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The effect of smoking on stem cell mobilization in allogeneic donors

Allojenik vericilerde sigaranın kök hücre mobilizasyonu üzerine etkisi

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ABSTRACT

Introduction: It has been shown that there is an increase in the number of progenitor cells in the bone marrow after smoking cessation. Adequate number of stem cells should be given to the patients to provide sustained engraftment after allogeneic stem cell transplantation. Therefore, determining the factors affecting the success of peripheral stem cell mobilization in allogenic donors is very important. In this study, we aimed to investigate the effect of smoking on the amount of stem cells collected after peripheral blood stem cell mobilization in allogeneic donors.

Material and Method: The data of 157 allogeneic donors who were performed peripheral stem cell mobilization in our center were analyzed retrospectively. The donors were divided into 2 groups:active smokers (n:80) and non-smokers (n:77). Smokers were divided into two groups as donors who smoked <15 cigarette pack year and those who smoked ≥15 cigarette pack year.

Results: The median CD34+ cell count in the peripheral blood on the 5th day before apheresis was found to be significantly lower in smokers than in non-smokers (p=0.001*). Compared to the donors who smoked <15 cigarette pack year, the median CD34+ cell count in the peripheral blood on the 5th day before apheresis was significantly lower in the donors who smoked ≥15 cigarette pack year (p=0.009*).

Conclusion: During the allogeneic stem cell donor assessment, donors should be questioned for their smoking history. Smoking should be considered as a negative risk factor for peripheral stem cell mobilization, especially in the donors who smoke ≥15 cigarette pack year.

Keywords: Cigarette, allogenic donor, stem cell mobilization

ÖZ

Giriş: Sigara kullananlarda, sigaranın bırakılmasından sonra kemik iliğindeki öncü hücre sayısında artış olduğu gösterilmiştir. Allojenik kök hücre nakli sonrası engraftmanın sağlanması için, hastalara yeterli miktarda kök hücre verilmelidir. Bu nedenle, allojenik vericilerde periferik kök hücre mobilizasyonunun başarısını etkileyen faktörlerin belirlenmesi çok önemlidir. Bu çalışmada, sigaranın sağlıklı allojenik vericilerin periferik kan kök hücre mobilizasyonu sonrası toplanan kök hücre miktarı üzerine etkisini araştırmayı amaçladık.

Gereç ve Yöntem: Merkezimizde periferik kök hücre mobilizasyonu yapılan 157 allojenik vericinin verileri retrospektif olarak incelendi. Vericiler aktif sigara içenler (n:80) ve sigara içmeyenler (n:77) olmak üzere 2 kola ayrıldı. Sigara içen vericiler kendi aralarında <15 paket yıl sigara içen ve ≥15 paket yıl sigara içenler olmak üzere 2 gruba ayrılarak incelendi.

Bulgular: Aferez işleminden önceki 5. gün periferik kandaki medyan CD34+ hücre sayısı sigara içen vericilerde sigara içmeyen vericilere göre anlamlı olarak daha düşük saptandı (p=0,001*). Vericilerden ≥15 paket yıl sigara içenlerde; <15 paket yıl sigara içen vericilere kıyasla aferez işleminden önceki 5. gün periferik kandaki medyan CD34+ hücre sayısı, anlamlı olarak daha düşük bulundu (p=0,009*).

Sonuç: Allojenik kök hücre verici değerlendirmesi sırasında, vericiler sigara öyküleri açısından sorgulanmalıdır. Sigara kullanımı, özellikle ≥15 paket yıl sigara içen vericilerde periferik kök hücre mobilizasyonu için negatif bir risk faktörü olarak düşünülmelidir.

Anahtar Kelimeler: Sigara, allojenik verici, kök hücre mobilizasyonu

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INTRODUCTION

Cigarette smoke contains over 7000 chemicals and 250 known toxins (1). In developed countries, the primary cause of chronic obstructive pulmonary disease (COPD) is cigarette smoking (2). Patients with COPD may have bone marrow (BM) dysfunction (3). It has been shown that smoking causes some changes in BM and complete blood counts. Smoking increases neutrophil differentiation and because of the chronic stimulation of hematopoiesis there is an increased transit into the circulation. Therefore, neutrophilia may be observed in complete blood counts. In addition to neutrophilia, CD8+ cytotoxic T cell lymphocytosis may also be observed in complete blood counts (4). Production of smoking-related reactive oxygen species (ROS) reduces the mobilization of precursor cells from the BM (5,6). After cessation of smoking the number of precursor cells in the BM increases (7). Previous studies about the effects of smoking on BM niche and different cell populations in BM including mesenchymal stromal cells (MSCs) and endothelial cells had conflicting results (8,9). Studies have shown that MSCs express the alpha nicotinic receptor subunit (10,11). Nicotine, the predominant toxin found in the cigarette, and the addictive component of cigarette significantly inhibit the regenerative potential of MSCs (12-15). In vitro high dose nicotine impairs MSC differentiation and increases apoptosis (16). There have been several theories to explain how nicotine decreases proliferation of MSCs. One study suggests that the decrease in proliferation is dependent on the production of ROS (17). The other theory is that the decrease in proliferation may be a result of changes in the cell cycle. Nicotine has been shown to induce an increase in the ratio of G0/G1 phase cells (18). The increased ratio of cells in G0 phase may explain the observed decrease in proliferation induced by nicotine (19). These nicotine induced changes have been considered to be the underlying causes of various smoking related diseases (20).

Allogeneic hematopoietic stem cell transplantation (Allo-SCT) is used as a curative treatment in a various of benign and malignant hematological diseases. Allogeneic donor selection is of critical importance for HSCT success. This selection directly affects HSCT success and overall survival of the patient (21). For sustained engraftment after Allo-SCT, patients should receive adequate amount of hematopoietic stem cell (HSC) (22, 23). Therefore, it is crucial to find out every factor effecting the success of HSC mobilization in allogeneic donors. There is only a limited number of studies about the in vivo effects of smoke exposure on the hematopoietic microenvironment. In this single center, randomized and controlled study, we aimed to research the effect of smoking on the quantity of CD34+ cells collected after the peripheral blood (PB) HSC mobilization in allogeneic donors.

MATERIAL AND METHOD

In this study, ≥18 years old, healthy, PB stem cell donors whose mobilizations were performed in our center were included. Donors with any chronic diseases and/or any previous operation were excluded. This study was approved by the university /local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was carried out with the permission of Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Ethics Committee (Date: 19.12.2018, Decision no: 2018-12/167).

Each donor signed an informed consent before HSC collection. The cigarette pack year was defined as the total number of cigarette packs those have smoked since the date of smoking. Donors who quit smoking were excluded from the study. Donors who had a history of alcohol abuse were also excluded. Donors were divided into 2 groups: Non smokers and active smokers. Smokers were divided into two groups as donors who smoked <15 cigarette pack year and those who smoked ≥15 cigarette pack year.

Allogeneic donors received once a day (1×10 mcg/kg/day) filgrastim. All donors received filgrastim through subcutaneous route. On the 5th day, CD34+ cells were counted by multicolor flowcytomety. Stem cells were started to be collected on the same apheresis device 2 hours after the administration of the last filgrastim dose in the morning. Instead of the number of CD34+ cells collected after apheresis, we preferred to evaluate the number of CD34+ cells in the PB after the last dose of filgrastim because there are many factors not related to donors but have effects on the number of CD34+ cells collected after apheresis, like the blood volume processed or the duration of the procedure.

Statistics

IBM SPSS Statistics (version 21) was used for analysis. Categorical data were expressed as a ratio, and numerical data were expressed as median and mean ± standard deviation. The differences of peripheral CD34+ cell count and age between groups were examined by the non-parametric Mann Whitney U test. Chi-square and Fisher exact tests were used to evaluate the difference of gender between groups.

RESULTS

Totally 157 allogeneic donors were included in the study. There were 80 active smokers and 77 non-smoker donors. There was not any significant difference between smoker and non smoker donors regarding age, gender and body weight. The characteristics of the donors were given in the **Table**.

Table. The characteristics of the allogeneic donors

	Non smokers	Active smokers <15 pack year	Active smokers ≥15 pack year
n	77	46	34
Median age	32	34	32
Male/Female	46/31	29/17	20/14
Median CD34+ cell no. on the 5th day	90.8/µl	59.9/µl	49.5/µl

Median CD34+ cell number in PB on the 5th day before apheresis was 58.8/µl in active smoker donors and 90.8/µl in non-smoker donors. Median CD34+ cell number in PB on the 5th day before apheresis was significantly lower in active smoker donors compared to non-smoker donors (p=0.001*).

When the active smoker donors were divided into 2 groups according to the number of cigarette pack year, median CD34+ cell number in PB on the 5th day before apheresis was 59.9/µl in the donors who smoked <15 pack year and was 49.5/µl in the donors who smoked ≥15 pack year. Median CD34+ cell number in PB on the 5th day before apheresis was significantly lower in donors who smoked ≥15 pack year compared to donors who smoked <15 pack year (p=0.009*).

DISCUSSION

Studies have shown that the number of HSCs infused is closely related to transplant outcomes. Since early engraftment are thought to have a positive effect on survival, risk factors for HSC should be identified (24,25). Previous studies have shown that nicotine exposure decreases the regenerative potential of periodontal ligament derived stem cells (15). Researchers found that human umbilical cord blood cells which were exposed to 0.5–1.5 mg/ml nicotine showed dose-dependent decreases in proliferation and increases in apoptosis (18). In addition, decreased proliferation rates have been observed in MSCs isolated from chronic smokers. These cells showed a 2.5 fold decrease in proliferation compared with nonsmoker derived control cells. Decreased proliferation was still observed even after sub-culturing cells 3–5 times, suggesting that the effects of nicotine exposure may be permanent or last for several generations of daughter cells (26). Although, there are several studies about the effects of smoking on MSCs, periodontal ligament derived stem cells and human umbilical cord blood cells, there is only a limited number of studies about the effects of smoking on HSCs. Previous studies showed that in smokers and patients with COPD, there are fewer CD34+ stem cells in PB (27,28). Ludwig et al. (29) revealed that in female smokers there was a decreased number of CD34+ cells. In another study, the researchers observed decreased number of PCs in the PB of male smokers, and smoking cessation caused a rapid increase in the number of PCs (27). In the study conducted by Panwalkar et al. (30) no relation was observed between poor mobilization and smoking. On the other hand, in our study, we found that smoking is a negative factor for HSC mobilization. Median CD34+ cell number in PB on the 5th day before apheresis was significantly lower in active smoker donors compared to non-smoker donors. In addition to this, we found that median CD34+ cell number in PB on the 5th day before apheresis was significantly lower in donors who smoked ≥15 pack year compared to donors who smoked <15 pack year. In a study, researchers studied the effect of nicotine on HSC mobilization with granulocyte stimulating factor (G-CSF) in myeloma patients. They observed that nicotine had a significant favorable effect on HSC mobilization with G-CSF in myeloma patients (31). This is contrary to our results. To study the effects of smoking on HSC mobilization, choosing healthy allogeneic donors instead of patients with hematological malignencies may be more realistic because in patients with hematological malignencies there are so many factors that may effect the HSC mobilization and BM like the therapies received and comorbidites.

In conclusion, while evaluating a donor, smoking history should be asked and if the donor smokes, pack-year should be calculated. Smoking should be thought as a negative factor for PB stem cell mobilization especially in the donors who smoked ≥15 cigarette pack year. There is only a limited number of studies about the in vivo effects of smoke exposure on the hematopoietic microenvironment. Our study reveals that smoking is a negative risk factor for HSC mobilization in healthy allogeneic donors.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Ethics Committee (Permission granted: 19.12.2018, Decision no:2018-12/167).

Informed Consent: Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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