BRIEF REPORT

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Association of Pre-Transplant Angiopoietin-2 Index with the Risk of Acute Graft-Versus-Host Disease after Hematopoietic Stem Cell Transplantation

Pre-transplant Anjiyopoietin-2 İndeksinin Hematopoietik Kök Hücre Transplantasyonu Sonrası Akut Graft Versus Host Hastalığı Riski ile İlişkisi

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Abstract

Objective: Angiogenic factors (AFs) released under endothelial stress are reflective of tissue healing, while some may also contribute to tissue damage/inflammation. We investigated whether alterations in the pre-transplant levels of AFs were associated with the risk of acute graft-versus-host disease (aGvHD).

Materials and Methods: The pre-conditioning plasma levels of angiopoietin-2 (Ang2), endoglin, and follistatin were measured for 37 patients together with inflammatory markers. The index values defined were evaluated to better identify the alterations.

Results: The patients had higher pre-conditioning levels of Ang2, endoglin, and follistatin compared to controls. The patients with aGvHD had higher Ang2 index and lower albumin index scores in comparison to those without aGvHD. Multivariate analysis revealed that the pre-transplant Ang2 index was an independent risk factor for aGvHD development.

Conclusion: Pre-transplant evaluation of plasma Ang2 levels along with inflammatory status even before conditioning is associated with endothelial vulnerability. The pre-transplant Ang2 index could be a promising candidate to estimate the risk of aGvHD.

Keywords: Graft-versus-host disease, Angiopoietin-2, Angiogenesis, Inflammation, Hematopoietic stem cell transplantation

Öz

Amaç: Endotelyal stres altında salınan anjiyojenik faktörler (AF), doku iyileşmesini yansıtırken, bazıları doku hasarına/iltihabına katkıda bulunabilir. Bu çalışmamızda pre-transplant AF düzeylerindeki değişikliklerin akut graft versus host hastalığı (aGvHH) riski ile ilişkili olup olmadığını araştırdık.

Gereç ve Yöntemler: Otuz yedi hastada plazma anjiyopoietin-2, endoglin ve follistatin seviyeleri, enflamatuvar belirteçlerle birlikte hazırlama rejimi öncesi değerlendirildi. Tanımlanan indeks değerleri AF düzeylerindeki değişiklikleri daha iyi tespit edebilmek için kullanıldı.

Bulgular: Kontrollere kıyasla hastaların nakil öncesi bakılan Ang2, endoglin ve follistatin seviyeleri daha yüksekti. aGvHH gelişen hastalarda, gelişmeyenlere kıyasla daha yüksek Ang2 indeks ve daha düşük albümin indeks değerleri saptandı. Çok değişkenli analizler, pre-transplant Ang2 indeksinin aGvHH gelişimi için bağımsız bir risk faktörü olduğunu ortaya koydu.

Sonuç: Plazma Ang2 düzeylerinin nakil öncesi hatta hazırlama rejimi verilmeden önce enflamatuvar durum ile birlikte değerlendirilmesi endotelin hasara yatkınlığı hakkında bilgi verebilir. Pre-transplant Ang2 indeksi, aGvHH riskini tahmin etmek için kullanabilecek bir belirteç olabilir.

Anahtar Sözcükler: Graft versus host hastalığı, Anjiyopoietin-2, Anjiogenez, Enflamasyon, Hematopoietik kök hücre transplantasyonu

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Introduction

Acute graft-versus-host disease (aGvHD) is one of the major complications of allogeneic hematopoietic stem cell transplantation (HSCT) with significant morbidity and mortality [1,2]. Despite the advances in our understanding of the pathogenesis of aGvHD, the mechanisms contributing to the development and severity of aGvHD are not yet fully elucidated [3]. Discovery of biomarkers for aGvHD has provided insight into the complex pathogenesis of aGvHD and suggests novel mechanisms of recipient tissue damage and impaired regenerative capacity for therapeutic targeting [4,5,6,7,8,9]. Recent studies have shown that epithelial cell damage, characteristic of aGvHD, develops secondary to vascular endothelial damage caused by alloreactive donor T cells [10,11]. Endothelial damage leads to endothelial cell activation and stimulates angiogenesis. Angiogenesis contributes to persistent inflammation leading to clinical presentation of aGvHD. This interaction between inflammation and angiogenesis leads to the development of aGvHD as well as other serious early-onset complications of HSCT known as vascular endothelial syndromes [12]. Therefore, it has been suggested that the vascular endothelium may be a target for the early diagnosis and treatment of HSCT complications. Levels of circulating angiogenic factors (AFs) associated with tissue repair, including epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and heparin binding EGF-like growth factor (HB-EGF), have been found to be significantly decreased in patients with aGvHD and steroid-refractory aGvHD compared to patients without aGvHD and those with steroid-responsive aGvHD [1,10,12]. On the other hand, endothelial damage and inflammation-related factors such as angiopoietin-2 (Ang2), soluble endoglin, follistatin, and placental growth factor have been shown to increase significantly in patients with aGvHD and steroid-refractory aGvHD [13,14,15,16,17,18]. Studies investigating the impact of circulating AFs on aGvHD have mostly been focused on the post-transplant period. However, taking into consideration that AF levels, and especially levels of those AFs involved in endothelial damage/inflammation, can provide useful information about endothelial vulnerability to damage, it might be a beneficial approach to assess AF levels during the pre-transplant period [19]. We propose that patients with alterations in circulating AF levels involved in damage or inflammation during the pre-transplant period would have higher risk for the development of aGvHD.

Materials and Methods

This study was approved by the Non-Interventional Ethics Committee of Hacettepe University (reference number: GO 18/235-29). Peripheral blood samples were collected before the conditioning regimen (day -9) and after completion of the conditioning regimen (day 0) prior to transplantation. The levels of Ang2, endoglin, and follistatin were studied from the plasma samples of patients and healthy controls simultaneously by Luminex immunoassay method using the Human Premix Multianalyte Kit (R&D Systems, Cat. # LXSAH) and Luminex 200 device. The results were analyzed with the Luminex analyzer with the X-Y platform. In addition, serum uric acid, albumin, and C-reactive protein (CRP) levels measured during the pre-transplant period (before and after conditioning regimen) were noted as systemic inflammatory markers for the patients.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 software (IBM Corp.). The risk factors for aGvHD were examined by logistic regression analysis. Receiver operating characteristic (ROC) curves were constructed for the significant indices predicting the incidence of aGvHD, and the area under the ROC curve (AUC) was calculated to examine index performance.

Results

Thirty-seven patients (19 male and 18 female patients; median age: 6 years, range: 1-22 years) were included in the study. Seven out of 37 patients underwent allogeneic bone marrow transplantation for non-malignant hematologic diseases (severe aplastic anemia and thalassemia), 13 patients for hematologic malignancies, 14 patients for primary immunodeficiency disorders, and 3 patients for neurometabolic disorders. Overall, 24 (65%) of 37 patients had non-malignant disorders and 13 (35%) had hematologic malignancies. All patients were transplanted from a fully HLA-matched sibling or family donor except one patient who received a bone marrow graft from a partially matched family donor. As the stem cell source, bone marrow was used for 34 (92%) patients, while peripheral blood was preferred for 3 patients. Among the 37 patients, 33 (89%) received a busulfan-based or total body irradiation-based myeloablative conditioning regimen. All patients received cyclosporin and low-dose methotrexate for GvHD prophylaxis. Upon successful engraftment in all patients, 16 patients were diagnosed with aGvHD (43%), whereas only one patient was diagnosed with chronic GvHD. Fifteen out of 16 patients with aGvHD had mild to moderate aGvHD and only one patient had severe aGvHD. Skin findings were reported in 15 patients, liver findings in 5 patients, and gastrointestinal system findings in 3 patients. Seven of 16 patients with aGvHD had a history of engraftment syndrome and 6 patients had a history of hepatic veno-occlusive disease.

First, we compared the pre-conditioning plasma levels of Ang2, endoglin, and follistatin of the 37 patients with the levels of 10 healthy controls. The patients showed significantly increased levels of all three AFs associated with damage and inflammation (Ang2, 2738.3±367 pg/mL vs. 867.5±151 pg/mL, $p<0.001$; endoglin, 2149±215 pg/mL vs. 1166.5±239 pg/

mL, p=0.008; follistatin, 12200.4±1093 pg/mL vs. 5832.9±732 pg/mL, p<0.001). Interestingly, the difference between the Ang2 and endoglin levels of patients and controls disappeared after conditioning; only the follistatin levels remained higher in the patients (11502.6±772 pg/mL vs. 5832.9±732 pg/mL, p<0.001). Next, pre- and post-conditioning serum uric acid, albumin, and CRP levels were evaluated. Significant elevations in serum uric acid (2.47±0.2 mg/dL vs. 6.64±0.4 mg/dL, p<0.001) and CRP (1.77±1.2 mg/dL vs. 8.14±0.7 mg/dL, p<0.001) levels were observed after conditioning, while albumin (3.78±0.1 g/dL vs. 2.9±0.1 g/dL, p<0.001) decreased in all patients. In order to eliminate the effects of inter-patient variations in AF levels, and to better evaluate the changes in AF levels after conditioning, the index value for each marker was calculated as the ratio of the pre-conditioning levels to post-conditioning levels. Patients with and without aGvHD were compared according the index values of the parameters that showed significant changes after conditioning (Ang2, endoglin, follistatin, uric acid, albumin, and CRP). The Ang2 index was higher (2.56 vs. 1.81, p=0.028) and the albumin index was lower (1.19 vs. 1.41, p=0.017) in the patients with aGvHD compared to the patients without aGvHD. The other indices studied did not reveal any significant alterations between the groups (Table 1). This result suggests a relationship between pre-transplant Ang2 levels and aGvHD.

We conducted univariable and multivariable logistic regression analyses to identify significant AFs and/or other inflammatory markers' index values that would be indicative of an increased risk for aGvHD (Table 2). Accordingly, we demonstrated that the pre-transplant Ang2 index was an independent risk factor for aGvHD development (p=0.04, odds ratio: 2.25, 95% confidence interval: 1.03-4.9). In addition, a low pre-transplant albumin index and the diagnosis of hematologic malignancy conferred higher risk of aGvHD (p<0.05). ROC curve analysis was then performed to determine the cutoff and assess the predictive value of the pre-transplant Ang2 index for aGvHD. As shown in Table 3, the cutoff of the Ang2 index in the pre-transplant period for aGvHD was 1.44 with an AUC of 72%, sensitivity of 100%, and specificity of 45%. We observed a difference in the frequency of aGvHD among the patients when compared regarding the Ang2 index cutoff value (above the cutoff: 57%

Table 1. Comparison of index values of plasma angiogenic factors and inflammatory markers of patients with and without acute graft-versus-host disease (aGvHD).

	aGvHD		
Index*, median (range)	Present	Absent	p
Angiopoietin-2***	2.56 (1.52-13.6)	1.81 (0.53-3.81)	0.028
Endoglin**	1.29 (0.53-3.13)	1.38 (0.48-2.82)	0.63
Follistatin***	0.97 (0.46-3.39)	1.08 (0.43-2.30)	0.86
Uric acid***	0.42 (0.12-1.27)	0.35 (0.12-0.79)	0.26
Albumin ** **C-reactive protein*****	1.19 (0.72-1.66) 0.22 (0.04-0.48)	1.41 (0.91-2.14) 0.23 (0.02-0.60)	0.017 0.98

*Index value: pre-conditioning plasma level/post-conditioning plasma level.
**The t-test was performed in independent groups.
*** Mann-Whitney U test in independent groups. Values of p<0.05 were considered statistically significant.

Table 2. Multivariable logistic regression model for acute graft-versus-host disease.

Parameters	p	Odds ratio	Odds ratio, 95% confidence interval	
			Minimum	Maximum
Primary disease (malignant/non-malignant)	0.032	9.716	1.214	77.747
Angiopoietin-2 index	0.043	2.245	1.027	4.905
Albumin index	0.025	0.016	0.001	0.586
Constant	0.138	41.593		

Table 3. Optimal threshold for the pre-transplant angiopoietin-2 (Ang2) index for predicting acute graft-versus-host disease.

Index (pre-/post-conditioning value)	Area under the curve	Cutoff point	Sensitivity (%)	Specificity (%)
Ang2	0.716	1.44	100	45

vs. below the cutoff: 0%, p=0.004). These results suggest that pre-transplant Ang2 index is predictive of aGvHD.

Discussion

Recent studies indicate the importance of the crosstalk between inflammation and angiogenesis in the pathogenesis and treatment outcomes of aGvHD [20,21,22]. However, most studies have mainly focused on the diagnostic/prognostic value of endothelial activation markers in patients who already present with aGvHD, rather than the possible implication of endothelial injury/inflammation marker profiles in the pre-transplant evaluation of patients [23,24,25].

Accordingly, we found elevated levels of Ang2, follistatin, and endoglin even prior to conditioning, indicating ongoing subtle inflammation/occult tissue injury. Interestingly, the levels of Ang2 and endoglin returned to normal while the level of follistatin, which predominantly reflects tissue damage and unresolved inflammation [26], remained high after conditioning. Although it seems controversial, post-conditioning alterations in AF levels have been reported in transplant recipients, suggesting that angiogenic response mechanisms in the early transplant period at the onset of inflammation may be different from those effective during the course of aGvHD [13,27,28]. Ang2 is a Tie2-binding antagonist of angiopoietin-1 that disrupts Ang1-mediated vessel integrity and reflects the susceptibility of the endothelium to damage [29,30]. In the present study, we showed that elevated pre-transplant Ang2 index was strongly associated with the risk of aGvHD together with low albumin index. Our determined cutoff value of 1.44 mg/dL for the pre-transplant Ang2 index, derived from ROC analysis, was predictive of aGvHD development and a difference in the frequency of aGvHD was observed among the patients when compared regarding the Ang2 index cutoff value. Hence, these results suggest that Ang2 promotes a more vigorous endothelial stress response to local alloreactive T-cell attack in patients with high pre-transplant Ang2 levels who later develop aGvHD. Similarly, recent studies have shown a continued increase in Ang2 levels for up to four weeks along with an increase in proinflammatory cytokines after allogeneic HSCT. Patients with high-grade aGvHD also exhibited significant increases in Ang2 levels compared to patients with low-grade aGvHD, and this increase was strongly associated with aGvHD severity and mortality [31]. In another study conducted by Luft et al. [21], patients with refractory aGvHD already showed significantly increased Ang2 levels before transplantation. They also found elevated Ang2/VEGF ratios after aGvHD onset in steroid-refractory but not in steroid-sensitive patients [21]. In this context, Porkholm et al. [18] concluded that pre-transplant high Ang2 plasma levels were associated with increased risk of intestinal aGvHD and non-relapse mortality in a pediatric study.

Conclusion

Our results suggest that pre-transplant evaluation of plasma Ang2 levels along with inflammatory status even before conditioning might be a reliable indicator of endothelial vulnerability. The pre-transplant Ang2 index as an independent risk factor for aGvHD seems to be a promising candidate for estimating the risk of aGvHD in allogeneic HSCT recipients. However, there is still a need for mechanistical studies to understand the precise role of angioregulatory factors in the pathogenesis of aGvHD.

Ethics

Ethics Committee Approval: This study was approved by the Non-Interventional Ethics Committee of Hacettepe University (reference number: GO 18/235-29).

Authorship Contributions

Concept: F.V.O., D.C.; Design: F.V.O., D.C.; Data Collection or Processing: Ö.S., D.C.; Analysis or Interpretation: Ö.S., İ.C.Z., B.A.; Writing: Ö.S., İ.C.Z., B.A., J.K., D.Ç., F.V.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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