

ResearchTJH-2020-0409.R1

doi: 10.4274/tjh.galenos.2020.2020.0409

Prediction of Stem Cell Mobilization Failure in Patients with Hodgkin and Non-Hodgkin Lymphoma

Haluk Demirođlu, Rafiye iftiler, Yahya Bykařık, Hakan Gker

Hacettepe University Faculty of Medicine, Department of Hematology, Ankara, Turkey

Hakan Gker, Hacettepe University Faculty of Medicine, Department of Hematology, Ankara, Turkey

hgoker1@gmail.com

+90 312 305 30 50

Submitted: 16 July 2020

Accepted: 4 November 2020

Abstract

Objective: Autologous stem cell transplantation (ASCT) is a significant and potentially curative treatment modality for patients with relapsed/refractory lymphoma. Insufficient mobilization and harvest of peripheral stem cells can be a major obstacle for performing ASCT. The aim of this study was to evaluate the factors which might influence mobilization failure in patients with lymphoma.

Materials and Methods: Eighty-seven patients with diagnosed non-Hodgkin and Hodgkin lymphoma who underwent stem cell mobilization after at Hacettepe University Medical School, Bone Marrow Transplantation Center, Turkey, between the years of 2000 and 2018 were evaluated.

Results: A total of 87 patients were included in this study. In 66 of 87 patients (75.9%) first mobilization trial was successful. Adequate ($\geq 2 \times 10^6/\text{kg}$) CD34+ cells were collected at first apheresis in 66 patients (9.5 ± 8.1). In 21 of 87 (24.1%) first mobilization trial was unsuccessful. Therefore, a second mobilization trial was made to these patients with plerixafor (5.5 ± 3.3). The number of CD34+ cell was significantly higher in patients who were successful in the first mobilization ($p=0.002$).

Conclusion: In conclusion, the success rate of the first mobilization trial was found to be higher in patients with high platelet count before mobilization and patients who received a chemotherapy-based mobilization protocol. In the patients who had mobilization failure for the first trial, plerixafor was used at a later mobilization, and those patients had an adequate amount of stem cells for ASCT. Parameters predicting mobilization failure would let a preemptive, more cost-effective use of such agents during the first mobilization attempt, however risk factors for mobilization failure are still not clear.

Keywords: Hodgkin lymphoma, Non-Hodgkin lymphoma, stem cell mobilization, mobilization failure

Introduction

Autologous stem cell transplantation (ASCT) is a significant and potentially curative treatment modality for patients with relapsed/refractory lymphoma. However, 5–40% of lymphoma patients fail to mobilize sufficient peripheral blood stem cells and thus cannot undergo ASCT that is known to improve survival (1). Hematopoietic stem cells generally circulate in very small numbers in the peripheral blood and have to be mobilized into the circulation prior to being collected by apheresis. Peripheral blood stem cell (PBSC) mobilization is accomplished by administration of G-CSF (granulocyte colony stimulating factor), alone or in combination with chemotherapy (2). Peripheral blood has been shown to be superior to bone marrow as a source of hematopoietic stem cells for ASCT (3). Insufficient mobilization and harvest of peripheral stem cells can be a major obstacle for performing ASCT. Currently, a minimum of 2×10^6 CD34+ cells/kg hematopoietic stem cells considered appropriate in most centers to proceed to ASCT. This threshold is necessary for a rapid and sustained blood count recovery and necessary for reduced hospitalization, blood product usage and infections (4). However, the optimal hematopoietic stem cells dose is about $5 \times 10^6/\text{kg}$ (5). Bone marrow infiltration,

advanced age, number of the prior cytotoxic therapies and myelodysplastic changes are the best defined factors associated with increased risk of mobilization failure (6, 7).

We have collected and analyzed data from a series of non-Hodgkin and Hodgkin lymphoma patients who received ASCT, in order to determine the frequency of harvest failure and to identify factors influencing PBSC mobilization outcome. The aim of this study was to evaluate the factors which might influence mobilization failure in patients with lymphoma.

Materials and Methods

Study Design and Data Collection

This study has been performed in a retrospective manner. Demographic data of the patients, treatment regimen and stem cell mobilization data updates were obtained from hospital database. As a result of application standards of the hospitals of Hacettepe University Medical School, Bone Marrow Transplantation Center, Turkey, it has been recognized from the patient records that all of the studied patients had given informed consents at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standards of care. Patients gave informed consent for the procedure, in accordance with Declaration of Helsinki.

Patients and Disease Characteristics

Eighty-seven patients with diagnosed non-Hodgkin and Hodgkin lymphoma who underwent stem cell mobilization after at Hacettepe University Medical School, Bone Marrow Transplantation Center, Turkey between the years of 2000 and 2018 were evaluated. The key inclusion criteria were patients ≥ 18 years of age with diagnosed non-Hodgkin or Hodgkin lymphoma who require systemic chemotherapy and underwent ASCT with Eastern Cooperative Oncology Group (ECOG) performance status < 2 (8); and there was an indication for ASCT.

Median age, gender, ECOG PS, lymphoma subtypes, stage at diagnosis, bone marrow infiltration at diagnosis, induction chemotherapy, salvage chemotherapy, chemotherapy cycles they received before mobilization, radiotherapy before mobilization, platelet count before the mobilization, mobilization protocols, and disease status before ASCT were compared in patients who had successful stem cell mobilization and stem cell mobilization failure. Additionally, disease status after ASCT, relapse rate and mortality results were evaluated between both groups. The target CD34+ cell dose for collection was $> 2 \times 10^6$ /kg for each planned

autograft. All patients received G-CSF at the dose of 10µg/kg from day +5 until the peripheral stem cell harvest. CD34+ cells were measured in peripheral blood and apheresis product by flow cytometry. We had 20 microliter CD34+ cut-offs level when to start apheresis. We harvested the cells fifth and/or sixth day after beginning of G-CSF administration. Peripheral blood CD34% and CD34/µL at the first day in which leucocytes reached the value of $1 \times 10^9/L$ and maintained over this threshold over at least 2 days were correlated with overall CD34+ collection. The harvest less than 2×10^6 CD34+/kg was considered a mobilization failure. Twenty-one patients received plerixafor as an additional mobilizing agent for second apheresis. Subcutaneous plerixafor (0.24 mg/kg) was applied to the patients on the evening of the 4th and 5th days of the mobilization protocol.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 25. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether they are normally distributed or not. Statistical comparisons were made using Chi-square for categorical data. Student t-test (for two independent samples) was used for comparison of continuous numerical data. Variables that are found to be significant ($p < 0.05$) in univariate analysis were tested in multivariate analysis, which was performed using a stepwise logistic regression model. Values of $p < 0.05$ were considered statistically significant.

Results

Patient Characteristics

A total of 87 patients were included in this study. The median age was 48 (18-70) years at the time of diagnosis. The baseline clinical and demographic characteristics of patients are listed in Table 1. In 66 of 87 patients (75.9%) first mobilization trial was successful. Adequate ($\geq 2 \times 10^6/kg$) CD34+ cells were collected at first apheresis in 66 patients (9.5 ± 8.1). In 21 of 87 (24.1%) first mobilization trial was unsuccessful. Therefore, a second mobilization trial was made to these patients with plerixafor (5.5 ± 3.3). The number of CD34+ cell was significantly higher in patients who were successful in the first mobilization ($p=0.002$). There were any differences in hematocrit at the time point of apheresis.

Between two groups, there was no statistically significant gender ($p=0.25$) or age ($p=0.07$) difference. There was no significant difference between ECOG PS of the patients ($p=0.72$). No

significant difference was found between the two groups in terms of lymphoma types ($p=0.45$). Number of chemotherapy cycle before stem cell mobilization was no statistically significant different in patients who had mobilization failure and in patients who had successful stem cell mobilization ($p=0.78$). The stages of both groups were similar at the time of diagnosis ($p=0.69$). There was no significant difference between bone marrow infiltration at diagnosis ($p=0.24$). There was no significant difference between the two groups in terms of induction chemotherapy protocols ($p=0.51$). Platelet count before the mobilization was higher in patients who had successful stem cell mobilization than patients who had stem cell mobilization failure ($p=0.041$). After relapse, no significant difference was found between rescue chemotherapies given before mobilization ($p=0.49$). Disease status before ASCT was complete response (CR) in 27 (40.9%) patients, partial response (PR) in 28 (42.4%) patients, stable disease in 5 (7.6%) patients and progressive disease in 6 (9.1%) patients in successful mobilization group. Disease status before ASCT was CR in 8 (38.1%) patients, PR in 10 (47.6%) patients, stable disease in 1 (4.8%) patients and progressive disease in 2 (9.5%) patients in stem cell mobilization failure group for the first trial ($p=0.95$). The use of filgrastim or lenograstim as G-CSF did not affect mobilization success. There was no significant difference between the two groups in terms of filgrastim or lenograstim mobilization ($p=0.20$). However, when the patients who received only G-CSF and chemotherapy-based mobilization protocol were evaluated, 19 (29.7%) of the patients who were mobilized with only G-CSF failed, while only 2 (8.7%) patients who received the chemotherapy-based mobilization protocol had mobilization failure ($p=0.04$). This also shows the superiority of chemotherapy-based mobilization.

Post-Transplant Outcomes

All of the patients finally underwent ASCT. Remarkably, disease status after ASCT (on Day +100) was CR in 38 (61.3%) patients, PR in 1 (1.6%) patients, stable disease in 20 (32.3%) patients and progressive disease in 3 (4.8%) patients in successful mobilization group. Disease status after ASCT (on Day +100) was CR in 13 (65%) patients, PR in 5 (5%) patients, stable disease in 4 (20%) patients and progressive disease in 2 (10%) patients in stem cell mobilization failure group for the first trial as shown in table 2. Relapse rate was significantly higher in patients who had stem cell mobilization failure than in patients who had successful stem cell mobilization (47.6% vs 21.2% $p=0.01$). Moreover, mortality rate was significantly higher in patients who had stem cell mobilization failure than in patients who had successful stem cell mobilization (38.1% vs 16.7% $p=0.01$).

Overall Survival

The overall survival (OS) for patients who had successful stem cell mobilization was 151.6 ± 9.3 versus 71.4 ± 7.8 months for patients who had stem cell mobilization failure for the first trial with statistically significant difference as shown in Figure 1 ($p=0.02$). The 3-year OS for patients had successful stem cell mobilization and patients who had stem cell mobilization failure for the first trial were 85% and 79%, respectively. The 5-year overall survival (OS) for patients had successful stem cell mobilization and patients who had stem cell mobilization failure for the first trial were 81% and 63%, respectively. OS was better in patients with lymphoma in whom the first mobilization trial was successful.

The disease free survival (DFS) for patients who had successful stem cell mobilization was 111.9 ± 10.6 versus 57.6 ± 6.4 months for patients who had stem cell mobilization failure for the first trial with statistically significant difference as shown in Figure 2 ($p=0.004$). The 3-year DFS for patients had successful stem cell mobilization and patients who had stem cell mobilization failure for the first trial were 82% and 74%, respectively. The 5-year DFS for patients had successful stem cell mobilization and patients who had stem cell mobilization failure for the first trial were 68% and 44%, respectively.

Discussion

Stem cell mobilization of a significant proportion of patients with lymphoma is still difficult. Factors predicting poor mobilization are still not fully explained. An obvious reason for these difficulties might be the fact that previous studies have been heterogeneous concerning diagnosis, prior therapy and mobilization regimen used (7). The frequency of mobilization failure was 24.1% in the first mobilization in this study. No factor was detected in analysis which would cause mobilization failure in lymphoma patients in this study. No statistically significant difference was found between age, sex, stage of diagnosis, ECOG PS, bone marrow infiltration at diagnosis, induction chemotherapy, chemotherapy cycle before stem cell mobilization, disease status before ASCT, receiving radiotherapy before mobilization, lymphoma types and mobilization regimen in both groups. On the other hand, OS and DFS were significantly longer in the group with successful mobilization in the first trial. It was observed that survival outcomes were worse in patients who needed plerixafor for mobilization. However, it was thought that the worse survival outcomes might be due to the poor bone marrow reserve and disease status before ASCT in patients who needed plerixafor for mobilization.

For successful ASCT, one of the most important factors is to mobilize sufficient numbers of CD34⁺ cell. In this study, the cut-off value of 2×10^6 /kg body weight CD34⁺ cells was determined as the target for a successful mobilization procedure. It can be thought that the necessity of using plerixafor can be predicted according to the number of peripheral CD34 cells. CD34 cells on apheresis days was reported to be the best mobilization failure predictor (10). Additionally, CD34 cell count was a hint for preemptive plerixafor use. The authors suggested a low level of CD34⁺ in peripheral blood on day +13 as a possible criterion for initiating plerixafor administration (11). In this study, the number of CD34⁺ cells of the apheresis product was observed to be significantly higher in patients who were successful in the first mobilization.

Recent studies reported that the incidence of mobilization failure was in lymphoma as high as 46% (12-14). Variables already reported to be associated with mobilization failure include age, body weight, diagnosis, type of lymphoma and dose of chemotherapy, extent of cell recovery from chemotherapy, bone marrow involvement of lymphoma cells, prior radiation therapy and interval from the diagnosis to mobilization (12-15). On the other hand, some hematological parameters such as cytopenia at any stage of mobilization, high MCV, long myelosuppression between salvage chemotherapies, poor bone marrow microenvironment can predict mobilization failure. Ozkurt et al. reported that CD34⁺ cell count of the first apheresis product was positively correlated with the white blood cell count, platelet count, peripheral CD34⁺ cell count and the grade of bone marrow reticulin fibrosis (16). In this study, chemotherapy-based mobilization was seen superior than G-CSF mobilization. Additionally, platelet count before the mobilization was higher in patients who had successful stem cell mobilization than patients who had stem cell mobilization failure. Apart from these two prognostic factors, none of the patient and disease characteristics we analyzed were associated with mobilization failure. Prognostic factors such as patients' characteristics (age, gender, diagnosis, bone marrow involvement, previous number of chemotherapy lines, previous radiotherapy) were also not found associated with mobilization failure in previous clinical studies (12, 14).

It is not clear that whether patients with treatment efficiency may be best mobilized by higher doses of chemotherapy and/or G-CSF. Previous some studies demonstrated the superiority of chemotherapy plus growth factors over growth factor alone for mobilization (6, 17, 18). On the other hand, Pusic et al. found similar rates of mobilization failure with chemotherapy plus growth factors and only growth factor. Additionally, Andre et al. found no significant difference in CD34⁺ cell harvest yields between 131 patients randomized to receive 5 or 10

µg/kg/day of G-CSF following mobilization chemotherapy (19). In our study, it was observed that mobilization regime did not affect mobilization failure. However, when the patients who received only G-CSF and chemotherapy-based mobilization protocol were evaluated, chemotherapy-based mobilization was seen superior.

As a result, the success rate of the first mobilization trial was found to be higher in patients with high platelet count before mobilization and patients who received a chemotherapy-based mobilization protocol. This study had a few limitations. First, this study was retrospective. Second, all patients did not receive the same induction chemotherapy before mobilization. Third, the diagnosis of the patients was very heterogeneous. In the patients who had mobilization failure for the first trial, plerixafor was used at a later mobilization, and those patients had an adequate amount of stem cells for ASCT. Parameters predicting mobilization failure would let a preemptive, more cost-effective use of such agents during the first mobilization attempt, however risk factors for mobilization failure are still not clear.

Conflict of Interests: The authors of this paper have no conflict of interests, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Role of the funding source: None.

Ethical approval: All of the ethical considerations had been strictly followed in accordance with the 1964 Helsinki declaration. As a standard care/action of the hospitals of the Hacettepe University Medical School, Bone Marrow Transplantation Center, Turkey, it has been recognized from the patient records that all of the studied patients had given informed consents at the time of hospitalization and before the administration of relevant diagnostic/therapeutic standard of care.

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Table 1. Baseline clinical and demographic characteristics of patients			
Parameters	Patients who had successful stem cell mobilization	Patients who had stem cell mobilization failure*	P
N (%)	66 (75.9%)	21 (24.1%)	
Male/female (%)	38/28 (57.6%/42.4%)	15/6 (71.4%/28.6%)	0.25
Median age at diagnosis (range), years	48 (18-70)	53 (18-66)	0.07
ECOG PS 0/1/2	2/49/15 (3%/74.2%/22.7%)	0/16/5 (0/76.2%/23.8%)	0.72
Type of lymphoma			0.45
Hodgkin lymphoma	18 (27.3%)	4 (19.0%)	
Nodular sclerosis classical HL	13 (19.7%)	3 (14.3%)	
Mixed cellularity classical HL	4 (6.1%)	1 (4.8%)	

Lymphocyte depleted classical HL	1 (1.5%)	0	
Non-Hodgkin lymphoma	48 (72.7%)	17 (81.0%)	
Diffuse Large B Cell Lymphoma	28 (42.4%)	9 (42.9%)	
Mantle cell lymphoma	9 (13.6%)	3 (14.3%)	
Follicular lymphoma	4 (6.1%)	1 (4.8%)	
Burkit lymphoma	2 (3%)	0	
Peripheral T cell lymphoma	4 (6.1%)	1 (4.8%)	
Angioimmunoblastic T cell lymphoma	0	1 (4.8%)	
Hepatosplenic T cell lymphoma	1 (1.5%)	0	
Stage at diagnosis	0/11/21/34	0/3/5/13	0.69
I/II/III/IV	0/16.7%/31.8%/51.5%	0/14.3%/23.8%/61.9%	
Bone marrow infiltration at diagnosis	25 (37.9%)	11 (52.4%)	0.24
Induction chemotherapy			0.51
ABVD	18 (27.3%)	5 (23.8%)	
CHOEP	3 (4.5%)	3 (14.3%)	
CHOP	35 (53.0%)	12 (57.1%)	
MPV	4 (6.1%)	0	
EPOCH	0	0	
CHOP/DHAP	2 (3%)	0	

H-MTX-ARA-C	4 (6.1%)	1 (4.8%)	
Rescue chemotherapy			0.49
ICE	42 (70.0%)	12 (66.7%)	
DHAP	5 (8.3%)	4 (22.2%)	
MPV	3 (5%)	0	
GDP	1 (1.7%)	1 (5.6%)	
H-MTX-ARA-C	3 (5.0%)	1 (5.6%)	
BEACOPP	3 (5.0%)	0	
Mobilization in first-line therapy	6 (9.1%)	3 (14.3%)	0.49
Mobilization after rescue therapy	60 (90.6%)	18 (85.7%)	0.49
Radiotherapy	21 (31.8%)	4 (19%)	0.26
Chemotherapy cycle before stem cell mobilization	10 (5-17)	10 (6-18)	0.78
Disease status before ASCT (9)			0.95
CR	27 (40.9%)	8 (38.1%)	
PR	28 (42.4%)	10 (47.6%)	
Stable disease	5 (7.6%)	1 (4.8%)	
Progressive disease	6 (9.1%)	2 (9.5%)	
Platelet count before the mobilization ($\times 10^9/L$)	258 (78–650)	120 (48–470)	0.041
CD 34+ $10^6/kg$ (mean \pm SD)	9.5 \pm 8.1	5.5 \pm 3.3	0.002

Mobilization protocol			0.20
Filgrastim	43 (65.2%)	18 (85.7%)	
Lenograstim	2 (3%)	1 (4.8%)	
Filgrastim + ICE	13 (19.7%)	2 (9.5%)	
Filgrastim + Cyclophosphamide	8 (12.1%)	0	

Abbreviations: ASCT: autologous stem cell transplantation; CR: complete response; G-CSF: Granulocyte colony stimulating factor; PR: partial response.

* Twenty-one patients received plerixafor as an additional mobilizing agent for second apheresis.

**Rituximab added to chemotherapy regimen in CD 20+ lymphoma

Parameters	Patients who had successful stem cell mobilization	Patients who had stem cell mobilization failure*	P
Disease status after ASCT (9)			0.53
CR	38 (61.3%)	13 (65.0%)	
PR	1 (1.6%)	5 (5.0%)	
Stable disease	20 (32.3%)	4 (20.0%)	
Progressive disease	3 (4.8%)	2 (10.0%)	

Relapse (%)	14 (21.2%)	10 (47.6%)	0.01
Mortality (%)	11 (16.7%)	9 (42.9%)	0.01

Abbreviations: ASCT: autologous stem cell transplantation; CR: complete response; PR: partial response.

* Twenty-one patients received plerixafor as an additional mobilizing agent for second apheresis.

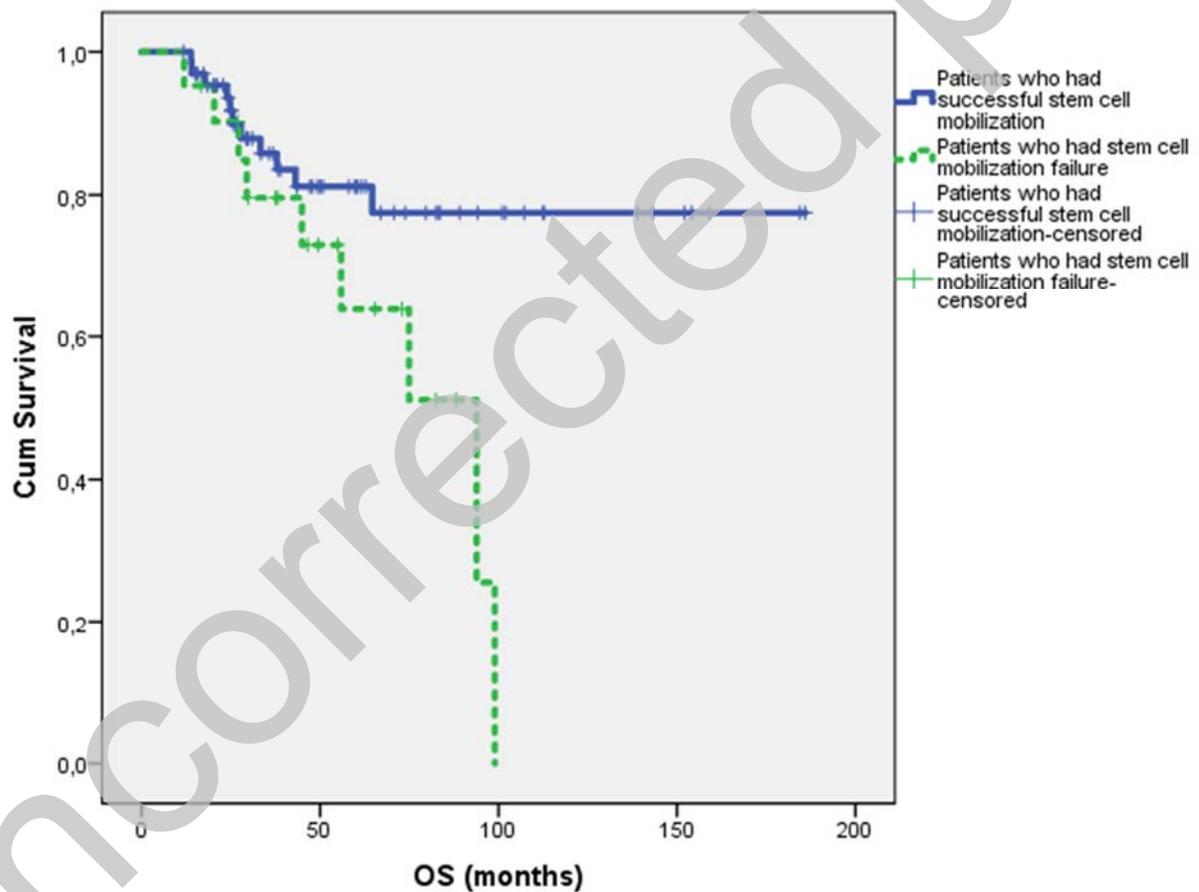


Figure 1. Overall survival patients who had successful stem cell mobilization and patients who had stem cell mobilization failure (p=0.02)

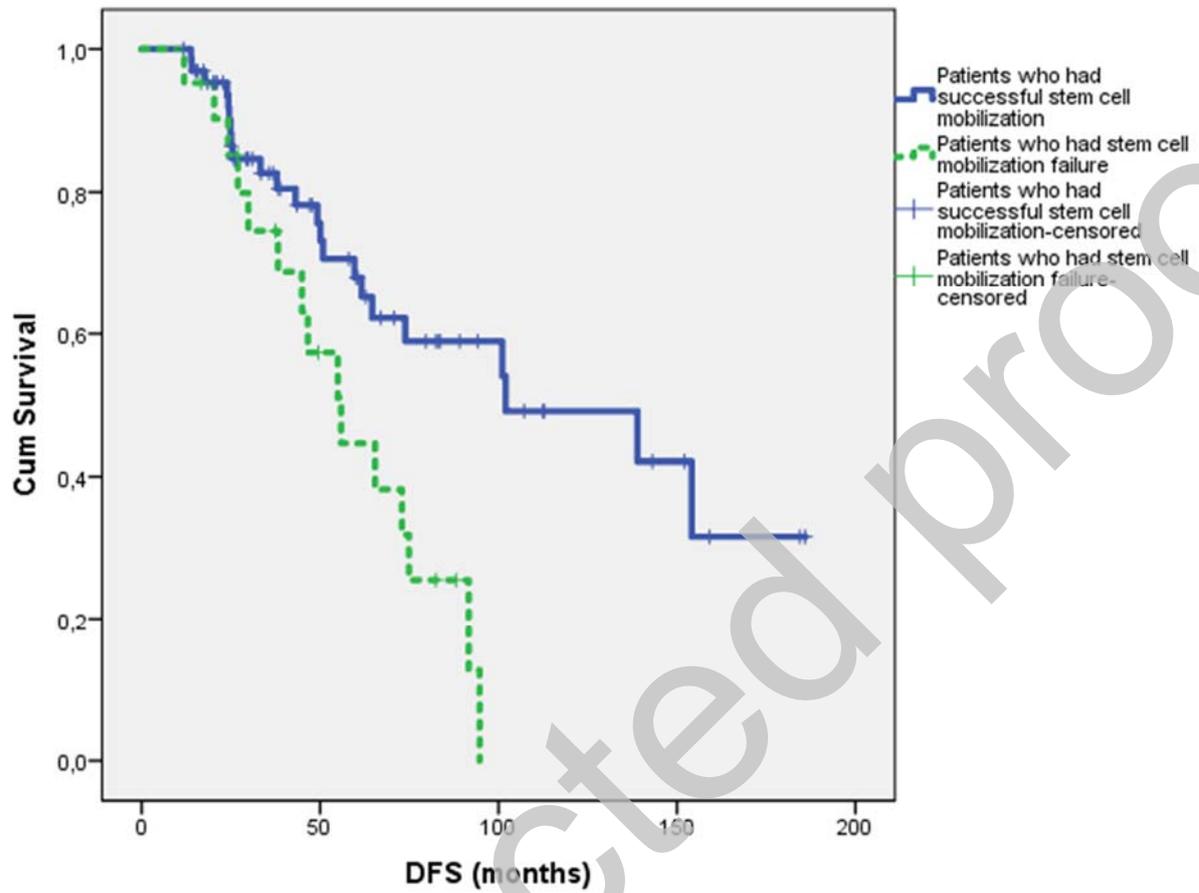


Figure 2. Disease free survival patients who had successful stem cell mobilization and patients who had stem cell mobilization failure (p=0.004).