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Comparison of Single Day Versus Two and Three Day Fractionated Infusion of Peripheral Stem Cells in Autologous Transplantation

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ABSTRACT

Purpose: The aim of this study was to investigate the safety, difference in duration of engraftment and relapse rates between autologous transplant patients who had their stem cell infusions during a single day or multiple days.

Methods: In this retrospective study the clinical data of 77 ASCT patients from a single center,30 of whom were transplanted in fractionated infusions were investigated. Duration of engraftment, side effects during the transplant, progression free survival (PFS) and overall survival (OS) data of the two groups was compared.

Results: There was no statistical difference between single day and fractionated infusion patients regarding neutrophil engraftment, toxic side effects, PFS, OS and relapse rate at 18 months. Platelet engraftment was delayed for one day in the fractionated group, which did not cause prolonged hospitalization. The transplant patients who had multiple day infusion had similar engraftment duration despite their lower average $CD34^+$ cell counts.

Conclusion: Fractionated infusions lead to similar engraftment duration to single day infusion for ASCT. The higher CFU cell number seen in the poorly mobilized patients may have a key role in the adequate engraftment. The fractionated infusion approach for such patients was feasible, safe and no increase of the disease relapse was observed with this procedure.

Keywords: Autologous; hematopoietic stem cell transplantation; fractionated stem cell; infusion.

ÖZET

Amaç: Bu çalışmanın amacı otolog kök hücre nakli yapılan hastalarda tek gün ve ardışık günlerde yapılan kök hücre ürün transfüzyonların güvenliğini,engraftman sürelerindeki farkı ve nüks oranları üzerindeki etkisini araştırmaktır.

Yöntemler: Bu retrospektif çalışmada 77 OKİT hastasının tek bir merkezdeki klinik verileri incelendi. Bu hastaların içinden 30 kişiye ürün volümü yüksek olması nedeniyle fraksiyone infüzyonla transplantasyon yapıldı, geri kalan 47 kişiye tek fraksiyonda transfüzyon yapıldı. iki grup arasında, nakil sırasındaki görülen yan etkilerin sıklığı, engraftman süreleri, hastanede yatış süreleri , progresyonsuz sağ kalım (PSK) ve toplam sağ kalım (TSK) verilerin karşılaştırılması yapıldı.

Bulgular: Ortanca 18 aylık takip süresi sonunda, tek günde kök hücre infüzyonu yapılan hastalar ile fraksiyone infüzyonlu hastalar arasında,nötrofil engraftmanı, toksik yan etkiler, PSK ve TSK oranları arasında istatistiksel olarak fark saptanmadı. Fraksiyone infüzyon alan grupta trombosit engraftmanı ortalama olarak bir gün daha uzun sürdü ancak bu durum klinik olarak anlamlı bir soruna yol açmadığı ve ortalama hastane yatış süresini uzatmadığı görüldü. hastaneye kaldırılma. Birden fazla gün infüzyon uygulanan nakil hastaların ortalama CD34+ kök hücre oranlarının daha düşük olmasına rağmen diğer hastalar ile benzer engraftman ve yatış süresine sahip oldukları gözlendi.

Sonuç: Otolog kök hücre transplantasyonlarında, fraksiyone kök hücre infüzyonları, tek günlük infüzyonlara benzer engraftman sürelerine sahiplerdir. Zor kök hücre mobilizasyonu olan hastaların hücre ürünlerindeki daha yüksek koloni oluşturan birim (CFU) sayısı, başarılı engraftmanda anahtar rol oynayabilir. Bu tür hastalarda fraksiyone infüzyon yaklaşımı güvenlidir, hastalık nüksünü arttırmamaktadır ve kolay uygulanabilir bir yöntemdir.

Anahtar Kelimeler: fraksiyone, kök hücre, infüzyon.

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Failure of stem cell mobilization occurs in %14 to %30 among ASCT candidates (1,2). Recent studies show that second mobilization attempt provides sufficient stem cell quantity in only %23 of these patients (3). The common practice in such cases is to combine the cryo preserved stem cell products from both previous and the last apheresis, in order to obtain sufficient total number of $CD34^+$ cells. The end result is very high volumes of stem cell product which cannot be infused in a single day safely because of the high total dymethyl sulfoxide (DMSO) quantity in the product. To avoid DMSO toxicity and volume overload the infusion of the stem cells is compulsory divided to multiple days (4,5,6). DMSO can be potentially cardiotoxic and affects the gas exchange in the alveoli (7,8). DMSO toxicity depends on the total volume infused and patients who undergo multiple apheresis for stem cell collection are at greater risk for DMSO side affects at the time of infusion (9,10). This was recognized by Martino et al, who proposed fractionated stem cell infusion to reduce cardiac toxicity (11). Fractionated infusion of stem cells in patients with multiple apheresis was since then employed without major acute side effects.

Other concerns about the fractionated stem cell infusions are delayed engraftment and the increased possibility of circulating tumor cell (CTC) contamination which may come with the large stem cell volume infused. The latter is a matter of concern especially in patients with poorly controlled or high risk disease.(12,13,14,15)

Despite the common practice and the increasing number of ASCT worldwide there is little information regarding the effect of fractionated infusions on engraftment duration.

The aim of this study was to analyze whether there is a difference in side effects, duration of engraftment and survival between autologous transplants who had their stem cell infusion during a single day or multiple days.

Material and Methods

Patients

Hospital records of a total of 77 patients, who underwent autologous peripheral hematopoietic stem cell transplantation (ASCT) between 2011 and 2013 in Acıbadem University Hospital in Istanbul were retrospectively analyzed. Only the patients, with eligible clinical data, diagnosed with multiple myeloma (n=47), Hodgkin's disease (n=12) and Non-Hodgkin lymphoma (n=18) were included in the study, because our clinic does not perform ASCT's for other indications. Single course of stem cell mobilization and successful harvesting was performed in 47 ASCT patients and 30 patients had poor stem cell mobilization after the first course which needed a second course of stem cell mobilization 3 weeks later.

Age, gender, diagnosis, remission status, Eastern Cooperative Oncology Group (ECOG) performance status, co-morbidities, number of previous treatment lines, number of infused $CD34^+$ cells per body weight (kg), amount of infused CFU–GM per body weight (kg), number of $CD34^+$ cell, infusion days, infused volume (L) of stem cells, time–to–neutrophil (TTNE) and platelet engraftment (TTPE), hospitalization days, cardiopulmonary toxicities observed during the stem cell infusion, febrile neutropenic episodes, pre transplant disease status and post transplant patient survival data was taken for investigation from the clinical records (Table.1).

Table 1: Patient characteristics

	Infusion days		
Variables	**1 (n=47)**	**≥2 (n=30)**	**P**
Age, years, median (IQR)	53 (46–62)	61 (52–65)	0.08
Gender, male, n (%)	21 (44.7)	17 (56.7)	0.31
Diagnosis			0.82
Multiple myeloma	29 (61.7)	18 (60.0)	
Non–Hodgkin lymphoma	10 (21.3)	8 (26.7)	
Hodgkin's disease	8 (17.0)	4 (13.3)	
Status of remission, n (%)			0.14
Complete response	21 (44.7)	13 (44.3)	
Partial response	25 (53.2)	13 (44.3)	
Stable disease	1 (2.1)	4 (13.3)	
ECOG performance status, ≥2, n (%)	4 (8.5)	7 (23.3)	0.10
Comorbidities, n (%)	19 (40.4)	21 (70.0)	0.01
Previous treatment lines, median (IQR)	1 (1–2)	1 (1–2)	0.77
Infused $CD34^+$/kg ($x10^6$), median (IQR)	5.21 (3.73–7.68)	3.98 (2.74–5.22)	0.003
Infused CFU–GM/kg, median (IQR)	22.3 (13.2–39.2)	47.6 (31.0–65.3)	<0.001
Infused volume, L, median (IQR)	0.72 (0.48–0.86)	1.30 (1.15–1.70)	<0.001

Local institutional ethical committee approved the retrospective study protocol in accordance with Turkish legal regulations and Helsinki declaration. Informed consent was obtained from all patients.

Stem Cell Collection

All patients underwent stem cell mobilization with cyclophosphamide 2gr/m^2/day for one day. Those with low creatinine clearance and age over 65 years were given total dose of 2gr/day cyclophosphamide. Seven days after the cyclophosphamide infusion the patients were administered subcutaneous filgrastim injections at a dose of 10µg/kg/day for 5 to 7 days and the stem cell apheresis was started on the 3'rd day of filgrastim. $CD34^+$ stem cell were collected with Fresenius-AS-TEC 204 (Fresenius Hemocare, Redmon , WA, USA) or Cobe Spectra (Gambro BCT, MA, USA). İn cases where the count of peripheral $CD34^+$ cells was less than 10/µL on the 3'rd day after filgrastim was commenced, the apheresis was either postponed for the next day until the peripheral $CD34^+$ cells reach the sufficient number or was cancelled in patients which never achieved that . Minimum of 2.0×10^6 $CD34^+$ cells/kg body weight was aimed for apheresis. Combination of autologous plasma,6% hydroxyethyl starch (HES), and 7,5% DMSO were utilized as the cryoprotectant solution. Initially, stem cells were kept at –4°C. A vapor phase container was used to store the samples at–156°C. In patients with insufficient $CD34^+$/kg quantities after 4 days of apheresis, the procedure was cancelled and they were called after 3 weeks for second stem cell mobilization and harvesting as described above.

Conditioning Regimens

In 30 patients with Hodgkin or Non–Hodgkin's disease, BEAM (BCNU, 300 mg/m^2 on day –6; Etoposide, 200mg/m^2, on days –5 to –2; ARA–C, 200mg/m^2, on days –5 to –2; and Melphalan, 140mg/m^2 on day –1) chemotherapy was administered. High dose Melphalan, 200 mg/m^2 on day –2 was used in 39 patients with multiple myeloma. Melphalan dose was reduced to 140 mg/m^2 in 8 myeloma patients with renal failure.

Study Endpoints

Primary endpoints of the study were time to neutrophil engraftment (TTNE) ,time to platelet engraftment (TTPE) and cardiac and pulmonary side effects attributable to DMSO toxicity . Neutrophil and platelet engraftments were defined as the time between the first stem cell infusion and first day of three consecutive days with an absolute neutrophil count greater than 500/µL, and platelet count >20,000/µL without transfusion within last seven days before the reconstitution, respectively. Cardiac and pulmonary toxicity was defined according to the Common Terminology Criteria for Adverse Events (CTCAE) volume 4.0.

Secondary endpoints include duration of hospitalization, frequency of febrile neutropenia episodes, time to progression and overall survival after 18 months of median follow up. Duration of hospitalization was estimated as the time from stem cell infusion to hospital discharge. Disease progression for multiple myeloma, Hodgkin's disease, Non-Hodgkin's lymphoma, was defined according the NCCN 2015 guidelines criteria.

Statistical Analysis

Patients were divided into two groups: single day versus fractionated day (infusion for 2 or more days) stem cell rescue. Shapiro–Wilks test was used to assess the distribution normality. Continuous variables were expressed as median [interquartile range (IQR)]. Skewed data was compared by Wilcoxon rank sum test. Student's t–test was employed to compare normally distributed data. Categorical variables were compared by χ^2 test with or without Yate's correction or Fisher exact testwhere appropriate.

Engraftment was defined to be the event. TTNE, TTPE and hospitalization days were presented as median [interquartile range (IQR)]. Differences between the survival groups were assessed usingKaplan–Meier survival curves and two–tailed log–rank test. Cox proportional hazard model was used to determine the predictors of TTNE, TTPE, hospitalization days, progression free survival (PFS) and overall survival (OS) in uni and multivariate analyses. Variables were dichotomized using median values before the univariate analyses. Variables with a $p \leq 0.25$ in univariate analyses were included into the multivariate analyses. The effect size of potential predictor was expressed as hazard ratio (HR) and 95% confidential interval (95% CI). Only predictors with a $p \leq 0.10$ were reported. A two-sided p value <0.05 was considered to declare statistical significance in all analyses.

Results

Demographic Characteristics

A total of 77 patients were included into the final analysis, 47 in single–day and 30 in multi–day infusion groups. Median number of infusion days in multi–day group was 2 (2–4). Patients in multi–day infusion group had a tendency to be older and to have poorer ECOG performance status (p= 0.08 and 0.10, respectively). Accompanying comorbidity conditions were more prevalent in multi–day infusion group (p= 0.01). Infused number of $CD34^+$ cells were lower in the multi-day patients , but the CFU–GM cells per body weight (kg) and the total volume of the apheresis product were higher as expected (Table 1).

Median follow up for all the patients was 18 months (range 11 to 36 months), with no difference between the groups (median 18 months for each).

Primary Endpoints

Engraftment failure did not occur in any of the patients included in the study. TTNE was 9 (9–10) days in single– and 10 (9–10) days in multi–day infusion groups (p= 0.053, Figure 1). TTPE was shorter in patients receiving single–day infusion [10 (10–11) versus 12 (11–13) days, p=0.001, Figure 2]. Only one patient in each group had signs and symptoms of transplant related toxicity. Both of the patients had symptoms of grade 2 heart failure (CTCAE vol.4.0) related to volume overload rather than DMSO toxicity (2.1% versus 3.3%, respectively, p= 0.75)

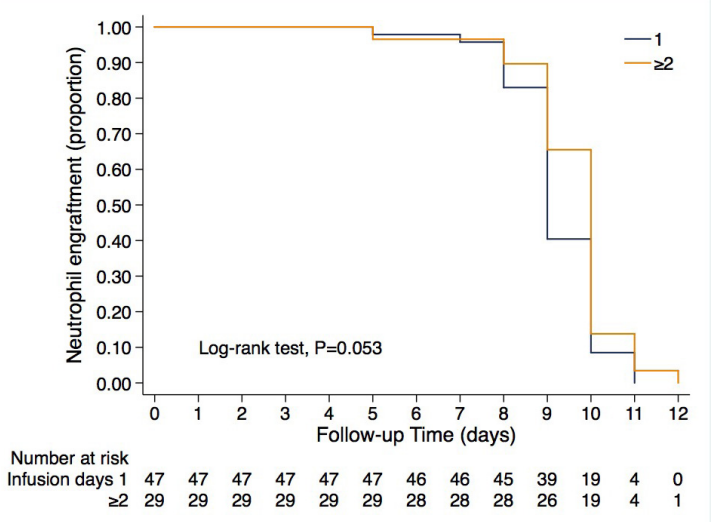

Figure 1: Time–to–neutrophil engraftment (TTNE) in patients receiving stem cells in single–day (1) and multi–day infusions (≥2).

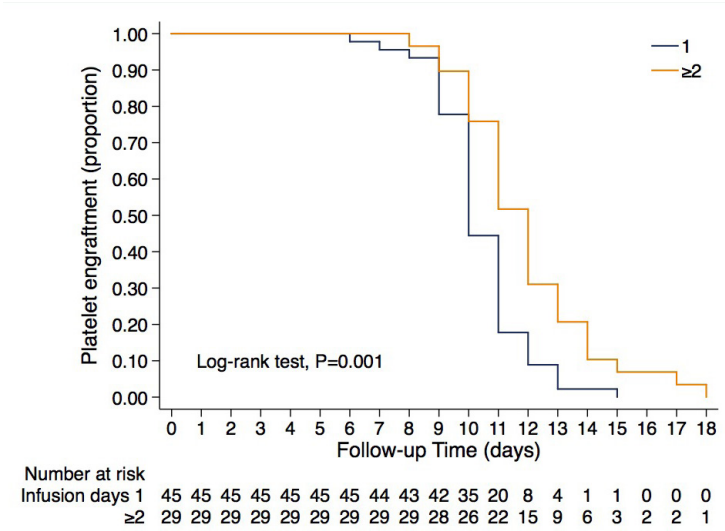

Figure 2: Time–to-platelet engraftment (TTPE)in patients receiving stem cells in single–day (1) and multi–day infusions (≥2).

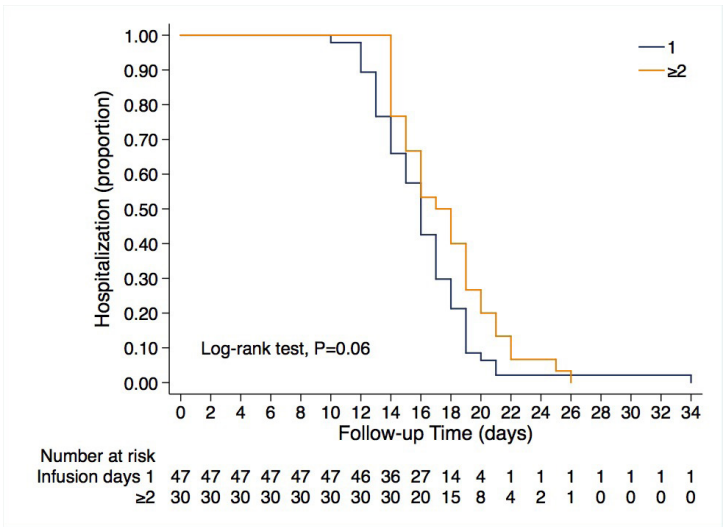

Figure 3: Duration of hospitalization in patients receiving stem cells in single–day (1) and multi–day infusions (≥2)

Secondary Endpoints

Duration of hospitalization was comparable in single– and multi–day infusion of stem cells [16 (14–18) versus 17 (15–20) days, p= 0.06, respectively, Figure 3]. Frequency of febrile neutropenia during the hospitalization in single–day infusion group was 20/47 (42.6%) and 14/30 (46.7%) in multi–day infusion group (p= 0.72). Median overall survival (OS) was not reached in both groups of patients and there was no statistical difference between them regarding OS after 18 months follow up. In the single-day group 41 of 47patients were alive at the end of the follow up and 6 died of relapsed disease. The patients of the multi-day

group had better OS - 28 /30 but this was statistically insignificant (OS single day infusion group:%88,3 *vs* OS in the fractionated infusions group:%93,1, *p*=0,85, %95 CI). The cause of death of the 2 patients in this group was progression of their primary disease.

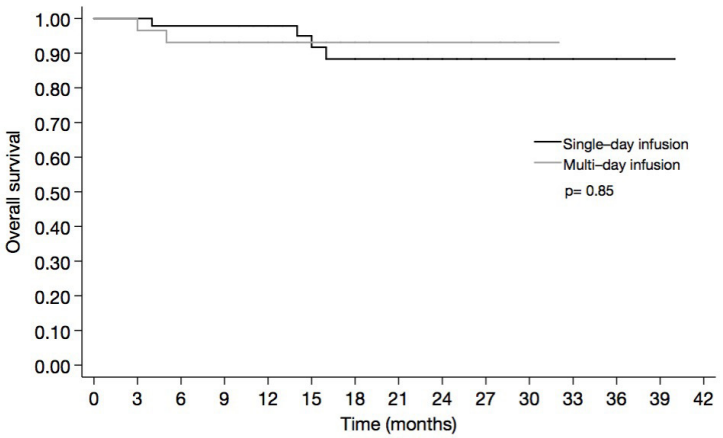

Figure 4: Overall survival (OS) of the patients receiving stem cells in single–day (1) and multi–day infusions (≥2)

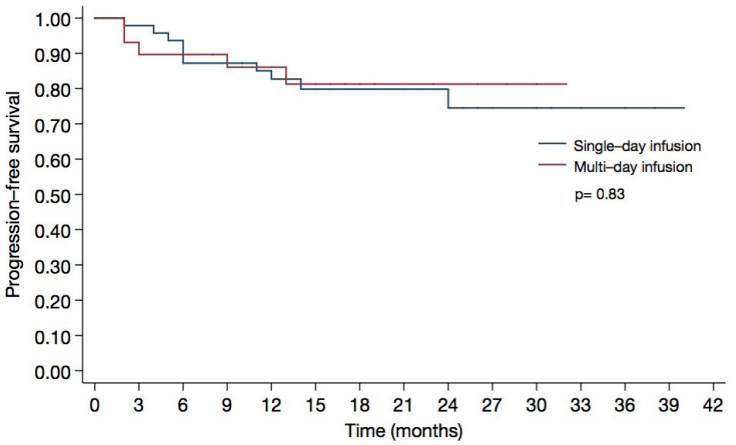

Figure 5: Progression-free survival (PFS) of the patients receiving stem cells in single–day (1) and multi–day infusions (≥2)

Progression free survival was also not reached in the patients of the two groups after the 18 months of follow up 35/47 patients in the single-day group and 24/30 patients of the multi-day group were disease free, but there was no statistical difference in the PFS between the groups (PFS in the single day infusion group:%79,8 *vs* PFS in the fractionated infusions %81,3,*p*=0,83,%95CI).

Confounding Factors

Multiple logistic regression analyses revealed that the only independent predictor of TTNE and TTPE was the infused number of $CD34^+$ cells per body weight (kg) (≥5 x 10^6) instead of number of infusion days (HR: 1.68, 95% CI 1.03 to 2.76, p= 0.04 for TTNE; and HR: 1.79, 95% CI 1.05 to 3.03, p= 0.03, for TTPE). None of the variables included into the model predicted the duration of hospitalization (HR: 1.58, 95% CI 0.96 to 2.60, p= 0.07, for $CD34^+$ cells/kg ≥5.0 x 10^6; and HR: 0.63, 95% CI 0.37 to 1.07, p= 0.09 for CFU–GM/kg ≥35)(Table 2).

Table 2: Statistical comparison of neutropenic fever episodes, hospitalization duration, cardiopulmonary side effects neutrophil engraftment, platelet engraftment time, overall survival (OS) and progression free survival (PFS) of the patients in both groups.

End points	Single day infusion group (n:47)	Fractionated infusion group (n:30)	P value
Median (IQR) neutrophil engraftment	9 days (9-10)	10 days (9-10)	0.053
Median (IQR) platelet engraftment	10 days (10-12)	12 days (10-13)	**0.001**
Median (IQR) duration of hospitalization	16 days (14-18)	17 days (15-20)	0.06
Febrile neutropenia	%42.6 (20 patients)	%46.7 (14 patients)	0.72
Cardio-pulmonary side effects	%2.1 (1 patient)	%3.3 (1 patient)	0.75
Median PFS (%95 CI)	NR	NR	-
18-month PFS	%79.8	%81.3	0.83
Median OS (%95 CI)	NR	NR	-
18-month OS	%88.3	%93.1	0.85

Discussion

High dose chemotherapy supported with autologous stem cell transplant is a well established treatment procedure used for disease consolidation especially in malignancies like multiple myeloma and lymphoma. It is a standard therapeutic modality which is included in many treatment guidelines for hematologic malignancies usually as a second line therapy. Although many years have passed since the first ASCT and the worldwide experience continues to increase, there are still some subjects of debate regarding the patients with poor stem cell mobilization.

Many transplant centers offer these patients other treatments for consolidation or just follow them up closely. The most important reason not to proceed with the stem cell harvesting is the disbelief that a subsequent mobilization cycle can provide enough quantity of stem cells. This may be true because usually the bone marrow stem cell mobilization capacity of these patients is heavily affected by the previous chemotherapies and other factors such as their age and other systemic illnesses (e.g. renal failure, liver failure and hypothyroidism). Nevertheless these patients can still provide some stem cells. This is an important point that deserves to be taken into account before excluding a patient from a possibly beneficial treatment like ASCT.

Another concern about the multiple harvested patients is the large volume of the end product which contains higher quantities of DMSO. Decreasing significantly the concentration of DMSO is not an option because it may also decrease the viability of cryopreserved stem cells which are already marginally sufficient. Thus the issue of the DMSO toxicity remains a threat especially for the patients with coexisting morbidities.

More than a decade ago Martinelli and his colleagues described a safe method for fractionated infusion of the stem cells. The pre-medications and close monitoring of the patient during the procedure reduces the side effects and toxic events. Today many transplant centers routinely perform fractionated ASCT's without major concern.

The focus of this study is to document the safety and side effects of the fractionated ASCT and to investigate the efficacy and long term effects of this type of transplant.

More than one third (%38) of patients in this study of 77 ASCT patients had fractionated transplants dispersed over 2 or more days as a result of larger stem cell volume. These patients experienced mobilization failure initially but all of them managed to provide more than $2x10^6$/kg $CD34^+$ cells after two mobilization courses with G-CSF and cyclophosphamide. None of the patients had disease progression in the gap between the two mobilizations. We think that the initial mobilization failure was due to factors such as older age and higher percentage of patients with active disease. All these factors and especially the number of previous chemotherapies have negative effect on the stem cell mobilization as described in some studies (4,16). The number of previous treatments was the same in both groups and this alone could not explain the lower levels of $CD34^+$ cells in the multi-day group. The patient number of this study is too small to make any conclusion that denies the impact of the previous chemotherapies ,given the solid data from the literature. Nevertheless it may be possible that other factors like poorly controlled disease and advanced age may have more prominent negative effect on stem cell mobilization than the previous chemotherapies. This was true for the patients in the fractionated group where the average age and the number of patients with poorly controlled disease was greater and both these factors were shown to have statistically significant effect over the stem cell mobilization in the univariate analysis. Interestingly the CFU levels were higher in the fractionated group despite lower $CD34^+$ cell levels. Generally it is assumed that the amounts of CD34 and CFU are correlated as the former is the progenitor of the latter. This can be possibly explained by longer exposure of fractionated transplant patients to G-CSF leading to shifting of $CD34^+$ cells to the committed CFU cell pool. The higher number of CFU/kg levels in the poorly harvested patients could have a positive effect on engraftment process and can compensate for the lower $CD34^+$ cell count (17).

The patients with poor mobilization in this study had median 8 apheresis cycles (7 to 9) which is twice than the normally harvested patients. Increasing the apheresis cycles could also increase the risk of apheresis complications some of which may be life threatening, but none of the patients in this study experienced major side effects. There were only 4 patients who had headache and muscle cramps, which did not mandate the cessation of the apheresis procedure.

During the fractionated infusions only 1 patient in the multi-day group had signs of grade 2 heart failure which occurred on the second day of infusions and was

managed quickly with diuretics and oxygen support. This patient did not have any other known pre existing cardiac disease except well controlled primary hypertension. The patient recovered completely and no permanent cardiac damage was seen during his long term follow up.

Overall the fractionated infusion was well tolerated and the patients remained clinically stable just as well as the single-day patients.

PFS and OS in the fractionated group was similar to the single day transfusion group patients (Table 3). A study by Kiel and his colleagues showed that extended stem cell apheresis can increase the risk of disease relapse by collecting and re infusing the circulating tumor cells (CTC) in the multiple myeloma patients(12).CTC counts prior to transplantation were not estimated in this study but relapse rate in the fractionated group during the 18 month follow up period was not statistically different from the single day infusion transplants. The reason for the lack of difference in the post transplant disease progression is the small number of patients included in this study. Another possible reason may be cyclophosphamide which was used in the mobilization regimen. Cyclophosphamide may have an in vivo purging effect on the remnant malignant cells which in turn helps the patient to enter the transplant with better controlled disease. More investigations and studies with more patients included are needed to enlighten this issue.

Table 3: Multiple logistic regression analysis of the variables and Cox proportional hazard models.

Neutrophil engraftment			
	Hazard ratio	**95% CI**	**P**
CD34 ≥5.0 x10^6	1.68	1.03–2.76	0.04
Platelet engraftment			
	Hazard ratio	**95% CI**	**P**
CD34 ≥5.0 x10^6	1.79	1.05–3.03	0.03
Hospitalization			
	Hazard ratio	**95% CI**	**P**
CD34 ≥5.0 x10^6	1.58	0.96–2.60	0.07
CFU–GM/kg ≥35	0.63	0.37–1.07	0.09

Remission status, infusion days, CD34, CFU–GM, age, ECOG, infused volume, and presence of comorbidities were included into models. Only variables with a p–value of ≤0.10 were presented here.

After almost 2 years of follow up, most of the patients in this heterogeneous group of poorly harvested ASCT patients still remain in remission and in good performance status, just like the normally harvested patients. Special medical attention, more medical interventions and expenses may be the major draw-backs when deciding to proceed with the mobilization in patients with poor stem cell harvesting, but we believe that these patients can still benefit from the ASCT just like the other patients.

The kinetics of stem cell mobilization and engraftment are still not completely understood and more studies are needed to clarify the most accurate assessment of the yield of harvesting and for predicting the successful engraftment and post transplant relapse risk.

This study shows that fractionated infusion leads to similar engraftment duration to single day infusion for ASCT and it is feasible, safe and has no adverse effects to the disease outcome. Therefore, failure to collect stem cells during the first mobilization may not be a cause for concern if it can be compensated during the second mobilization.

Conclusion

Large volumes of stem cell products that have been thawed from poorly mobilized aotulogous stem cell transplant candidates can be safely infused when fractioned in consecutive days. This approach does not compromise engraftment and does not cause additional DMSO toxicity in patients.

Declarations

Funding

Not applicable:

Conflicts of Interest

The author declares that there is no conflict of interest.

Ethics Approval

Acibadem University and Acibadem Healthcare Institutions Medical Research Ethics Committee (ATADEK)

Date: 11.02.2014. Nr: 2014-592

Availability of Data and Material

Data can be provided upon reasonable request, however, can not be public due to legislations.

Authors' Contributions

AU: Design, Data collection, Statistical Analysis, Writing of the paper.

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