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Poor hematopoietic stem cell mobilizers: A single institution study of incidence and risk factors in patients with recurrent or relapsed lymphoma

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Abstract

The purpose of this retrospective study was to determine the incidence and predictive factors if any, of mobilization failure in lymphoma patients referred for autologous stem cell transplantation. A total of 588 lymphoma patients were referred for transplant consultation from January 2003 to December 2004. Predictors of mobilization failure were evaluated using logistic regression analysis including diagnosis, mobilization regimen, age, sex, type and number of prior chemotherapies, bone marrow cellularity, platelet count, white count, prior bone marrow involvement with malignancy, and prior radiation therapy. Two hundred and six patients were eligible for transplantation and underwent stem cell mobilization. Twenty-nine (14%) patients failed to mobilize adequate stem cells after the first attempt. For the entire group age (>60 versus <60 years), diagnosis (Hodgkin's versus non-Hodgkin's lymphoma), use of cytokines alone, platelet count $<150 \times 10^9/L$, and bone marrow cellularity $<30\%$ were significant predictors for mobilization failure on univariate analysis. In view of small number of patients multivariate analysis was not possible. However, a low platelet count ($150 \times 10^9/L$) was the only significant predictor when the analysis was restricted to non-Hodgkin's lymphoma patients who were mobilized with chemotherapy. Mobilization failure rates are higher in patients with non-Hodgkin's lymphoma compared with those with Hodgkin's lymphoma. In the subset of patients who undergo chemomobilization for non-Hodgkin's lymphoma platelet count at the time of mobilization is a predictor of mobilization failure.

Background

High-dose chemotherapy (HDT) followed by autologous stem cell transplantation (SCT) is considered standard of care for patients with relapsed, chemosensitive, lymphoid malignancies [1–6]. Autologous peripheral blood stem cells (PBSCs) have largely replaced autologous bone marrow (BM) as the source of stem cells. Advantages of autologous PBSC graft over BM graft include faster engraftment after high-dose chemotherapy and reduced

contamination with tumor cells in case of bone marrow involvement with tumor [7] and lower morbidity and mortality [8].

Hematopoietic stem cell mobilization is generally accomplished by administration of hematopoietic growth factors like granulocyte colony stimulating factor (G-CSF) or a combination of myelosuppressive chemotherapy and hematopoietic growth factors. A number of factors have been reported to impact progenitor cell mobilization but the predictive factors vary from one study to the other.

The purpose of this retrospective analysis was to identify the incidence and predictive factors if any, for mobilization failure in patients with lymphoid malignancies.

Results

Between January 2003 and December 2004, a total of 588 patients with NHL or HL were referred for consideration of HDT and SCT. Of these, 206 (35%) patients were deemed eligible for autologous transplant and attempted stem cell mobilization. The reasons why 382 patients were not considered eligible for HDT and, therefore, did not undergo stem cell mobilization were as follows: chemorefractory disease 200 (52%), patient refusal 69 (18%), poor performance status 32 (8%), autologous transplant not indicated 76 (20%). Of the 76 patients for whom autologous transplant was not indicated, 59 patients had undergone prior HDT and SCT, 13 patients were in first complete remission, 4 patients had failed stem cell mobilization at an outside institution, and 5 patients had financial issues.

A total of 206 patients attempted stem cell mobilization, 187 (90.7%) were mobilized with chemotherapy followed by cytokines as previously described [9,10] and 19 (9.2%) were mobilized with cytokines alone. The most commonly used chemotherapy regimens was ifosfamide/etoposide $\pm$ rituximab in 142 patients (76%). Other chemotherapy regimens included cyclophosphamide (8%), hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) $\pm$ rituximab (6%), ICE (ifosfamide, carboplatinum and etoposide) $\pm$ rituximab (3%), IGEV (ifosfamide, gemcitabine, vinorelbine) in 3%, and ESHAP etoposide, cytarabine, cisplatinum, and methylprednisolone) $\pm$ rituximab in 1%. The most commonly used cytokine was G-CSF at a starting dose of 10–12 mcg/kg/day. G-CSF dose was increased to 24 mcg/kg/day before classifying a patient as mobilization failure. Twenty-nine (14.1%) patients failed to mobilize adequate stem cells on first attempt. The baseline patient characteristics of the 206 patients in whom stem cell mobilization was attempted are summarized in Table I. Majority of the failures (26/29) were in the NHL group. The failure rate in NHL patients was 26/141 (18%).

Stem cell mobilization

In patients who mobilized adequate stem cells, the median CD34 dose collected/apheresis procedure was 5×10^6 /kg ($0.38\text{--}89.4 \times 10^6$ /kg) and the median number of apheresis procedures required to reach the target dose was 2 (range, 1–8). The median stem cell dose collected was 13.7×10^6 CD34⁺ cells/kg (range, $2.5\text{--}89.4 \times 10^6$ /kg).

Risk factors analysis

For the entire group age (≥ 60 versus <60 years), diagnosis (non-Hodgkin's versus Hodgkin's lymphoma), use of cytokines alone, platelet count $<150 \times 10^9/L$, and bone marrow cellularity $<30\%$ were significant predictors for mobilization failure on univariate analysis. Eighteen percent of patients (26 of 141 patients) in the NHL group and 5% of patients in the HL group (3 of 65 patients) failed to mobilize adequate stem cells [odds ratio (OR) = 4.7, 95% CI 1.3–16, $P = 0.01$].

Further evaluation of risk factors for failure to mobilize was restricted to patients with NHL only because of the small number of failures in the HL group (Table II). On univariate analysis in the NHL group mobilization regimen was the strongest predictor of failure. Sixty-two percent of patients who received mobilization with G-CSF alone (8 of 13 patients) failed to mobilize, compared with 21% (3 of 14 patients) in patients mobilized with cyclophosphamide and 13% (12 of 96 patients) of patients who received ifosfamide/etoposide. Platelet count of $<150 \times 10^9/L$ before mobilization ($P < 0.001$) and low bone marrow cellularity ($<30\%$, $P = 0.02$) were also significant predictors of mobilization failure on univariate analysis. Age, gender, number of prior chemotherapy regimens, prior BM involvement with lymphoma, prior radiation therapy (pelvic or other), prior flu-darabine therapy, white blood cell count at the time of mobilization did not significantly impact stem cell mobilization in this group. Multivariate analysis evaluating the independent effects of mobilization regimen, platelet count and bone marrow cellularity was not possible because of limited statistical power given the small number of patients and failures in some subgroups. Comparable results were obtained when analysis was restricted to the 128 patients with NHL who were mobilized with chemotherapy plus cytokines except for the impact of low cellularity which was no longer statistically significant (OR = 1.7, 95% CI 0.6–4.8, $P = 0.3$).

Discussion

A number of factors have been reported to impact stem cell mobilization. These include patient age, weight [11], diagnosis, [11,12] type and number of prior chemotherapeutic regimens administered [13–15], bone marrow involvement with lymphoma at baseline [11,16], extent of cell recovery from previous chemotherapy at the time of starting mobilization treatment, prior radiation therapy [16,17], time from diagnosis to harvest, and disease status. Other factors include type of cytokine used and type and dose of chemotherapy regimen if any for mobilization [13,18].

The purpose of this analysis was to identify the incidence and risk factors for mobilization failure and thus patients who may benefit from newer agents like plerixafor for stem cell mobilization. A major limitation of the present study is that the data was collected retrospectively. Also, multivariate analysis was not always possible because of limited statistical power given the small number of events in some subgroups.

In the overall group, diagnosis (HL versus NHL) was the most significant factor for mobilization failure on univariate analysis. At least two other studies reported similar

findings [11,12]. whereas others found no difference [17]. One possible explanation for this observation may be that patients with HL were younger than patients with NHL (median age 33 versus 55 years, $P < 0.001$). We could not assess if age was a confounding factor in the entire group because only 11 patients in the NHL group were ≥ 33 years of age. Other significant factors were age (≥ 60 versus <60 years), use of cytokines alone, platelet count $<150 \times 10^9/L$, and bone marrow cellularity $<30\%$ were significant predictors for mobilization failure on univariate analysis.

When analysis was restricted to patients with NHL factors that were significant predictors of mobilization failure included type of mobilization regimen (chemotherapy versus cytokines alone), platelet count prior to mobilization ($<150 \times 10^9/L$ versus $\geq 150 \times 10^9/L$), and bone marrow cellularity ($<30\%$ versus $\geq 30\%$). Low platelet count at mobilization has been reported as a significant factor for mobilization failure in at least two other studies [19,20]. Low platelet count is a surrogate for low BM cellularity and more reproducible. Patients who were mobilized with G-CSF alone had a higher failure rate but because of the small number of patients multivariate analysis evaluating the independent effect of mobilization regimen was not possible. Others have similarly reported that combination of chemotherapy and cytokines often mobilize more progenitor cells than cytokines alone [13,18]. Recent study by Pusic et al. [21] found that patients who were mobilized with chemotherapy plus cytokines were more likely to reach the target stem cell dose and had higher stem cell yield but the initial failure rate was similar in the two groups.

The exact incidence of poor mobilizers is unknown but has varied between 5% to 40% in different subsets of patients [22–24]. The definition of poor mobilizers in literature has also not been consistent. Some reports use a cutoff value of 1×10^6 CD34⁺ cells/kg, whereas others consider poor mobilizers as inability to mobilize $<2 \times 10^6$ CD34⁺ cells/kg [25] In a recent study by Pavone et al. [23], 17.9% of patients were poor mobilizers (stem cell yield of less than 2×10^6 CD34⁺ cells/kg) and 10% were very poor mobilizers ($<1 \times 10^6$ CD34⁺ cells/kg). This is comparable with our data where 14.1% patients failed to mobilize a minimum of 2×10^6 CD34⁺ cells/kg in four leukapheresis procedures.

In conclusion, failure to mobilize adequate progenitor cells for HDT and SCT is more common in patients with non-Hodgkin's lymphoma when compared with patients with Hodgkin's lymphoma. A variety of factors may affect stem cell mobilization and the yield. In our study type of mobilization regimen used, the platelet count and marrow cellularity at the time of mobilization were significant predictors of mobilization failures in non-Hodgkin's lymphoma patients. Clinical and laboratory parameters that predict poor mobilizers will help clinicians tailor the mobilization regimen to individual patients. These patients may benefit from novel agents like plerixafor, which increase the stem cell yields without increasing toxicity.

Patients and Methods

Patients

Medical records of all patients with NHL or HL referred to the Department of Stem Cell Transplantation and Cellular Therapy at The University of Texas M.D. Anderson Cancer

Center between January 2003 and December 2004 were reviewed. Permission to review patient charts was granted by the Institutional Review Board. Data collected included age, sex, diagnosis, status at transplantation, number of prior chemotherapy regimens, bone marrow cellularity and complete blood counts at the time of mobilization, mobilization regimen, and number of apheresis procedures needed to reach target. If the patient was not considered an appropriate candidate for transplantation the reason for that decision was documented. For the purpose of this study, poor mobilizers were defined as patients who failed to collect at least 2×10^6 CD34⁺ cells/kg of body weight in 4 leukapheresis procedures, failed to achieve a circulating PB CD34 count of $>10 \times 10^9/L$ or collected $<0.5 \times 10^6$ CD34⁺ cells/kg/day on the first two days of collection.

Stem cell collection

Stem cell collection was started when the peripheral blood CD34 count was $>10/\mu L$. The target stem cell dose was 5×10^6 CD34⁺ cells/kg. All patients underwent leukapheresis using the COBE Spectra cell separator (COBE BCT, Lakewood, CO). Three times the estimated blood volume was processed during each collection. Anticoagulant citrate dextrose solution (ACD-A) was used as an anticoagulant. Calcium was given by continuous infusion through the return line. The total nucleated cell count and the CD34⁺ cell concentration was measured immediately after completion of apheresis.

Statistical analysis

Risk factors for failure to mobilize were evaluated using logistic regression analysis. This was limited to univariate analysis because of sample size considerations. Statistical significance was set at the 0.05 level. Statistical analysis was performed using STATA 8.0 (StataCorp. 2001. Stata Statistical Software: Release 7.0. College Station, TX: Stata Corporation).

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TABLE I

Patient Characteristics (n = 206)

Characteristic	Mobilized	Failed to Mobilize	Total	P value
N	177	29 (14)	206	
Age (yrs)				
Median (range)	46 (19–81)	61 (19–78)	48 (19–81)	<0.001
Age				
60	41	15	56	0.001
<60	136	14	150	
Sex				
Male	112	18	130	
Female	65	11	76	0.9
Diagnosis				
Non-Hodgkin's lymphoma	115	26	141	0.009
Hodgkin's lymphoma	62	3	65	
No. of Prior Chemoregimens				
0–2	92	14	106	0.9
3	84	13	97	
Missing	1	2		
Previous BM involvement				
Yes	44	10	54	0.29
No	131	19	150	
Missing	2			
Previous Radiation				
Yes	69	8	77	0.39
No	102	21	123	
Missing	6			
White count				
$4 \times 10^9/L$	53	13	66	0.1
$<4 \times 10^9/L$	124	16	140	
Platelet count				
$<150 \times 10^9/L$	29	15	44	0.001
$150 \times 10^9/L$	146	14	160	
Missing	2			
Cellularity				
<30%	38	13	51	0.01
30%	138	16	154	
Missing	1			
Regimen				
G-CSF alone	10	9	19	0.001
Ifos/VP 16 ± Rituximab	133	14	147	
Cyclophosphamide ± Rituximab	11	3	14	

Characteristic	Mobilized	Failed to Mobilize	Total	<i>P</i> value
Other	23	3	26	

BM, bone marrow; Ifos, ifosfamide; VP16, etoposide; G-CSF, granulocyte-colony stimulating factor.

TABLE II

Univariate Analysis in Patients with non-Hodgkin's lymphoma (N = 141)

	N (%)	Poor Mobilizers, N (%)	Odds Ratio	95% CI	P
Platelet count					
<150 x10 ⁹ /L	34	14 (41)	ref		
150 x10 ⁹ /L	106	12 (11)	0.2	0.1–0.4	<0.001
Missing	1				
Cellularity					
<30%	44	13 (30)	2.7	1.1–6.5	0.02
30%	97	13 (13)	ref		
Regimen					
Ifosfamide/etoposide ± Rituximab	96	12 (13)	ref		
G-CSF	13	8 (62)	11.2	3.1–40	<0.001
Cyclophosphamide ± Rituximab	14	3 (21)	1.9	0.5–7.8	0.4
Other	18	3 (17)	1.4	0.3–5.6	0.6

G-CSF, granulocyte-colony stimulating factor.