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Pre-conditioning Serum Uric Acid as a Risk Factor for Sinusoidal Obstruction Syndrome of the Liver in Children Undergoing Hematopoietic Stem Cell Transplantation

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Abstract
Uric acid, a known danger signal released from injured cells, is one of the valuable signs of inflammation. We aimed to evaluate the association of serum uric acid level before the start of conditioning regimen with the risk of hepatic SOS development after HSCT. Two hundred and twenty-two children who underwent allogeneic HSCT at the Pediatric BMT Unit of Hacettepe University between 2000 and 2014 were included in this retrospective study. Serum UA levels were measured before conditioning as an indicator of the pre-transplant inflammatory status of patients. Patients with or without diagnosis of SOS were compared regarding primary diagnosis, previously described risk factors for SOS and pre-conditioning serum UA. SOS was diagnosed in forty-two patients who had higher pre-conditioning serum UA levels compared to those who did not. Pre-transplant serum creatinine, GGT, bilirubin, ferritin and CRP didn't differ significantly among the patients with or without SOS except serum albumin which was lower in the patients who developed SOS. ROC analysis revealed that pre-conditioning UA level higher than 3,32 mg/dl was predictive of SOS. When subjected to a multivariate model, only pre-conditioning UA and albumin levels remained significant risk factors for SOS (UA; OR, 2.54; 95%CI,1.26 to 5,12; P=0,009 and albumin; OR, 0.45;

95%CI,0.22 to 0.95; P= 0.037). Our results suggest that pre-conditioning serum UA is an independent risk factor for SOS, and it might be used as an early predictor of hepatic SOS together with previously described clinical/laboratory parameters.
Keywords: Sinusoidal obstruction syndrome, hematopoietic stem cell transplantation, uric acid and inflammation

Introduction

Hepatic sinusoidal obstruction syndrome (SOS), also known as hepatic veno-occlusive disease (VOD), is a serious complication of hematopoietic stem cell transplantation (HSCT) and clinically characterized by fluid retention, painful hepatomegaly, and hyperbilirubinemia. It is the most frequent and well-studied one among early-onset vascular endothelial syndromes developed after hematopoietic stem cell transplantation. It occurs in 5% -15% of the patients after allogeneic HSCT. The variations in the incidence are attributed to multiple factors such as diagnostic criteria used, center experience, year of HSCT and patient type [1] . Although the reported incidence of SOS has been decreased with new transplantation strategies, severe form of SOS is still associated with significant mortality, and early identification of SOS remains challenging [2] . Patient-, disease- and transplant-related clinical risk factors have been well established including preexisting liver dysfunction, disease type and/or disease status, young or old age, allogeneic HSCT and myeloablative conditioning regimen, but precise prediction of SOS in individuals remains elusive. Early identification and monitoring of high-risk patients using predictive markers will lead to timely treatment implications which might have a significant impact on survival [3].

SOS is initiated with the sinusoidal endothelial cell damage caused mainly, by cytotoxic effects of intensive conditioning regimens including chemotherapy and/or radiotherapy given before transplantation. Prophylactic immunosuppressive therapies, growth factors used to support engraftment, developing infections, and transplantation itself can also cause to endothelial damage [4, 5]. The clinical evidence suggests that endogenous ‘danger signals’ from injured cells have a role in the pathogenesis of SOS through induction of a non-infectious inflammatory reaction in the allogeneic setting [6]. Uric acid (UA) is an endogenous danger signal released from injured cell, induces maturation of dendritic cells and expansion of alloreactive T cells via activation of the NOD-like receptor protein (NLRP)3 inflammasome [7]. Recently, a pre-clinical study has shown the role of NLRP3 inflammasome-mediated IL-1 production on acute graft-versus-host disease (aGVHD) [8]. There is a limited number of clinical studies about the association between serum UA level and aGVHD ,but their results are controversial [9, 10]. The role of serum UA in pre-transplant period as a risk factor for SOS remains unclear [4, 6, 11, 12]. Although, laboratory/clinical markers of endothelial injury preceding SOS development have been described, they are not adopted to clinical use due to practical limitations. Thus, there is still a need for dynamic laboratory parameters that can predict SOS development. Therefore, we evaluated the association between pre-transplant serum uric acid levels as a sensitive marker of inflammation with SOS development after allogeneic HSCT in pediatric patients.

Methods

Two hundred and twenty-two children (median age 7 years, range: 0,3-19; male/female: 150/72) who underwent allogeneic HSCT at the Pediatric BMT Unit of Hacettepe University between 2000 and 2014 were included in the retrospective data analysis. Serum uric acid levels measured before the initiation of conditioning regimen (day -9) and after conditioning regimen completed (at day 0 before transplantation) were analyzed to assess any change in serum uric acid which would be indicative for the pre-transplant inflammatory status of

individual patients. Pre-conditioning serum creatinine, transaminases, gamma-glutamyl transferase (GGT) and total bilirubin levels, iron overload and CMV serology were also recorded in all patients for the exclusion of other potential causes of hyperuricemia and hepatic dysfunction. Inflammatory markers (C-reactive protein, albumin) were also noted at the same time point. The association of serum uric acid levels at the pre-transplant period with the development of SOS was assessed. HSCT was performed according to standard institutional transplantation procedures. The patients received either myeloablative (i.v. Busulfan-based with no AUC targeting) or reduced- intensity conditioning (Fludarabine-based) regimens depending on the primary diseases or disease status. GVHD prophylaxis consisted of cyclosporine and methotrexate with or without rabbit anti-thymocyte globulin. Enoxaparin, vitamin E and ursodeoxycholic acid were administered for SOS prophylaxis to all patients beginning with conditioning. None of the patients received allopurinol before or after transplant. Defibrotide was started when the clinical manifestations of SOS developed with the exclusion of other potential diagnoses. Hepatic SOS was diagnosed when two or more of the diagnostic criteria (refractory thrombocytopenia, weight gain > 5% above baseline, hepatomegaly, ascites and bilirubin value ≥ 2 mg/dL) were present based on the EBMT diagnostic criteria and EBMT severity grading system was used[12],[13] . The study was approved by the Institutional Ethics Committee.

The association between clinical variables including patient- and transplant-related risk factors (primary disease, conditioning regimen, HLA compatibility, CMV status, ferritin, GGT, pre-/post-conditioning serum uric acid levels, albumin, and C-reactive protein) and hepatic SOS was analyzed using logistic regression model. Only the variables with $P < 0.2$ in the univariate analysis were subjected to multivariate analysis. The variables with a $P < 0.05$ were considered significant. The comparisons within and between the groups were calculated using Wilcoxon signed-rank and Mann-Whitney U test respectively. Median follow up time and overall survival were estimated using Kaplan-Meier limit estimation. The Cox proportional hazards model for multivariate analyses of survival was used. Receiver operating characteristic curve analysis was performed to calculate sensitivity, specificity and area under the curve for peak pre-conditioning serum uric acid 3,32 mg/dl.

Results

The patient and transplant characteristics were summarized in Table 1. There were 222 children enrolled in the study with a median age of 7 years (range 0.3-19). Sixty-eight percent was male and most patients were transplanted for non-malignant diseases (69%) mainly, non-malignant hematological diseases, and primary immunodeficiencies while rest of the patients were transplanted for hematological malignancies (31%). Most patients received a bone marrow graft (71%) from an HLA-matched family donor (89%) following myeloablative conditioning (70%). Median values of pre-transplant serum creatinine, transaminases, and total bilirubin levels were all within the normal range for age (Table 1).

When the median serum uric acid levels of all patients evaluated; pre-conditioning UA levels were found significantly higher than the post-conditioning levels 3,1 mg/dl, range: 0,68-6,9 at day -9 vs. 2,8 mg/dl, range: 0,61-6,94 at day 0 (post-conditioning) P=0,02. After grouping patients by the development of hepatic SOS, forty-two patients (19%) who developed mostly mild/moderate hepatic SOS (91%) were found to have a higher median pre-conditioning uric acid levels compared to those who did not develop SOS (3,6 mg/dl vs. 3,0 mg/dl, P= 0,01). Pre-transplant serum creatinine, GGT, total bilirubin, ferritin, CRP and albumin were checked and didn't differ significantly regarding SOS groups (P> 0,05) except albumin which was found lower in the patients with SOS compared to those without SOS (P= 0,02) (Table 2). Among forty-two patients who diagnosed with SOS, twenty-five (60%) had mild, thirteen (31%) had moderate and four had severe disease. Thirty patients out of forty-two recovered

from SOS, while four patients with severe SOS and eight patients with other early transplant-related complications died.

While a significant decrease in the serum UA levels of the patients who did not develop SOS was observed at the day of HSCT following conditioning (3,05 ±0.09 mg/dl vs. 2,89 ±0.09 mg/dl *P*= 0,03), there wasn't any significant change in the serum UA levels of patients who developed SOS (3,75 ±0,25 mg/dl vs. 3,2 ±0,18 mg/dl *P*>0.05). The development of SOS was associated with a higher pre-conditioning uric acid levels (*P*= 0.002). The ROC curve was drawn to determine a cutoff and evaluate the predictive value of pre-conditioning UA for hepatic SOS development. As shown in Table 3, the cutoff value of UA in pre-transplant period before the start of conditioning for hepatic SOS was 3,32 mg/dL with the AUC of 62,4%, sensitivity of 62% and specificity of 61%. Hence, pre-conditioning UA level seems to be predictive of hepatic SOS. We observed a difference in the frequency of SOS among the patients when compared regarding the UA cutoff value (above the cutoff; 26,8% vs. below the cutoff 12,8%, *P*=0,008) Next, we conducted a univariate analysis in order to investigate the association between pre-conditioning serum UA, previously described risk factors and hepatic SOS, as illustrated in Table 4. When subjected to a multivariate model, the pre-conditioning UA remained significant as a risk factor for SOS (UA; OR, 2.54; 95%CI,1.26 to 5,12; *P*=0,009). The odds of SOS incidence in patients with the UA higher than 3,32mg/dL was 2,5 times more than patients with the UA below the cutoff. The pre-transplant serum albumin was also associated with SOS (OR, 0.45; 95%CI,0.22 to 0.95; *P*= 0.037) among all the other risk factors included in the model.

The probability of 10-year overall survival after HSCT was 75% for all patients enrolled with a median survival of 114 months. There was a significant difference between survival rates of patients who developed SOS (64%; mean survival, 77,5□8,5 months) and of those who did not (77%; mean survival, 82□3,2 months) (*P*= 0,047). However, the cutoff value of pre-conditioning UA at 3,32mg/dL had no significant effect on the survival of the patients (OR: 0,86, 95%CI: 0.63-1.18 *P*= 0,35).

Discussion

Sinusoidal obstruction syndrome of the liver is thought to result from conditioning regimen-related cytotoxic injury to hepatic sinusoidal endothelium and hepatocytes intensified by cytokine-mediated alloimmunity. Although the different combinations of biomarkers for endothelial injury and hemostasis have been described to predict the occurrence of SOS by various studies, early and precise prediction of SOS is still challenging, probably due to lack of well-defined specific marker panels[14, 15]. In the present study, we aimed to investigate the association of serum uric acid levels measured before initiation of conditioning regimen with hepatic SOS in 222 pediatric patients who underwent allogeneic HSCT, retrospectively. Our results indicate that high pre-conditioning serum UA level is an independent pre-transplant risk factor for SOS development after allogeneic HSCT.

Even though danger-associated molecular patterns (DAMPs) released from injured cells including extracellular adenosine triphosphate, high mobility group box chromosomal protein 1 (HMGB1) and UA are recognized to play a role in acute GvHD pathogenesis, the role of uric acid, as a proinflammatory mediator in allogeneic immune responses is still ambiguous [11] (Figure 1). A phase I study reported that the patients with acute GvHD had higher serum uric acid levels during the pre-transplant period compared to the patient without acute GvHD [10]. The incidence of grade II to IV acute GvHD was significantly decreased in the group treated with urate oxidase during conditioning. On the contrary, a retrospective study indicated a significant association between acute GvHD and low serum uric acid level [9]. The controversy between previous reports on the role of uric acid in the development of acute GVHD probably rises from both the paradoxical actions of uric acid as a pro- and anti-oxidant [16] and its complex role in inflammation. The preclinical studies suggest that decreasing

serum uric acid levels during conditioning before HSCT may suppress recipient antigen-presenting cell (APC) activation and T cell response [7, 17]. Thus, considering the current understanding of SOS pathogenesis; uric acid, as an endogenous danger signal released from injured cells seems to be an attractive target for SOS prediction and preventive measures. There is no previous preclinical and clinical study that have investigated the impact of UA, as a proinflammatory mediator on SOS and its predictive role. Thus, it could be reasonable to consider that a common mechanism of initiation and/or maintenance of inflammation through endogenous ‘’danger signals’’ from injured cells underlies development of SOS after HSCT. The results of this study support our initial hypothesis about the association of high pre-transplant serum UA levels with SOS and are in parallel with previous reports about significant role of high UA levels in transplant outcomes such acute GvHD and survival [18-20]. Unlike most of the other studies assessing the prognostic value of several biomarkers at different time points after transplantation, either before or during early stage of hepatic SOS, we preferred to evaluate serum UA levels before initiation of conditioning which could be a critical period for early detection of inflammatory background of individual patients. Interestingly, serum UA levels were higher in the patients with SOS even before start of conditioning regimen compared to the patients without SOS. In addition, the UA levels decreased after conditioning in the patients without SOS, while they remain high in those with SOS. This seems to conflict with previous studies reporting elevated serum uric acid levels following the conditioning because of its cytotoxicity [10, 21]. High pre-conditioning uric acid levels that remained unchanged following conditioning together with low serum albumin levels in our patients with SOS might be attributed to ongoing subtle inflammation, occult tissue injury and accelerated cell turnover related to primary disease/disease status, previous therapies and infections [22]. Post-conditioning decrease in UA levels in the patients without SOS might be explained by suppressive effect of myeloablative/ lymphodepleting conditioning regimen on recipient immune system indicating the presence of a fine balance between pro-inflammatory and anti-inflammatory mechanisms during the peri-transplant period. Newly developing bone marrow aplasia could also contribute to this change in UA levels. Hean et al. reported that serum uric acid levels remained low until incipient hematological recovery in HSCT patients and leukemia patients undergoing induction chemotherapy. They emphasized the role of uric acid as a potential marker for bone marrow activity during aplasia besides its role in immune activation and inflammation [23]. Endothelial damage related to conditioning, acting as a second hit potentiates immune activation leading to alloimmunization and the development of SOS. Dysregulation of cytokine homeostasis is common after conditioning. Proinflammatory cytokines including TNF-α, IL1, and IL6 have been reported to activate xanthine oxidase, thus stimulating uric acid production which is involved in the pathogenesis of early non-infectious transplant complications, such as SOS. Even in the absence of clinically defined hyperuricemia (serum UA >7 mg/dL) based on the solubility limit of urate in body fluids, this positive feedback loop may cause a further release of cytokines and endogenous adjuvants that contribute to the development of endothelial cell injury at an inflammatory setting [24, 25], as in the case of our patients with high pre-conditioning UA who developed hepatic SOS over transplant course. There are several reports investigating the association of serum UA and transplant outcomes, they define their cutoff value for their own patient cohorts [18, 26]. Our determined cutoff value of 3,32 mg/dL for pre-conditioning UA was derived from ROC analysis and it was predictive of hepatic SOS development after allogeneic HSCT. The multivariate analysis confirmed the association of serum UA higher than 3,32 with the risk of hepatic SOS. Low serum albumin in pre-transplant period was also identified as a risk factor for SOS. Serum albumin serves as a laboratory marker of inflammatory status, and the prognostic value of low serum albumin on transplant outcomes has been revealed by previous studies. One of the

limitations of our study is its retrospective nature. Therefore, a serial measurements of serum UA and other pro-inflammatory and/or endothelial injury markers over transplant course was not performed. Also, the design of our study did not allow us to investigate whether uric acid plays an active role in the pathogenesis of hepatic SOS through induction of a non-infectious inflammatory reaction in the allogeneic setting or it is just a biomarker of inflammatory status. Since our patient population mostly included the pediatric patients who received bone marrow grafts from matched related donors after a myeloablative conditioning for non-malignant disorders, we could not make any conclusion about the impact of serum UA on SOS development in different transplant settings such as unrelated and haploidentical transplants which carry higher risk for SOS. But we think that the association of serum UA higher than the cutoff value with SOS in such a restricted population could be accepted as a proof of its predictive strength.

In conclusion, this is the first report about the association of pre-conditioning serum uric acid level and hepatic SOS in HSCT recipients and it supports the use of pre-transplant serum UA level as a risk factor for SOS. There is a need for mechanistical studies to understand the precise role of uric acid in the pathogenesis of SOS as an inflammatory mediator at the allogeneic transplant setting. Also, further studies in independent cohorts and at different transplant settings may help to clarify the role of UA in predicting high-risk patients for SOS together with other defined clinical and laboratory markers of endothelial injury.

Table1. Patient and Transplant Characteristics

Variable	**Total** (N= 222)
Age	
Median in years (range)	7 (0,3-19)
Sex	
Male	150 (68%)
Female	72 (32%)
Diagnosis	
Hematologic malignancies	69 (31%)
Non-malignant hematologic	111 (50%)
Primary immunodeficiencies	42 (19%)
Conditioning regimen	
Myeloablative	156 (70%)
Reduced intensity	66 (30%)
Donor	
Matched related	198 (89%)
Mismatched related	24 (11%)
Stem cell source	
Bone marrow	148 (67%)
Peripheral stem cell	60 (27%)
Umbilical cord	5 (2%)
Bone marrow and umbilical cord	9 (4%)
Acute GvHD	
Grade I-II	24 (59%)
Grade III-IV	17 (41%)

Veno-occlusive disease Yes No	 42 (19%) 180 (81%)
Serum creatinine[a] (mg/dl) median (range)	0,26 (0,01-1,43)
Transaminases[a] (IU/ml), median (range) ALT AST	 24 (3-235) 31 (4-199)
Total bilirubin[a](mg/dl), median (range)	0,45 (0,06-3,6)
Recipient CMV status positive	183 (82%)
Ferritin[a] (µg/L) median (range)	879,4 (7-11365)
[a]The values given for all these parameters present the pre-conditioning levels	

Table 2. Comparision of patients with and without hepatic sinusoidal obstruction syndrome			
Variable	**Hepatic SOS** (n= 42)	**No Hepatic SOS** (n= 180)	***P* value**
Primary disease Hematologic malignancy Non-malignant hematologic Primary immunodeficiency	 13 (31%) 22 (52%) 7 (17%)	 56 (31%) 89 (49%) 35 (20%)	0,90
Conditioning regimen MAC RIC	 31 (74%) 11 (26%)	 123 (68%) 57 (32%)	0,42
HLA compatibility MSD MMRD	 39 (93%) 3 (7%)	 159 (88%) 21 (12%)	0,58
Recipient CMV status positive negative	 29 (69%) 13 (31%)	 154 (86%) 26 (14%)	**0,01**
Ferritin (µg/L)	842,7 (28,2-11365)	891,7 (7-9505)	0,77
Serum creatinine (mg/dL)	0,3 (0,03-0,6)	0,26 (0,02-1,4)	0,29
Total bilirubin (mg/dL)	0,43 (0,1-2,7)	0,46 (0,06-3,6)	0,74
GGT (U/L)	16,15 (8-487,3)	17,4 (2,9-398,7)	0,99
Albumin (g/dL)	3,9 (2,8-5,2)	4,1 (2,6-5,6)	**0,02**
CRP (mg/dL)	0,49 (0,1-8,8)	0,64 (0,1-24,6)	0,86
Pre-conditioning uric acid (mg/dL)	3,6 (0,7-6,9)	3,0 (0,7-6,4)	**0,01**
Post-conditioning uric acid (mg/dL)	3,0 (1,2-5,4)	2,7 (0,6-6,9)	0,10

Table 3. ROC analysis for pre-conditioning uric acid				
Parameter	AUC	Cutoff Point	Sensitivity (%)	Specificity(%)
Pre-conditioning uric acid (mg/dl)	0,624	3,32	62	61

Table 4. Risk factors for hepatic sinusoidal obstruction syndrome by logistic regression analysis				
Factors	**Univariate HR (95% CI)**	***P*-value**	**Multivariate HR (95% CI)**	***P*-value**
Primary disease Hematologic malignancy Non-malignant hematologic Primary immunodeficiency	0,94 (0,44-2,01) 0,81 (0,32-2,06)	0,87 0,91 0,66	-	-
Conditioning regimen	1,38 (0,63-3,01)	0,42	-	-
HLA compatibility	0,58 (0,16-2,05)	0,40	-	-
Recipient CMV status	0,38 (0,17-0,82)	0,014*	0,59 (0,26-1,36)	0,21
Ferritin (µg/L)	1,00 (1,00-1,00)	0,72	-	-
CRP (mg/dL)	1,01 (0,88-1,16)	0,88	-	-
Albumin (g/dL)	0,46 (0,22-0,66)	0,039*	0,45 (0,22-0,95)	0,037*
GGT (U/L)	1,00 (0,99-1,01)	0,093*	1,00 (0,99-1,01)	0,26
Pre-conditioning UA ≥ 3,32 mg/dL	2,49 (1,25-4,98)	0,009*	2,54 (1,26-5,12)	0,009*

*Serum ferritin, GGT, albumin and CRP values represents pre-conditioning levels. Variables with $P < 0,2$ in the univariate analysis were subjected to multivariate analysis in which $P < 0,05$ were accepted as significant

Authors Contributions:
FVO and DC contributed to the study conception and design. FVO coordinated and supervised the study. She also made the interpretation of the results. BK, MK and KW acquired patients' samples and contributed to the data collection. UEA made the statistical analyses. All authors contributed to, reviewed and approved the manuscript.

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Figure 1. Potential explanation for the role of uric acid in the development of SOS at the inflammatory setting. High levels of uric acid activate the RAGE/HMGB1 signaling pathway in sinusoidal endothelial cells and increases NF-κB expression. NF-κB overexpression increases the secretion of pro-inflammatory cytokines i.e TNFα and IL-6 from damaged sinusoidal endothelial cells resulting in cytokine derangement within the hepatic sinusoids leading to immune activation. HMGB-1also increases the expression of adhesion molecules (VCAM and ICAM) and PAI-1 resulting in the activation of the pro-coagulant cascade and sinusoidal obstruction [24, 27]. *(RAGE: receptor for advanced glycation end products. HMGB1: high mobility group box chromosomal protein 1. IL-6: Interleukin 6. TNF-α: tumor necrosis alpha. NF-κB: Nuclear factor κB. ICAM-1: Intercellular Adhesion Molecule 1. VCAM-1: Vascular cell adhesion protein 1. PAI-1: plasminogen activator inhibitor-1)*