

ORIGINAL ARTICLE

Early lymphocyte recovery after autologous stem cell transplantation predicts superior survival in mantle-cell lymphoma

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Autologous stem cell transplantation (ASCT) is an effective treatment strategy for mantle-cell lymphoma (MCL) demonstrating significantly prolonged progression-free survival (PFS) when compared to interferon- α maintenance therapy of patients in first remission. The study of absolute lymphocyte count at day 15 (ALC-15) after ASCT as a prognostic factor in non-Hodgkin lymphoma (NHL) included different lymphoma subtypes. The relationship of ALC-15 after ASCT in MCL has not been specifically addressed. We evaluated the impact of ALC-15 recovery on survival of MCL patients undergoing ASCT. We studied 42 consecutive MCL patients who underwent ASCT at the Mayo Clinic in Rochester from 1993 to 2005. ALC-15 threshold was set at 500 cells/ μ l. The median follow-up after ASCT was 25 months (range, 2–106 months). The median overall survival (OS) and PFS times were significantly better for the 24 patients who achieved an ALC-15 \geq 500 cells/ μ l compared with 18 patients with ALC-15 $<$ 500 cells/ μ l (not reached vs 30 months, $P < 0.01$ and not reached vs 16 months, $P < 0.0006$, respectively). Multivariate analysis demonstrated ALC-15 to be an independent prognostic factor for OS and PFS. The ALC-15 \geq 500 cells/ μ l is associated with a significantly improved clinical outcome following ASCT in MCL. *Bone Marrow Transplantation* (2006) 37, 865–871. doi:10.1038/sj.bmt.1705342; published online 13 March 2006

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Introduction

Mantle-cell lymphoma (MCL) is characterized by an aggressive clinical course and poor prognosis with a median survival of only 3–4 years.^{1,2} Unlike other aggressive non-

Hodgkin lymphoma (NHL), patients with MCL have a poorer complete response rate with standard anthracycline-based or non-anthracycline-based regimens.^{3,4}

High-dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT) is an effective form of treatment for relapsed NHL.⁵ In the case of MCL, this type of treatment has been shown to be relatively successful, with 50–70% of patients free of disease at 2 or 3 years, if patients are transplanted in first remission.^{6,7} The European MCL Network completed the only currently available prospective randomized study comparing ASCT vs interferon- α (IFN α) maintenance in 1st remission in patients with advanced stage MCL.⁸ This multicenter trial demonstrates a significant improvement in progression-free survival (PFS) of patients with advanced stage MCL who were treated with myeloablative radiochemotherapy followed by ASCT compared with patients on IFN α maintenance. The outcome of MCL patients after ASCT has been associated with age and levels of C-reactive protein at diagnosis, levels of β 2-microglobulin at the time of diagnosis or transplantation, conditioning regimens including total body irradiation (TBI), morphologic variants, tumor score, and expression of P53.^{9–11}

Absolute lymphocyte count (ALC) recovery \geq 500 cells/ μ l at day 15 (ALC-15) after ASCT has been reported to be a powerful and independent prognostic factor for clinical outcome in NHL,^{12–14} Hodgkin lymphoma,^{12,15} multiple myeloma (MM),¹⁴ acute myelogenous leukemia,¹⁶ amyloidosis,¹⁷ and breast cancer.^{18,19} The fact that the recovery of lymphocytes after ASCT influences survival points toward the clinical presence of an autologous graft-vs-tumor effect, as immune reconstitution after ASCT, may play an important role in the antitumor response.

To assess whether ALC-15 post ASCT has prognostic significance in MCL post ASCT, we conducted a retrospective analysis of the role of ALC-15 on survival in MCL patients undergoing ASCT.

Patients and methods

Patient population

Forty-two consecutive patients with the diagnosis of MCL underwent ASCT at the Mayo Clinic between November

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1993 and March 2005. Twenty-one MCL patients in this study were included in a previous publication.²⁰ Data from transplant recipients used in this retrospective study were collected prospectively and entered into a computerized database. Response to therapy, relapse, and survival data were updated continuously. No patients were lost to follow-up. All patients gave written, informed consent allowing the use of their medical records for medical research. Approval for the retrospective review of these records was obtained from the Mayo Clinic Institutional Review Board and was in accordance with US federal regulations and the Declaration of Helsinki.

End points

The primary end point of the study was to determine if ALC-15 after ACST is a prognostic factor for PFS or overall survival (OS) in patients with MCL undergoing ASCT. The ALC-15 was calculated from the standard complete blood cell count at day 15 after ASCT.

Prognostic factors

This study used the following prognostic factors for patients with MCL: international age-adjusted prognostic index (IPI):²¹ (age (≥ 60 vs < 60), lactate dehydrogenase (LDH) $>$ normal, performance status (PS-ECOG) (≥ 2 vs < 2), extranodal sites (≥ 2 vs < 2), and stage (III/IV vs I/II)), in addition to the number of pre-transplant treatments, stem cell source (bone marrow (BM) vs peripheral blood stem cells (PBSCs)), type of conditioning regimen, disease status (complete response (CR)1/partial response (PR)1 vs CR $>$ 1/PR $>$ 1) before transplantation based on response to prior treatments, neutrophil recovery at day 15 after ASCT, and platelet recovery at day 15 after ASCT.

Conditioning regimens

Conditioning regimens were as follows: nine patients received BEAC (BCNU (300 mg/m²), Etoposide (100 mg/m²), ARA-C (100 mg/m²), and Cyclophosphamide (35 mg/kg)), 30 patients received BEAM (BCNU (300 mg/m²), Etoposide (100 mg/m²), ARA-C (100 mg/m²), and Melphalan (140 mg/m²)), and three patients received Cyclophosphamide (60 mg/m²) and TBI (12 Gy). All patients underwent stem cell re-infusion after HDC. Hematologic engraftment was defined as absolute neutrophil count (ANC) reaching 500 cells/ μ l or more for more than 3 consecutive days.

Stem cell source

The stem cell source for the ASCT included BM or PBSCs. Forty-one patients received PBSCs, and one received a mixture of PBSCs and BM stem cells. The decision to change from BM stem cells to PBSC was made when PBSCs became the standard for stem cell collection. Patients who did not mobilize adequate stem cells through PBSC underwent BM harvest.

Response and survival

Complete remission (CR) was defined as complete regression of all measurable or evaluable disease including

radiologically demonstrable disease, BM involvement, or peripheral blood involvement. Partial remission (PR) was defined as a reduction in the sum of the products of measurable lesions' longest diameters and perpendicular diameters of 50% or greater, with a 30% or greater decrease in hepatomegaly or splenomegaly (measured from the costal margin), if there was previous known liver or spleen involvement. Disease progression was defined as a 25% or more increase in the sum of the products of the longest diameter and its perpendicular diameter of measurable lesion(s) from the pre-study measurement, the appearance of new lesions, or a 2-cm increase in spleen or liver size due to lymphoma.

Overall survival time was measured from the date of transplantation to date of death or last follow-up. Progression-free survival was defined as time from transplantation to disease progression, relapse, or death.

Statistical analysis

The OS and PFS times were analyzed using the method described by Kaplan and Meier.²² Differences between survival curves were tested for statistical significance using the two-tailed log-rank test. The Cox proportional hazards model²³ was used to assess ALC-15 as a prognostic factor for post transplant OS and PFS times as well as to adjust for other known prognostic factors. Hazard ratios reported are for risks associated with patients having high (greater than 500 cells/ μ l) vs low (less than 500 cells/ μ l) ALC values. The cutoff of an ALC of 500 cells/ μ l or more was based on data from our previous study.¹⁴ Multivariate analysis using Cox regression models tested all variables with a $P < 0.2$ on univariate analysis. Pearson's χ^2 or approximation to the Fisher's exact test was used to determine relations between nominal variables; nonparametric tests were used for continuous variables. All P -values were two-sided, and statistical significance was set at $P < 0.05$.

Accuracy of ALC-15 after ASCT as a predictor of PFS during the study follow-up was evaluated by the Harrell's method, that is, concordance (c)-statistic,²⁴ which is equivalent to the area under the receiver operating characteristic (ROC) curve. This statistic may vary from 0 to 1, with 1 indicating perfect discrimination and 0.5 indicating the value to be expected by chance alone.

Results

Patient characteristics

A total of 42 patients (nine female and 33 male subjects) were included in the study; the median age for the cohort group at transplant was 57 years (range, 37–71). Forty of the patients had a histologic type of MCL of intermediate variant and two had blastic mantle-cell type. The analysis of patient baseline characteristics that may impact upon survival and recovery of ALC-15 after ASCT show similar distribution of characteristics when comparing patients who recovered ALC-15 ≥ 500 cells/ μ l after ASCT and patients who did not (Table 1). We identified no association between neutrophil recovery at day 15 and ALC-15 ($r_s = 0.03$, $P = 0.84$), platelet recovery at day 15 and

Table 1 Baseline characteristics of patients according to recovery of the absolute lymphocyte count at day 15 after ASCT (ALC-15)

Characteristics	ALC-15 ≥ 500 cells/ μ l (N = 24)	ALC-15 <500 cells/ μ l (N = 18)	P-value
Age			0.92
≥ 60	7	5	
< 60	17	13	
Sex			0.51
Female	6	3	
Male	18	15	
LDH			0.76
\leq Normal	12	9	
> Normal	3	3	
PS (ECOG)			0.38
≥ 2	1	0	
< 2	23	18	
Stage (Ann Arbor)			0.16
I/II	5	1	
III/IV	19	17	
# pre-transplant treatments			0.90
1	12	10	
2	11	7	
3	1	1	
Initial treatment regimen			1
2-CDA	2	2	
CHOP	5	4	
R-CHOP	3	3	
HyperCVAD	1	1	
Conditioning regimen			0.23
BEAC	2	4	
BEAM	20	14	
Cyclophosphamide/TBI	2	0	
Laboratory tests prior to mobilization, median (range)			
ALC ($\times 10^9/\mu$ l)	1.01 (0.31–1.94)	1.2 (0.78–2.17)	0.23
Hb (g/dl)	12.5 (10–16.5)	12.8 (10.3–14.8)	0.49
WBC ($\times 10^9/\mu$ l)	4.95 (3.1–8.5)	5.45 (3.5–9.6)	0.44
Platelets ($10^3/\mu$ l)	192 (136–526)	216 (128–544)	0.89
Laboratory tests at day 15 after ASCT, median (range)			
Hb (g/dl)	10.2 (7.2–12.6)	9.75 (8.3–11.3)	0.08
Neutrophils ($\times 10^9/\mu$ l)	1.43 (0.11–4.4)	1.33 (0.1–2.79)	0.82
Platelets ($\times 10^9/\mu$ l)	60.5 (17–239)	44.5 (17–115)	0.17
Disease status at transplant			0.15
CR1	11	4	
PR1	2	2	
CR2	6	3	
PR2	4	9	
CR3	1	0	
# CD34 ⁺ cells transplanted			0.12
Median	4.37 $\times 10^6$	2.87 $\times 10^6$	
(range)	(2.28–8.44 $\times 10^6$)	(2.0–10.3 $\times 10^6$)	
Post transplant cytokines			0.40
G-CSF	3	4	
GM-CSF	21	14	

Abbreviations: ASCT = autologous stem cell transplantation; BEAC = BCNU (300 mg/m²), Etoposide (100 mg/m²), ARA-C (100 mg/m²), and Cyclophosphamide (35 mg/kg); BEAM = BCNU (300 mg/m²), Etoposide (100 mg/m²), ARA-C (100 mg/m²), and Melphalan (140 mg/m²); CR1 = complete response 1; PR1 = partial response 1; LDH = lactate dehydrogenase; PS = performance status; 2-CDA = Cladribine (3.4 mg/m²); CHOP = Cyclophosphamide (750 mg/m²), Doxorubicin (50 mg/m²), vincristine (1.4 mg/m²), and prednisone (100 mg/m²); R-CHOP = Rituxan (375 mg/m²), Cyclophosphamide (750 mg/m²), Doxorubicin (50 mg/m²), vincristine (1.4 mg/m²), and prednisone (100 mg/m²); HyperCVAD = Cyclophosphamide (300 mg/m²), Doxorubicin (50 mg/m²), vincristine (2 mg/day), and dexamethasone (40 mg/day).

ALC-15 ($r_s=0.193$, $P=0.22$), or the use of post transplant cytokines (granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) and ALC-15 ($P=0.21$).

Prognostic factors for progression and survival

The median follow-up after ASCT was 25 months (range, 2–106 months). At the time of analysis, 25 of the 42 patients were alive and 17 were dead. Median survival was 47 months. Causes of death were AML in one case, progression of lymphoma in 14 patients, sepsis in one case, and unknown in one case. The patient who died with AML had ALC-15 ≥ 500 cell/ μ l; of the 14 patients who died of lymphoma progression, only three had ALC-15 ≥ 500 cell/ μ l and the patient who died with sepsis had ALC-15 < 500 cell/ μ l. All patients were treated similarly regarding supportive care (antibiotics, transfusions, growth factors) according to Mayo Clinic protocols.

Median OS (Figure 1) and PFS (Figure 2) times were significantly better for patients with an ALC-15 ≥ 500 cell/ μ l than for those with an ALC-15 < 500 cell/ μ l (not reached vs 30 months, $P<0.01$ and not reached vs 16 months, $P<0.0006$, respectively).

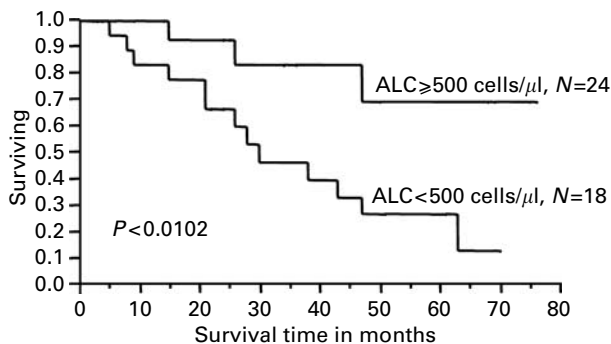


Figure 1 Overall survival for 42 patients with MCL after ASCT as a function of recovery of the absolute number of lymphocytes at day 15. Median OS for patients with ALC ≥ 500 cells/ μ l was not reached and median OS for patients with ALC < 500 cells/ μ l was 30 months ($P=0.01$, log-rank test).

Prognostic factors were tested as predictors for OS and PFS for the 42 MCL patients studied (Table 2). Age at transplant (≥ 60 vs < 60), LDH, stage (III/IV vs I/II), IPI ≥ 2 vs < 2 , number of pre-transplant chemotherapy regimens (1 vs 2, or 3), neutrophil or platelet recovery at day 15, and type of conditioning regimen were not predictors of OS or PFS. Recovery of ALC-15 after ASCT (≥ 500 cells/ μ l vs < 500 cells/ μ l) and being transplanted in first CR/first PR vs second or more CR/PR were significant predictors of OS and/or PFS by univariate analysis. Age at transplant was also tested as a continuous variable and was not associated with disease progression or patient survival (data not shown). The effect of conditioning regimens was tested by comparing patients conditioned with BEAC to patients conditioned with BEAM. The three patients who received Cyclophosphamide/TBI were excluded. Presence of disease at extranodal sites and performance status (PS) were not included in the analysis because only one patient had two or more extranodal sites involved and only one patient had a PS ≥ 2 .

Recovery of ALC-15 ≥ 500 cells/ μ l after ASCT was identified as an independent prognostic factor for OS (HR = 0.24, $P=0.02$) and PFS (HR = 0.18, $P=0.0006$) by multivariate analysis when adjusted to disease status at

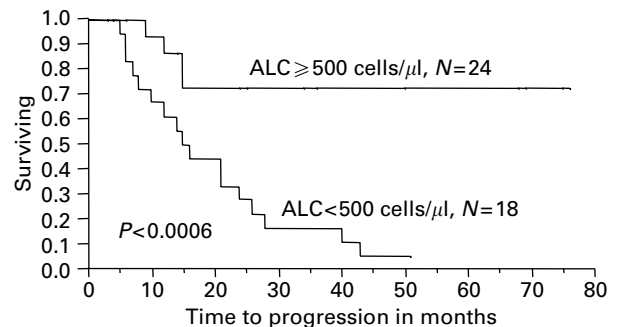


Figure 2 Progression-free survival for 42 patients with MCL after ASCT as a function of recovery of the absolute number of lymphocytes at day 15. Median OS for patients with ALC ≥ 500 cells/ μ l was not reached and median OS for patients with ALC < 500 cells/ μ l was 16 months ($P=0.0006$, log-rank test).

Table 2 Univariate analysis for patients with mantle cell lymphoma – overall survival (OS) and progression-free survival (PFS) rates

Prognostic factors at the time of transplantation	OS			PFS		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (≥ 60 vs < 60)	0.84	(0.23–2.43)	0.77	1.06	(0.38–2.62)	0.90
LDH (normal vs $>$ normal)	0.51	(0.03–2.89)	0.49	0.73	(0.11–2.81)	0.67
IPI (≥ 2 vs < 2)	1.08	(0.37–2.9)	0.87	1.48	(0.60–3.51)	0.38
Stage (III/IV vs I/II)	1.64	(0.31–30)	0.61	3.85	(0.79–69)	0.11
# pre-ASCT chemotherapy regimens (1 vs 2 or 3)	0.89	(0.31–2.45)	0.83	0.75	(0.31–1.80)	0.51
Condition regimen (BEAC vs BEAM)	1.35	(0.78–2.32)	0.27	1.34	(0.83–2.11)	0.21
ALC-15 (≥ 500 cells/ μ l vs < 500 cells/ μ l)	0.22	(0.05–0.70)	0.0086	0.19	(0.05–0.49)	0.0005
Disease status at ASCT (CR1/PR1 vs CR $>$ 1/PR $>$ 1)	0.42	(0.11–1.21)	0.11	0.25	(0.08–0.65)	0.0037
Neutrophil recovery at day 15 after ASCT	0.94	(0.47–1.79)	0.85	1.19	(0.68–2.04)	0.53
Platelet recovery at day 15 after ASCT	1.00	(0.98–1.02)	0.80	1.00	(0.99–1.01)	0.93

Abbreviations: ASCT = autologous stem cell transplantation; BEAC = BCNU (300 mg/ m^2), Etoposide (100 mg/ m^2), ARA-C (100 mg/ m^2), and Cyclophosphamide (35 mg/kg); BEAM = BCNU (300 mg/ m^2), Etoposide (100 mg/ m^2), ARA-C (100 mg/ m^2), and Melphalan (140 mg/ m^2); CR1 = complete response 1; PR1 = partial response 1; HR = hazard ratio; IPI = international age-adjusted prognostic index; LDH = lactate dehydrogenase.

Table 3 Multivariate analysis of patients with mantle cell lymphoma: overall survival (OS) and progression-free survival (PFS) rates

Prognostic factors at the time of transplantation	OS			PFS		
	HR	95% CI	P-value	HR	95% CI	P-value
ALC (≥ 500 cells/ μ l vs < 500 cells/ μ l)	0.24	(0.06–0.80)	0.02	0.18	(0.05–0.50)	0.0006
Disease status at ASCT (CR1/PR1 vs CR > 1 /PR > 1)	0.54	(0.15–1.58)	0.27	0.25	(0.08–0.66)	0.005

Abbreviations: ALC = absolute lymphocyte count at day 15; ASCT = autologous stem cell transplantation; 95% CI = 95% confidence interval; CR1 = complete response 1; HR = hazard ratio; PR1 = partial response 1. Multivariate model contains all prognostic factors listed.

transplant (Table 3). The hazard risk for death is four times less for patients who recover an ALC-15 ≥ 500 cell/ μ l after ASCT compared with MCL patients who do not recover this value of ALC-15. When the risk of lymphoma recurrence was assessed based on ALC-15, the hazard risk of recurrence was five times less for patients who recovered ALC-15 ≥ 500 cell/ μ l.

In addition, multivariate analysis demonstrated that disease status, that is, being in first CR or first PR, was an independent prognostic factor for lymphoma recurrence, independent of the immune recovery after ASCT in terms of ALC-15. Patients who were transplanted in CR1 or PR1 had a five times less risk of recurrence compared to patients who were transplanted in second or more CR or PR (HR = 0.25, $P = 0.005$).

Discrimination of ALC-15 in MCL patients as predictor of PFS

To compare the accuracy of ALC-15 as a predictor of recurrence accounting for censored data, the Harrell's method, which yields the concordance c -statistic, was calculated.²⁴ The c -index estimates the probability that, of two randomly chosen patients, the patient with the higher value of the prognostic factor will outlive the patients with the lower value. Values of c near 1 indicate that a higher value of the prognostic factor virtually always determines that a patient has a better prognosis. This new independent prognostic factor (ALC-15) alone can predict recurrence of MCL after ASCT with a discrimination power of 61%.

Discussion

Our study shows that ALC-15 ≥ 500 cells/ μ l after ASCT is a strong and independent prognostic factor for OS and PFS in MCL patients. In our MCL patient population, those patients who recovered an ALC-15 ≥ 500 cells/ μ l after ASCT have a five times less risk of progression and a four times less risk of death compared to patients with an ALC-15 < 500 cells/ μ l after ASCT.

The c -statistic allows quantification of the discrimination power of prognostic factors of time-dependent events. The quantitative–qualitative relationship between the c -statistic and discrimination power of the prognostic factor follows a fairly linear pattern. The value of 61% demonstrates that the accuracy of ALC-15 in predicting recurrence of MCL after ASCT in this group of patients is satisfactory. From our data, it is clear that patients with MCL who do not recover an ALC-15 ≥ 500 cells/ μ l after ASCT should be

considered for new and investigational therapeutic strategies, as the risk of early recurrence or death is very high.

This is the first time these results have been published specifically for patients with MCL. Previously, we showed an association between ALC-15 and survival in NHL,¹⁴ which included several histological subtypes but not MCL. Our study also shows that ASCT does not offer a cure to MCL patients as the OS curve does not reach a plateau if patients are analyzed independently of their lymphocyte recovery (data not shown). Immunotherapy is a reasonable treatment option in these patients after ASCT, as the use of rituximab in combination with ASCT has shown promising results.^{25,26} However, the benefit of immunotherapy may be investigated in the context of the patients' own immune system recovery and potential. One hypothesis is that the maximal effect of immunotherapy, including monoclonal antibodies or cytokine treatment, depends on the robustness of the patient's own immune system at the time of treatment.

Multivariate analysis indicates that the ALC-15 level of ≥ 500 cells/ μ l after ASCT remains a strong prognostic factor when adjusted to other important prognostic factors. These results contribute to the recent concept of autologous graft vs tumor (GVT) effect, which is based on the fact that immune recovery after ASCT in several malignancies (hematological and nonhematological) has been shown to be an independent prognostic factor for survival.²⁷ The interest in immunotherapy after hematopoietic stem cell transplantation has come from clinical observation of the GVT effect in the allogeneic context,^{28–30} where the recognition of allo-major histocompatibility complex (MHC) leads to the killing of residual tumor cells as well as graft vs host disease.^{31–33} In the autologous setting, patient survival is associated with a rapid recovery of lymphocytes, suggesting that the autologous immune system has the ability to fight residual tumor cells. It is fundamental to be able to understand the precise role played by each subset of lymphocytes in the immune response against residual tumor cells after ASCT. A recent report demonstrated that polyclonal immunoglobulin administration is able to increase TCR repertoire diversity in an animal model with a contracted T-cell repertoire.³⁴ This could represent a possible approach to be tested clinically. The possibility of improving repertoire diversity and function of the T cells that populate the immune system after ASCT will allow better immune function and, possibly, a lower recurrence rate.

This study shows the significance of early lymphocyte recovery on survival in MCL patients treated with ASCT and warrants further study of strategies for improving immune reconstitution which will have a direct impact on clinical outcomes after ASCT.

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