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Beta-2 microglobulin predicts the outcome after autologous stem cell transplantation in non-Hodgkin lymphoma

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ABSTRACT

Autologous stem cell transplantation (ASCT) is an established therapeutic modality in the treatment of lymphomas, especially in the relapse setting. In the present study, we aimed to define pretransplantation factors including Beta-2 microglobulin (β2m) that influence outcomes following ASCT in patients with non-Hodgkin lymphoma (NHL). We analyzed retrospectively 78 NHL patients who had undergone ASCT from August 2010 to January 2013. The 2-year overall survival (OS) was 70% and the progression-free survival (PFS) was 60%. While remission status less than complete remission (CR) emerged to be a poor prognostic factor for OS in univariate analysis, high β2m levels and comorbidity indices revealed to be independent poor risk factors for both OS and PFS. The present study demonstrated that even if the patient is in CR before ASCT if he has high β2m, the 2-year OS decreases from 100% to 49%. Moreover, lymphopenia for the first time was demonstrated to predict PFS in ASCT in NHL patients. Our findings suggest that β2m at transplantation predict the outcome after ASCT in NHL and further investigation with larger sample sizes is warranted.

1. Introduction

High-dose chemotherapy (HDC) followed by autologous hematopoietic stem cell transplantation (ASCT) is an established therapeutic modality in the treatment of lymphomas, especially in the relapse setting. It is also under investigation after first-line therapy, for example, in patients with mantle cell or T cell lymphomas [1]. Despite the widespread use of high-dose therapy combined with ASCT, the outcomes of lymphoma treatment remain variable. Based on the classical Parma study, ASCT is considered the standard of care in patients with chemosensitive relapse [2]. Several studies were conducted to designate prognostic factors for ASCT in non-Hodgkin lymphoma (NHL). Although serum beta-2 microglobulin (B2M) has been suggested as an independent prognostic factor for several lymphoproliferative diseases, it has rarely been investigated in following ASCT in patients with NHL. In the present study, we aimed to define pretransplantation factors including beta-2 microglobulin (β2m) that influence outcomes following ASCT in patients with NHL.

2. Materials and methods

We analyzed retrospectively 78 adult NHL patients who had undergone ASCT from August 2010 to January 2013. Since most of the patients had been referred for transplantation from other centres, the treatment regimens before transplantation varied strongly. Patients were qualified for AHSCT if they fulfilled one of the following criteria: [1] patients who relapsed after initial response (relapsed patients were treated with chemotherapy to obtain CR/PR), [2] patients who did not achieve CR after the first-line chemotherapy and achieved best response after salvage therapy, [3] Patients with lymphomas (e.g. mantle cell lymphoma) in whom AHSCT were indicated in CR1. Additional

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criteria were ECOG status 0 to 2, and adequate pulmonary and cardiac functions. Patients over the age of 65 years were also transplanted if they fulfilled all these criteria. All patients signed informed consent approved by the local ethical committee.

Detailed information concerning patients' presentation at diagnosis as well as the disease status, comorbidity indices and other variables of known prognostic importance were evaluated before the initiation of conditioning chemotherapy for AHSCT. For the laboratory parameters such as lactate dehydrogenase (LDH), beta-2 microglobulin (β2m) and erythrocyte sedimentation rate (ESR), upper normal limits of the parameters in local laboratory were chosen as the cut-off point (for LDH 225 IU/l, for β2m 2,5 mg/l, for ESR 30 mm/h). Anemia was defined as hemoglobin (Hb) < 12 g/dl and lymphopenia was defined as absolute lymphocyte count $<1.0 \times 10^9$/l). Low immunoglobulin G (IgG) was defined as <600 mg/dl and high ferritin was defined as ≥1000 ng/ml. Comorbidity indices of the patients were calculated by using hematopoietic cell transplantation (HCT)-specific comorbidity index and patients were grouped as those with comorbidity indices ≥3 and those with comorbidity indices <3 [3]. The characteristics of the patients grouped according to β2m levels at ASCT are reported in Table 1.

ASCT response assessments were performed at day +100 of ASCT with physical examination, radiological studies (PET-CT or CT) and complete blood counts and serum biochemistry. Then the patients were evaluated with the same parameters every 3 months or when clinically indicated. Revised response criteria were used for response assesment [4].

Transplant related mortality (TRM) was defined as death within 100 days after ASCT that was unrelated to the disease, relapse or progression. Non-relapse mortality (NRM) was defined as death from non-relapse causes; overall survival (OS) was defined as the time from transplantation to death from any cause. Progression-free survival (PFS) was calculated from the date of transplantation to the date of disease progression or relapse.

2.1. Statistical analysis

Statistical analysis was performed with SPSS version 21. 0 software (SPSS, USA). OS and PFS were estimated according to the Kaplan–Meier method. The univariate effects of prognostic factors that were anticipated to be related to OS and PFS were investigated using the log-rank test. Comparisons among those variables of interest were performed by the log-rank test. Multivariate analysis with the variables that proved to be significant in univariate analysis was performed according to the Cox proportional hazard regression model. All p-values reported were two-sided and statistical significance was defined at $p < 0.05$.

3. Results

Chemotherapy regimens used for mobilization were etoposide in 47 (60,3%) patients, DHAP in 9 (11,5%) patients, ICE in 21 (26,9%) patients and ESHAP in 1 (1,3%) patient. BEAM chemotherapy was employed as conditioning regimen in all patients (Table 2). Rituximab was not used for in vivo purging in any patient. The median follow-up time is 20 months (range 2–41 months). Number of transfused CD34+ stem cells were shown in Table 2.

Only 4 out of 78 NHL patients (5,2%) died within 100 days of transplantation. Two of the dying patients' diagnosis were mantle cell lymphoma and the other 2 dying patients' diagnosis were diffuse large B cell lymphoma. Two patients had relapsed within 2 months of tranplantation (52 days and 60 days, respectively) and died due to sepsis while they were neutropenic due to salvage chemotherapy. One died due to septic shock in the 48th day of transplantation. The forth patient relapsed with massive ascites and pleural

Table 1
The characteristics of the patients grouped according to β2m levels at ASCT.

	β2m <2,5	β2m >2,5	p
n (%)	44 (63,8)	25 (36,2)	
Median age (range) years	46 (19–73)	57 (30–72)	0,003
Patients >65 years (%)	3 (6,8)	5 (20)	0,12
Male/Female	29/15	20/5	0,21
Histology, n of patients(%)			0,26
DLBCL	25 (56,8)	8 (32)	
MCL	8 (18,2)	7 (28)	
FL	2 (4,5)	3 (12)	
T cell lymphoma	9 (20,5)	7 (28)	
Stage at diagnosis(%)			0,004
I	7 (16)	0 (0)	
II	12 (27,3)	2 (8)	
III	5 (11,4)	10 (40)	
IV	12 (27,3)	8 (32)	
Unknown	8 (18)	5 (20)	
Median months from diagnosis to ASCT (range)	14 (4–91)	11 (6–80)	0,44
Prior lines of chemotherapy (different regimens)			0,08
1	14	2	
2	25	16	
3	4	6	
4	1	1	
Prior radiotherapy			0,11
Yes	11	2	
No	33	23	
Response to 1st line treatment			0,05
CR/PR	33	13	
Refractory	11	12	
Disease status at ASCT			0,33
CR1 after 1st line therapy	9 (20)	2 (8)	
CR1 after more than 1 regimen	4 (9)	4 (16)	
PR1 after 1st line therapy	4 (9)	0 (0)	
PR1 after more than 1 regimen	6 (14)	5 (20)	
CR after relapse	11 (25)	10 (40)	
PR after relapse	10 (23)	4 (16)	
Comorbidity index at ASCT			0,08
<3	40 (90)	19 (76)	
≥3	4 (10)	6 (24)	
Laboratory parameters at ASCT (%)			
High LDH	21 (48,8)	11 (45,8)	0,81
High ESR	23 (56,1)	15 (65,2)	0,47
High ferritin	4 (11,1)	6 (37,5)	0,052
Low IgG	5 (11,6)	11 (50)	0,001
Anemia	33 (73,3)	23 (92)	0,006
Lymphopenia	24 (53,3)	8 (34,8)	0,14

Abbreviations: DLBCL: diffuse large B cell lymphoma, MCL: mantle cell lymphoma, FL: follicular lymphoma, CR: complete remission, PR: partial remission, LDH: lactate dehydrogenase, ESR: erythrocyte sedimentation rate, IgG: immunoglobulin G.