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The risk factors for a poor hematopoietic stem cell mobilization in lymphoma patients

Lenfoma hastalarında yetersiz hematopoiteik kök hücre mobilizasyonu için risk faktörleri

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Abstract

Aim: Poor mobilization is an important problem in autologous stem cell transplantation. The ratio of poor mobilization is higher in lymphoma patients. There is limited data about poor mobilization in lymphoma patients. We aimed to identify the possible risk factors for poor mobilization using data from 57 lymphoma patients.

Materials and Methods: We retrospectively reviewed the data of 57 lymphoma patients (40 with non-Hodgkin lymphoma and 17 with Hodgkin lymphoma) who have been mobilized during 1998 - 2011. Patient data were recruited from the archives of the hematology clinic.

Results: We documented poor mobilization in 13 (22.8%) patients. Bone marrow involvement (odds ratio [OR] =15.52, p=0.002) and being treated with more than ten cycles of chemotherapies (OR=6.25, p=0.04) were found to be possible risk factors.

Conclusion: Leukapheresis staff should be aware of the increased risk of poor mobilization in these cases and remobilization strategies should be considered from the beginning in these patients with risk factors for more effective resource utilization.

Keywords: Hematopoietic stem cell mobilization, lymphoma, poor mobilization, risk factors.

Öz

Amaç: *Yetersiz mobilizasyon otolog kök hücre naklinde halen önemli bir sorun olmaya devam etmektedir. Lenfoma hastalarında yetersiz mobilizasyon daha sık izlenmekle birlikte nedenleri konusunda yeterli bilgi bulunmamaktadır. Bu çalışmamızda, 57 lenfoma hastasında yetersiz maobilzasyona neden olabilecek risk faktörlerini belirlemeye çalıştık.*

Gereç ve Yöntem: *1998-2011 tarihleri arasında mobilizasyon uygulanan 57 (40 non-Hodgkin lenfoma ve 17 Hodgkin lenfoma) lenfoma hastasını geriye dönük olarak taradık. Hasta bilgilerine hematoloji kliniği arşivinden ulaşıldı.*

Bulgular: *On üç hastada (%22.8) yetersiz mobilizasyon saptandı. Kemik iliği infiltrasyonu (odds ratio [OR] =15.52, p=0.002) ve 10'dan fazla kür kemoterapi almış olmak (OR=6.25, p=0.04) risk faktörü olarak belirlendi.*

Sonuç: *Yetersiz mobilizasyona neden olabilecek risk faktörlerinin bilinmesi ve bu risk faktörlerine sahip olan hasta grubunun önceden belirlenmesi kaynakların daha verimli kullanılması açısından önem taşımaktadır.*

Anahtar Sözcükler: *Hematopoetik kök hücre mobilizasyonu, lenfoma, yetersiz mobilizasyon, risk faktörleri.*

Introduction

Mobilized peripheral blood stem cells (PBSC) are widely used as rescue treatment after high dose chemotherapy for various malignancies (1,2). The most important problem is poor mobilization. Although there have been many improvements in mobilization methods and technical devices in leukapheresis, there are still many patients who cannot be mobilized.

Many methods such as granulocyte colony-stimulating factor (G-CSF) with or without different chemotherapies can be used for mobilization of stem cells and new agents such as plerixafor can be an alternative method for patients who can not be mobilized by routine procedures (3). Although studies have demonstrated that combination of plerixafor and G-CSF result in higher rates of successful mobilization (4-7), its usage has been restricted by governments and cost and availability of the drug is still a problem. Therefore, identification of risk factors for poor mobilization is important for optimal resource utilization.

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Different risk factors (e.g. previous chemo-radiotherapies, disease and chemotherapy types, interval between diagnosis and mobilization, mobilized CD34+ cell adhesion molecule profiles) have been identified in different studies (8-13). Ozkurt et al showed that poor mobilization frequency was higher in lymphoma patients (14). In our previous study, we have identified a diagnosis of lymphoma was a risk (odds ratio [OR] = 6.02, p = 0.001) factor (15). Recently, Han et al demonstrated that chemotherapy regimens more than 2 and chemotherapy cycles more than 8, radiotherapy, low platelet count could be risk factors for mobilization failure in lymphoma patients (11).

There are many studies about poor mobilization but many of these studies consist of a heterogeneous group of diseases including hematological and non hematological malignancies. Beside this, there is only limited data published recently including only lymphoma patients in which there are increased risk of poor mobilization in the literature (11). The aim of this study was to identify the possible risk factors for poor mobilization in lymphoma patients. We retrospectively, evaluated data of our mobilized patients over a 14-year period to demonstrate possible risk factors for poor stem cell mobilization in lymphoma patients.

Materials and Methods

Patients

We retrospectively reviewed the data of 57 lymphoma patients (40 with non Hodgkin lymphoma and 17 with Hodgkin lymphoma) who have been mobilized during 1998 - 2011. Patient data (diagnosis, type of the disease, age, gender, weight, bone marrow involvement, radiotherapy, treatment protocols, the number of the chemotherapy cycles and the rituximab administration) were recruited from the archives of the hematology clinic (Table-1).

Previous therapies

In patients with non-Hodgkin lymphoma, CHOP (the cyclophosphamide, doxorubicin, vincristine, and prednisone) ± rituximab was administered as the first line treatment. In patients with Hodgkin lymphoma, ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) ± involved field radiation therapy were administered as the initial therapy.

In aggressive lymphomas, hyper-CVAD (cyclo-phosphamide, vincristine, doxorubicin, and dexamethasone) chemotherapy was administered. In relapsed or refractory lymphoma patients, ESHAP (methylprednisolone, cisplatin, and cytarabine), ICE (ifosfamide, carboplatin, and etoposide) with or without rituximab, IGEV (ifosfamide, gemcitabine, and vinorelbine), rituximab plus bortezomib with dexamethasone especially for mantle cell lymphoma patients, protocol 7704 (cyclophosphamide, methotrexate, vincristine, adriamycin, prednisone) PROMACE (prednisolone, doxorubicin, cyclophosphamide, and etoposide), DHAP (dexamethasone, ARA-C, cisplatin), IVAC (ifosfamide, etoposide, and methotrexate), protocol 89C41 (etoposide, ifosfamide, ARA-C, and methotrexate) regimens were administered as the relapse or refractory therapy.

Table-1. Characteristics of the Patients.

	All patients	**Good mobilizing patients**	**Poor mobilizing patients**
Number of patients	57	44	13
Gender (male/female)	34/23	28/16	6/7
Age (years, median, range)	44 (19-66)	42 (19-63)	48 (30-66)
Diagnosis			
Non- hodgkin lymphoma	40	29	11
Diffuse large B cell	21	16	5
Mantle cell	6	6	None
Follicular lymphoma	5	3	2
Small lymphocytic lymphoma	4	1	3
Others*	4	3	1
Hodgkin lymphoma	17	15	2
Nodular sclerosis	10	8	2
Mixed cellularity	6	6	None
Lymphocyte rich	1	1	None
Number of patients with bone marrow involvement	15	7	8
Number of patients treated with radiotherapy	14	12	2
Number of chemotherapy cycles (median, range)	9 (1-20)	9 (2-20)	9 (1-15)
Weight (kg, median, range)	71 (50-134)	70.5 (50-134)	79.5 (55-95)
Rituximab administration (yes/no)	27/30	20/24	7/6

*****Lymphoblastic lymphoma, primary cutenous lymphoma, T-cell lymphoma.

PBSC mobilization

A mobilization was performed by administering G-CSF (10 µg/kg/day, mostly filgrastim) with or without disease specific chemotherapies (17 patients ESHAP with or without rituximab, one patient with IGEV, 25 patients with ICE with or without rituximab, three patients hyperCVAD, four patients IVAC and seven patients only with G-CSF). In the patients receiving G-CSF and

chemotherapy, an apheresis was initiated when the circulating CD34+ cell count was higher than 10 cells/L[16]. In the patients receiving only G-CSF, an apheresis was initiated on the 5th day.

Collection of peripheral blood stem cells

A leukapheresis was performed by using various types of automated apheresis systems (Comtec/Astec 204, Fresenius, Bad Homburg; Model CS3000 plus, Baxter Fenwal, Lake Zurich, IL; COBE Spectra [Version 5.1 - 6.0], GambroBCT, Lakewood, CO; excel pro, Dideco, Mirandola). Among the 57 patients who underwent leukapheresis, the median leukapheresis number was 3 (range 1-8).

Mobilization insufficiency was defined as the peripheral blood CD34+ cell count that is less than 10/μL during the post-mobilization period or total collected CD34+ cell count less than $2.5x10^6$/kg with 6 apheresis.

Statistical analysis

We analyzed the relationship between mobilization and different variables (diagnosis, type of the disease, age, gender, weight, bone marrow involvement, radiotherapy, treatment protocols, the number of the chemotherapy cycles and the rituximab administration). For this purpose, we first analyzed the variable using univariate analysis. The described variable statistically significant in univariate analysis was calculated using the multivariate test (logistic regression). p values less than 0.05 were considered as significant. The results were given as median (range). The data were analyzed using computer software (SPSS 16.0, SPPS, Inc., Chicago, IL).

Results

Fifty-seven patients diagnosed with lymphoma were consisted of 34 males and 23 females. The median age was 44 (range 19-66) years old and the median weight was 71 (range 50-134) kg. The median number of apheresis per patient was 3 (range 1-8). A total of 158 procedures were performed in 57 patients. The median number of collected CD34+ cells was 5.33 (range 0.28 - 29) x 10^6/kg body weight (Table-1).

There are 17 patients with Hodgkin lymphoma and 40 non-Hodgkin lymphoma. The subtypes of the non Hodgkin lymphoma are diffuse large B cell (21 patients), mantle cell (6 patients), follicular lymphoma (5 patients), small lymphocytic lymphoma (4 patients) and 4 patients with other types including lymphoblastic lymphoma, T-cell lymphoma and primary cutenous lymphoma. The patients were treated with chemotherapy with (14 patients) or without (43 patients) radiotherapy. The median number of the chemotherapy cycles is 9 (range 1-20) and the median of the number of the chemotherapy regimens is 2 (range 1-5). The number of the patients who were treated with rituximab was 27.

Poor mobilization was documented in 13 (22.8%) patients. Two of the poor mobilizers were Hodgkin lymphoma and 11 of them were non-Hodgkin (five patients with diffuse large B cell, three patients with small cell lymphoma, two of them with follicular lymphoma and one patient with lymphoblastic lymphoma) lymphoma (Table-1).

We documented bone marrow involvement in 15 patients (one Hodgkin lymphoma and 14 non-Hodgkin lymphoma). The Hodgkin lymphoma patient with bone marrow involvement was poor mobilizer. Seven non-Hodgkin lymphoma patients with bone marrow involvement can't be mobilized and seven of them can be mobilized effectively.

Poorly mobilized three patients (two of them were non-Hodgkin and one of them was Hodgkin) were remobilized with G-CSF (one patient) or chemotherapy (IGEV and ICE) plus G-CSF. However, none of the patients who could not be mobilized at the first attempt could be mobilized at the subsequent attempts.

Bone marrow involvement (OR=15.52, 95% confidence interval [95% CI]=2.78-86.48, p=0.002) and treatment with more than ten cycles of chemotherapy (OR=6.25, 95% CI=1.04-37.63, p=0.04) were found to be risk factors for a poor mobilization (Table-2).

Diagnosis (OR=1.98, 95% CI=0.13-29.51, p=0.61), age (<40 versus ≥ 40, OR=2.14, 95% CI=0.22-20.25, p=0.50), gender (OR=4.6, 95% CI=0.64-33.06, p=0.12), weight (<50 kg versus ≥ 50 kg, OR=10.14, 95% CI=0.85-120.2, p=0.06), radiotherapy (OR=0.98, 95% CI=0.10-9.28, p=0.99) and rituximab administration (OR=0.24, 95% CI=0.02-2.54, p=0.23) was not documented as a risk factor (Table-2).

Table-2. Risk Factors for a Poor Hematopoietic Stem Cell Mobilization.

Risk factors	Odds Ratio	95% Confidence Interval	p value
Bone marrow involvement	15.52	2.78 - 86.48	0.002
More than ten cycles of chemotherapy	6.25	1.04 - 37.63	0.04
Weight (<50 kg versus ≥ 50 kg)	10.14	0.85 - 120.2	0.06
Gender (male versus female)	4.6	0.64 - 33.06	0.12
Age (<40 versus ≥ 40)	2.14	0.22 - 20.25	0.50
Diagnosis (HL versus NHL)	1.98	0.13 - 29.51	0.61
Radiotherapy treatment	0.98	0.10 - 9.28	0.99
Rituximab treatment	0.24	0.02 - 2.54	0.23

Discussion

Our results revealed that bone marrow involvement was the most important risk factor (OR=15.52) for poor mobilization. Han et al. (11) could not find a statistical significance between poor and good mobilizers in terms of bone marrow involvement. Although some other studies reported similar conclusions (17-19), there are studies which could not demonstrate a statistical difference between the patients with or without bone marrow involvements (11,20,21).

Being treated with more than ten cycles of chemotherapy is found to be second risk factor for poor mobilization in lymphoma patients (OR=6.25, p=0.04). Han et al also found that number of he chemotherapy cycles is a risk factor in Chinese lymphoma patients (11). In our study the threshold of the number of the chemotherapy cycle is ten on the other hand they documented the threshold as 8 cycles. This was also demonstrated by other studies (21-23). A study consisted of heterogeneous group of patients with nonmyeloid malignancies documented that number of chemotherapy courses was a risk factor (p=0.001) for mobilization insufficiency (9).

Radiotherapy is an important treatment modality in lymphoma patients. It can be used for palliative or curative purposes. It can be used as involved or extended field radiotherapy for organs such as central nervous system or only for involved lymph nodes. In our study, we could not identify radiotherapy as a risk factor in lymphoma patients. Like our study, Hosing et al. (20) could not demonstrate radiotherapy as a risk factor for poor mobilization, but Han et al. (11) reported it as a risk factor in lymphoma patients. Another possible risk factor for insufficient mobilization was age, but in our study we could not identify age as a risk factor. Although age Han et al could not demonstrate age as a risk factor (11), Hosing et al. (20) found that more than 60 years of age could be a risk factor. After rituximab became a standard therapy in non-Hodgkin lymphoma patients, its effects on mobilization were studied. Although some authors found that it affected the CD34 + cell yield negatively (22), others could not find a statistical difference (21,23,24). In our study, we could not find a statistical difference between two groups regarding rituximab effects.

Predicting poor mobilizers is gaining more importance; especially effective treatment methods such as plerixafor are becoming available (25). Since plerixafor treatment is more expensive and its use and back payment is restrained by the reimbursement companies in various countries, in lymphoma patients treated with high number of chemotherapy cycles or patients with bone marrow involvement, more effective protocols may be started from the beginning for more effective resource utilization.

Conclusion

Presence of bone marrow involvement and number of chemotherapy cycles were risk factors for poor mobilization in lymphoma patients. Leukapheresis staff should be aware of the increased risk of poor mobilization in these cases and remobilization strategies should be considered from the beginning in these patients with risk factors for more effective resource utilization.

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