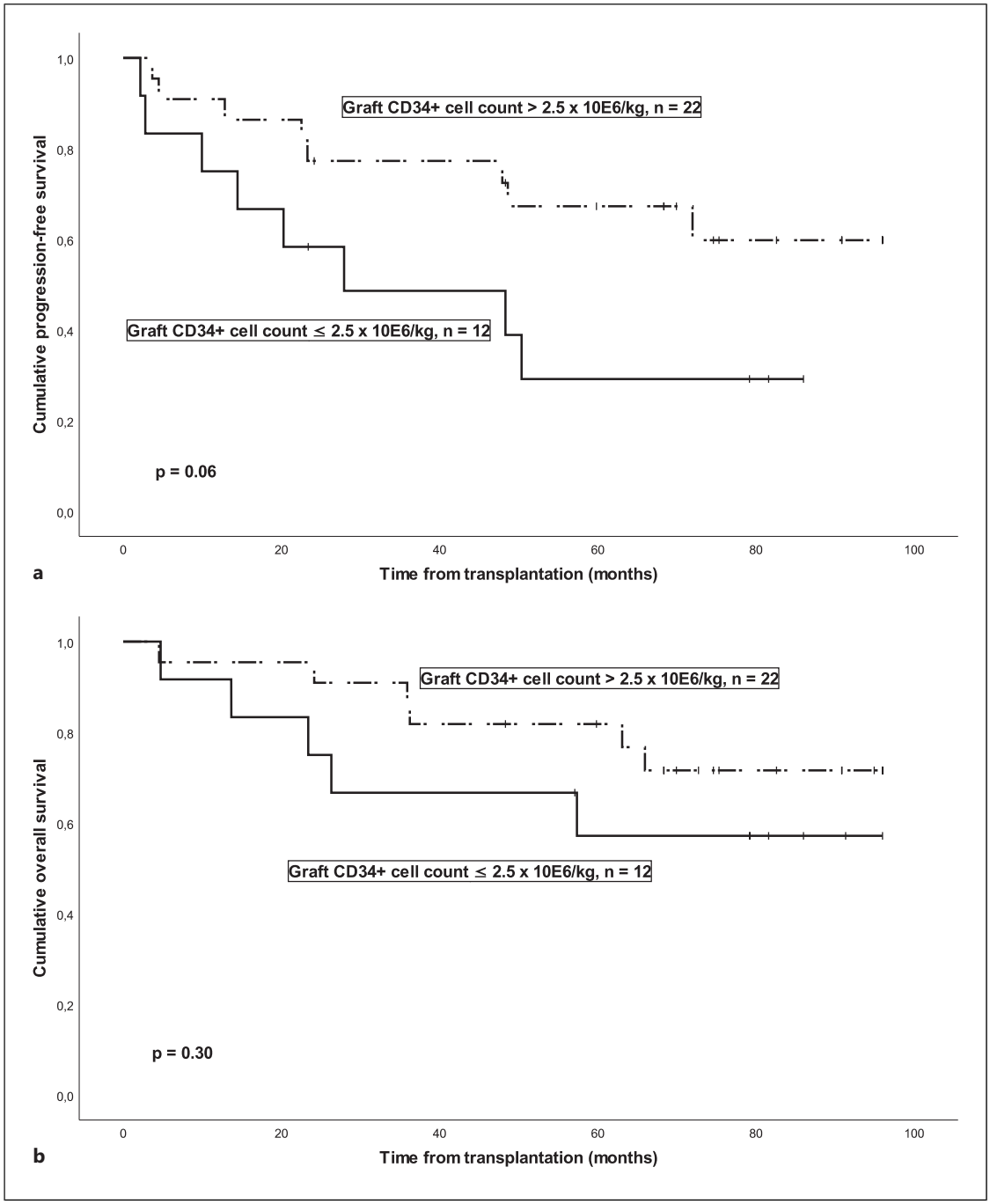

Fig. 4. Progression-free (**a**) and overall survival (**b**) of MCL patients according to the infused graft viable $CD34^+$ cell count. The figures are truncated at 8 years.

Fig. 3). In patients who received plerixafor, the PFS and OS were comparable with the rest of the patient cohort (online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000531799).

The median PFS in patients with a higher post-thaw viable graft $CD34^+$ cell count (>2.5 × 10^6/kg, $n = 22$) was superior (100 vs. 28 months, $p = 0.06$), while no difference in OS according to the graft $CD34^+$ count was observed (median NR in either group, $p = 0.30$, Fig. 4). A very low graft $CD3^+CD8^+$ cell count (≤10 × 10^6/kg, $n = 7$) was associated with worse PFS (HR 4.136, 95% CI 1.547–11.059, $p = 0.005$). A very low graft $CD3^+$ (≤22.5 × 10^6/kg, $n = 5$; HR 2.859, 95% CI 0.980–8.338, $p = 0.05$) and NK cell counts (≤1.4 × 10^6/kg, $n = 8$; HR 2.375, 95% CI 0.891–6.330, $p = 0.08$) were also linked with a trend toward worse PFS. In contrast, a higher graft $CD3^+CD4^+$ cell count (>40 × 10^6/kg, $n = 16$) was linked with a trend toward improved PFS (HR 0.415, 95% CI 0.146–1.181,

Table 3. Associations between graft cellular components and selected patient characteristics and PFS and overall survival in MCL patients in univariate Cox regression analysis

	PFS		OS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age >60 years	1.143 (0.440–2.971)	0.784	3.074 (0.663–14.259)	0.151
Sex (female)	0.641 (0.210–1.961)	0.436	1.665 (0.486–5.705)	0.417
Peak blood $CD34^+$ cell count >30 × 10^6/L	0.803 (0.299–2.158)	0.663	**0.294 (0.089–0.972)**	**0.045**
Use of plerixafor	1.284 (0.458–3.598)	0.635	3.139 (0.915–10.763)	0.069
Graft cellular component (× 10^6/kg)				
$CD34^+$ cells with 7-AAD >2.5	0.400 (0.150–1.072)	0.068	0.541 (0.165–1.778)	0.321
$CD3^+$ cells ≤22.5	2.859 (0.980–8.338)	0.054	1.475 (0.189–11.525)	0.711
$CD3^+CD4^+$ cells >40	0.415 (0.146–1.181)	0.099	1.495 (0.455–4.911)	0.508
$CD3^+CD8^+$ cells ≤10	**4.136 (1.547–11.059)**	**0.005**	0.424 (0.054–3.317)	0.413
NK cells ≤1.4	2.375 (0.891–6.330)	0.084	1.202 (0.319–4.533)	0.786
Disease status at transplantation				
I CR	1			
I PR	1.424 (0.522–3.885)	0.490		
Progressive disease	**10.840 (1.180–99.617)**	**0.035**		

p = 0.10). The graft $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, and NK cell counts had no impact on OS (Table 3). A higher absolute lymphocyte count (>2.5 × 10^9/L, n = 8) at 1 month after ASCT (ALC-30) was associated with better PFS (NR *vs.* 99 months, p = 0.045) and also OS (median NR in either group, p = 0.05, Fig. 1). The ROC analysis data regarding mobilization parameters, graft cellular components, and lymphocyte count at 1 month after ASCT are presented in online supplementary Table 1.

Discussion

Based on the prospective multicenter GOA study population, this study evaluated the impact of $CD34^+$ cell mobilization and graft cellular composition on outcome in MCL patients. A better $CD34^+$ mobilization capacity in terms of higher peak blood $CD34^+$ cell count was linked with better OS. A higher infused graft viable $CD34^+$ cell count was associated with faster early platelet and neutrophil recovery. In addition, very low graft $CD3^+CD8^+$ cell count was linked with worse PFS. Higher total lymphocyte count 1 month after ASCT was linked with improved survival, reflecting better immune recovery.

The best induction therapy for MCL patients is under debate. In the MCL2-study, a median 6-year PFS of 66% and OS of 70% were observed after rituximab plus maxi-CHOP alternating with rituximab and HD-AraC-containing induction therapy followed by ASCT [14]. Roughly comparable results have been published also with different induction regimens [15–17]. Consolidation with ASCT following first-line chemoimmunotherapy is recommended by several international guidelines [1, 18, 19]. The results from a large randomized European MCL Network study (NCT02858258) which evaluates the addition of ibrutinib to the first-line chemoimmunotherapy with or without ASCT may challenge the role of ASCT in the near future. Especially patients in complete response after induction treatment [20] and those without a TP53 mutation [4] seem to benefit the most from ASCT. Our results with an induction according to MCL2 protocol followed by ASCT are in line with previous data with a PFS of 57% and OS of 74% after a median follow-up more than 6.5 years from the diagnosis. In our study, there was no difference in PFS or OS between patients transplanted in first complete versus partial remission, possibly due to the lack of routine use of PET scans in response evaluation.

Several previous studies have demonstrated a linkage between higher collected graft $CD34^+$ cell count and improved survival after ASCT in NHL patients [5–7, 21]. None of these studies have included more detailed graft composition analyses. In this study with a concordant MCL2-like first-line treatment in the vast majority of patients followed by HD-AraC mobilization, higher peak blood $CD34^+$ cells correlated with better OS. However, the graft $CD34^+$ cell count had no statistically significant impact on outcome. Thus, it is possible that other graft cells than $CD34^+$ cells may, at least in part, explain these findings. It is also possible that mobilization capacity serves merely as a surrogate marker, and patient-related factors and disease biology could explain both worse mobilization and survival. Randomized studies on the topic are lacking, and the mechanism responsible for better survival regarding higher collected $CD34^+$ yields remains unclear.

The addition of plerixafor in poorly mobilizing NHL patients has increased the absolute number of lymphocytes and also the $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, and NK cell subset counts in the graft in previous studies [8, 9, 22]. Similar impact on graft cellular composition was observed also in this study. Higher amount of lymphocytes in the graft

has correlated with higher posttransplant lymphocyte count at day +15 after transplantation in NHL patients [23]. A lymphocyte count ≥0.5 × 10^9/L on day +15 posttransplant has correlated with improved PFS and OS also in MCL patients in a retrospective analysis [24], respectively. However, this was not observed in our study but a higher lymphocyte count 1 month after ASCT was associated with better outcome.

We observed a correlation between higher graft $CD3^+CD8^+$ cell count and better PFS in this study. Contradictory results regarding the role of $CD3^+CD8^+$ cells have also been published. A higher $CD3^+CD8^+$/$CD3^+CD4^+$ ratio and a higher central memory $CD3^+CD8^+$ cell count in the blood measured 28 days prior to ASCT correlated with worse PFS in DLBCL and MCL patients in a retrospective study in which the $CD3^+CD8^+$/$CD3^+CD4^+$ ratio at day + 100 after ASCT was associated with worse OS [25]. These findings suggest that immune profile of the patients is pivotal in disease control. More detailed analyses regarding the role of immune profile over the disease course in MCL should be performed in future studies.

To our knowledge, this is the first study to assess autograft cellular composition in more detail in MCL patients. The induction treatment given to patients prior to ASCT in this study reflects the current treatment landscape. Other obvious benefits of this study are the use of a homogenous mobilization regimen, prospective study design with centralized graft cellular composition analyses, and a decent follow-up. However, some limitations should be acknowledged. The size of the study population is quite small, and thus, multivariate analyses could not be performed reliably. Data on MCL histology and Ki-67 proliferation index were lacking in a considerable amount of patients and, thus, not reported. Finally, this kind of study design does not allow for evaluation of causality.

To conclude, better mobilization capacity, higher infused graft $CD3^+CD8^+$ cell count, and earlier lymphocyte recovery had a positive prognostic impact following ASCT in MCL patients. These results need to be validated in another study with a larger patient cohort.

Acknowledgments

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Statement of Ethics

All patients gave their written informed consent prior to inclusion into the study. The North Savo Hospital District Ethics Committee gave approval to the GOA study in 2012 (13/2012) with an amendment in 2016 regarding NHL patients transplanted at Kuopio University Hospital in 2017–2018. The study was performed following the principles of the Declaration of Helsinki.

Conflict of Interest Statement

Dr. Partanen reports honoraria from Behring and AbbVie and has participated in Scientific Advisory Board meetings organized by AbbVie, Janssen-Cilag, Novartis, and Takeda. Dr. Varmavuo reports consultancy fees from AbbVie, Amgen, Celgene, Janssen-Cilag, Roche, and Sanofi. Dr. Mäntymaa reports support for attending a meeting from BeiGene. Other authors report no conflicts of interest.

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Author Contributions

Antti Turunen, Esa Jantunen, and Anu Partanen: study design, data collection, data analysis, and writing. Outi Kuittinen, Hanne Kuitunen, Kaija Vasala, Karri Penttilä, Minna Harmanen, Leena Keskinen, and Pentti Mäntymaa: data collection. Jukka Pelkonen, Pentti Mäntymaa, and Ville Varmavuo: study design. All authors have read and approved the manuscript.

Data Availability Statement

All data analyzed during this study are included in the article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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