Non-Infectious Early Complications of Allogeneic Stem Cell Transplantations

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ABSTRACT
Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is the only curative option in many benign and malign hematological disorders. Recent developments in posttransplant supportive care, graft versus host disease (GVHD) prophylaxis and treatment as well as reduced intensity conditioning regimens (RIC) have improved posttransplant survival. However, infections, GVHD related organ injury, increased incidence of human leukocyte antigen (HLA) mismatched unrelated or haploidentical transplantations effect posttransplant mortality in a negative manner. Allo-HSCT related complications can be classified into early (within 3 months of transplantation) and long term complications (after 3 months of transplantation). Some early complications which will be briefly discussed in this review are graft failure, sinusoidal obstruction syndrome, capillary leak syndrome, engraftment syndrome, diffuse alveolar hemorrhage and thrombotic microangiopathy.

Keywords: Early Complication, Non-Infectious, Allogeneic stem cell transplantation

ÖZET
Allojenik kemik iliği transplantasyonunun enfeksiyon dışi erken komplikasyonları
Allojenik hematopoietik kök hücre nakli (Allo-HKHN) benign ve malign birçok hematolojik hastalıktaki küratif tek tedavi alternatifidir. Son dönemde destek tedavileri, graft vs host hastalığı (GVHH) profilaksisi ve tedavisi, düşük yoğunluklu hazırlık rejimlerindeki ilerlemeler sayesinde nakil sonrası sağkalım iyileşmiştir. Fakat, infeksiyonlar, GVHH ile ilişkilidir organ hasari, insan lökosit antijen (HLA) uyumsuz veya haploidentikal transplantasyonlar nakil sonrası mortalite önemli rol oynamaktadır. Allo-HKHN sonrası komplikasyonlar erken (3 ay içinde) veya geç (3 ay sonrasında) olarak sıralanmıştır. Bu derlemede erken komplikasyonlardan graft yetmezliği, sinüzoidal obstrüksiyon sendromu, kapiller geçiş sendromu, engraftman sendromu, diffüz alveolar hemorrhage ve trombotik mikroanjiopati tartışılacaktır.

Anahtar Kelimeler: Erken komplikasyon, Non-infectious, Allojenik stem cell transplantation
INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is the only curative option in many benign and malign hematological disorders. Recent developments in posttransplant supportive care, graft versus host disease (GVHD) prophylaxis and treatment as well as reduced intensity conditioning regimens (RIC) have improved post-transplant survival. However, infections, GVHD related organ injury, increased incidence of human leukocyte antigen (HLA) mismatched unrelated or haploidentical transplantations effect post-transplant mortality in a negative manner.

Allo-HSCT related complications can be classified into early (within 3 months of transplantation) and long term complications (after 3 months of transplantation). We will focus on and briefly discuss the early complications in this review. Some early complications which may be a challenge for practising hematologists and oncologists in this field are graft failure, sinusoidal obstruction syndrome, capillary leak syndrome, engraftment syndrome, diffuse alveolar hemorrhage and thrombotic microangiopathy.

1. Graft Failure

Myeloid engraftment day is described as the first day of three consecutive days of an absolute neutrophil count of above \(0.5 \times 10^9/L\) without support. Myeloid engraftment should be expected during the first 28 days regardless of type and stem cell origin of the transplant. The platelet engraftment is described as the platelet count of \(20 \times 10^9/L\) and above without the support at least for 7 consecutive days.\(^1\) Hemoglobin (Hb) level of more than 8 g / dl without support is regarded as the threshold for red cell engraftment. Graft failure is defined as the evidence of hematopoietic cell engraftment or hematologic recovery following an allo-HSCT.\(^5\)\(^,\)\(^6\) Graft failure is divided into two subtypes: primary (early) and secondary (late).

Primary graft failure is a condition that specified as thresholds which can not be reached at first 28 days. Low blood count levels despite a documented chimerism most likely refer a poor graft function but lack of full donor chimerism associated with absence of hemogram levels define a graft rejection. After an initial engraftment, at any time, the loss of donor cells is named as secondary graft failure which is more common after allo-HSCT.\(^1\) Acute GVHD and immune-mediated transient cytopenias should be considered in the differential diagnosis of primary graft failure whereas persistent or progressive disease, infections and residual host immunity-related GVHD should be considered in the differential diagnosis of secondary graft failure.\(^5\) Donor effector cells in allograft may attack or react to immune system because of the the genetic mismatch between donor and the patient resulting in graft rejection. Insufficient engraftment may be related to abnormal bone marrow microenvironment, or is triggered by so-called graft-versus-marrow effect.\(^5\) Essential point here is to separate graft failure from infections especially cytomegalovirus (CMV), the use of various drugs such as ganciclovir and chronic GVHD that cause secondary severe bone marrow suppression.

Engraftment failure due to graft related rejections are detected in low incidences in HLA-identical siblings; this percentage rises with HLA mismatch.\(^11\) In related to this, compared with the high-resolution, low-resolution HLA-mismatched grafts are reported to increase the risk of failure.\(^2\) ABO blood group incompatibility, which is a risk factor for graft failure in HLA-matched allo-HSCT, is seen by approximately 23-30%.\(^2\)\(^,\)\(^3\) The adverse effects of both the donor and patient’s age on the graft failure of allo-HSCT is not so obvious. However, the negative effect of the donor age was detected in animal engraftment kinetics studies.\(^5\)

One of the factors that have an impact on graft failure is the conditioning regimen. In particular, by the combination treatment modalities, more patients achieve the eradication of immune effector cells and thus a reduction in the rate of engraftment failure is detected.\(^5\)\(^,\)\(^14\) After a myeloablative regimen the usual rate of graft failure for about 1-5% compared to as high as 30% in RIC regimen.\(^15\) Based on the reported study results, in both autologous and allo-HSCT, the progenitors infused under a certain threshold value of the cells are known to cause graft failure development. Optimal threshold to achieve engraftment is \(5 \times 10^8 / \text{kg nucleated cells per recipient body weight in a patient treated}\)
with full dose conditioning whereas below 3 x 10^8 kg nucleated cells per recipient body weight increase the risk of graft failure development.\(^5\)

Practical approaches to prevent the graft failure in related and unrelated transplants can be summarized as follows: 1) HLA mismatch between donor and recipient (mismatching) significantly increases the degree of graft failure risk. The donor should be chosen from the least incompatible or exactly matched donor 2) Risk of graft failure is associated with recipient homozygosity at the mismatched locus; therefore mismatching at the locus for which recipient is homozygous should be avoided.\(^16\) 3) Presence of anti-HLA antibodies increase the risk of graft failure therefore a cross-matching test is recommended prior to transplant. 4) Graft failure risk is higher in case of antigen mismatch compared to allele mismatch. In the absence of HLA compatible donor, allele-mismatched donor should be preferred.

Treatment choices of primary graft failure are second allo-HSCT associated with an immunosuppressive or cytotoxic therapy or the original donor hematopoietic stem cell infusion (boost) without therapy or a second allo-HSCT from a different donor.\(^17\) The second allo-HSCT option was used in a study in patients with acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and aplastic anemia (AA) and engraftment rate had been reported as 73%.\(^18\) The utilization rate of original donor in the second allo-HSCT was 68% and 20 patients received additional hematopoietic growth factors. It is known that re-grafting after a conditioning can successfully improve the graft failure with response rates of 66% to 100%.\(^19\)

However, GVHD and infection increase the non-relapse mortality (NRM) and transplant-related mortality (TRM) rates which are around 53 to 60% with myeloablative conditioning regimens.\(^20\) The leading cause of death after the second transplantation have been reported as infection.\(^18\) Therefore, 3-year overall survival rate was detected as 43% in unmanipulated stem cell infusions.\(^21\) However, in the same study, the acute and chronic GVHD rates were reported as 31% and 50%, respectively. Klyuchnikov et al. used CD34 positive selected stem cell booster without prior conditioning in 32 poor graft functioned patients with a 2-year overall survival rate of 45%, while acute and chronic GVHD rates of 17% and 26%, respectively.\(^19\) Application steps of myeloid growth factors in poor graft function or graft failure in allo-HSCT were not clarified.\(^6\) Myeloid growth factors stimulate the production of neutrophils and delay platelet recovery as well as trigger the development of acute and chronic GVHD.\(^22\) The stimulation of transplanted stem cells could also be obtained by modulation of the microenvironment of the stem cell niche.\(^19\) For this purpose, the use of mesenchymal stem cells was reported to have significant positive effect on the poor graft function.\(^23\)

### 2. Sinusoidal Obstruction Syndrome:

Sinusoidal obstruction syndrome (SOS), a life threatening complication within the first 35-40 days following myeloablative preparation regimen, is presented by painful hepatomegaly, weight gain and fluid retention and characterized by elevated serum bilirubin levels. The diagnostic criteria described by the Seattle group are the most widely used, however description of the the Baltimore group permit a more precise diagnosis.\(^24\) The diagnosis of SOS is defined by the presence of ≥ 2 Seattle criteria before day 30 post-HSCT: bilirubin ≥ 2 mg/dL, hepatomegaly, ascites with or without unexplained weight gain of >2% over baseline. Baltimore criteria narrows the time to 21 post-HSCT days and accepts weight gain of > 5% over baseline. Although in the past it was named as veno-occlusive disease, the underlying pathobiology is not essential for occlusion of the hepatic venules; actually changes in the hepatic sinusoids induces liver injury and as a result major problem is the endothelial injury. In the early stages, subintimal part in central and sublobular venula thickens due to edema. Immunohistochemical studies indicate the presence of fibrin and FVIII in intramural and periadventisyal region of venules. Subintimal thickening of the venules leads to narrowing of the lumen which creates resistance to blood flow. Reduction in venous flow shown in the histological examination causes serious hepatic congestion and sinusoidal dilatation, which ultimately leads to portal hypertension. The changes are evident of hepatocyte injury and death and is mainly seen
Pre-transplant risk factors that may expedite SOS are liver dysfunction (hepatitis, fibrosis, cirrhosis, etc.), hepatic metastases, history of liver radiotherapy, hepatotoxic agents such as acyclovir or vancomycin etc., infectious attacks, history of stem cell transplantation and advanced age. Likewise, transplant-related factors are myeloablative conditioning regimen, TBI, conditioning regimens with busulfan and cyclophosphamide, HLA mismatched related or unrelated donor selection and use of methotrexate for GVHD prophylaxis.

Although SOS signs are often detected right after the end of the first or second week of transplantation, some authors suggest that the period elongates to postransplant day-40.8,24 Busulfan, melphalan or the use of alkylating agents such as thiopeta are among the risk factors for the late onset SOS.33,36

The initial finding is asymptomatic weight increase due to fluid and sodium retention. The degree and rate of bilirubin elevation often determines the severity and course of SOS. The first and often the only symptom in patients with SOS is right upper quadrant pain, sometimes severe enough to require narcotic analgesic. Ascite and weight gain may be refractory to diuretic therapy therefore half of patients with renal impairment may need dialysis. Deterioration in liver failure depresses the coagulation factors that causes elongation in prothrombin time. As the disease progresses, severe encephalopathy and interstitial pneumonitis may develop in some patients.37,41

A prospective analysis conducted by EBMT Chronic Leukemia Working Party showed that the incidence of SOS after allo and autologous HSCT was found to be 8.9% and 3.1%, respectively.42,43 In another analysis, following myeloablative conditioning with high-dose therapy ± cytoreductive TBI, the incidence of SOS has been reported to be as high as 54%.36 However, in 237 allo-HSCT patients transplanted with RIC regimens the incidence of SOS was only 5.9%.34

Most useful initiatives in clarifying the diagnosis of SOS despite practical difficulties are transjugular liver biopsies and manometric monitoring of hepatic blood flow. The hepatic venous pressure gradient (HVPG) of ≥ 10 mmHg in a patient without a previous liver disease allows an exact diagnosis with a high degree of specificity.33 However, a normal HVPG does not exclude the diagnosis. In Ultrasonography / Doppler ultrasonography, a variety of abnormalities can be observed such as the gallbladder wall thickening, hepatomegaly, ascites and reduced or reversed portal flow. Despite the serum of patients with SOS shows increased levels of fibrinolytic inhibitor, PAI-1 (a marker with the highest specificity and sensitivity for SOS), vWF, thrombomodulin, E-selectin, intracellular adhesion molecule, aminopropeptides of type III collagen and hyaluronic acid, they are rarely used in daily clinical practice.35,45

It is essential to identify very high-risk patients and implement effective preventive strategies both in the pretransplant and peritransplant periods in order to reduce the increased mortality rate. Based on
this; delaying allo-HSCT in case of liver dysfunction, adjusting the busulfan dose and applying intravenous rather than oral forms, administration of cyclophosphamide before busulfan, using fractionated TBI, preferring RIC conditioning and avoiding hepatotoxic drugs are preventive measures that can be implemented in the first place.33

Symptomatic treatment in first place is salt and water restriction which can be combined with diuretics. Studies in SOS treatment showed that the most promising agent, so far, is defibrotide.46,47 It is a new oligodeoxyribonucleotide derivate which has specific binding sites in vascular endothelial cells and adenosine receptors which reduces the endothelial leukocyte adhesion and aggregation.48 It increases PGE2, PGI2, thrombomodulin and endogenous tPA in endothelial surface and decreases PAI-1 levels. Defibrotide does not lead to serious bleeding because it is obvious that it has no anticoagulant properties.49 Therefore, the recommended schedule of administration in daily practice is 4 x 6.25 mg/kg/day, with a 2-hour intravenous infusion at least for 21 days until sign and symptoms are resolved.49 The clinical response will be obtained sooner if treatment starts as soon as it is suspected.50 There are several reports showing the positive effect of glutathione, vitamin E and N-acetylcysteine in the treatment of SOS.51-53 There are some reports recommending a portosystemic shunt in order to reduce the portal pressure in serious portal hypertension.33 Transjugular intrahepatic portosystemic shunt can be performed in patients who are unsuitable for surgery.54 In advanced liver failure, liver transplantation can be a treatment option in few cases.24

3. Capillary Leak Syndrome

Endothelial damage as a result of allo-HSCT is diffuse capillary endothelium damage and capillary leak syndrome emerging due to leakage of intravascular fluid and content into interstitial area. Chemo-radiotherapy, various cytokines released from injured tissues, microbial components easily passing from damaged mucosal barriers, granulocyte-colony stimulating factor (G-CSF) and various drugs such as calcineurin inhibitors are defined as several etiologic factors.55 Until now, many groups investigated various biological markers to predict post allo-HSCT endothelial injury development such as von Willebrand factor (vWF), VWF-cleaving protease activity, soluble thrombomodulin, TNF-α, PAI-1, soluble adhesion molecules (soluble E-selectin, soluble ICAM-1 [intercellular adhesion molecule-1] and soluble vascular cell adhesion molecule-1 [sVCAM-1]).56 None of them was proved to be a prognostic marker. While Ueda N et al indicated that high level of angiopoietin-2 (Ang2) can be a good indicator of posttransplant endothelial injury; Xie Z et al reported that vascular endothelial growth factor (VEGF) and Ang2 levels were quite high during the attack periods of systemic capillary leak syndrome compared to remission period.56,57

Capillary leak syndrome generally emerges within the first 15 days of post allo-HSCT, it can also be detected in late periods: it is especially characterized with rapid weight gain (>5% within 24 hours), ascites non responsive to diuretic treatment and pleural or pericardial effusion that might be a prodrome of common edema development.33 Renal failure caused by hypoalbuminemia or pre-renal azotemia, hypotension and tachycardia can also accompany to clinic. Unrelated and HLA mismatched donor graft use are among the risk factors.33 Early differential diagnosis, discontinuation of growth factors and application of systemic corticosteroids even with suspected efficacy are management steps in which the risk of development of multiorgan failure is quite high.

4. Engraftment Syndrome

Engraftment syndrome (ES) emerges during the neutrophil recovery period after HSCT and it progresses with non-infectious fever, skin rush, non-cardiogenic pulmonary edema, weight gain, liver and renal dysfunction, and/or encephalopathy. Although mostly it has a self-limited course, the syndrome can result with multiorgan failure.58 Vascular leak, organ dysfunction and constitutional signs such as fever are secondary to activated leucocytes and pro-inflammatory cytokines during engraftment process.59 It was reported that IL-1, TNF-alpha, interferon gamma, IL-2 receptor-alpha and TNF-receptor levels increased in ES as in acute
GVHD. Soluble thrombomodulin and plasminogen activator type I, CRP increase and complement activation are changes detected in ES.

The incidence of ES is varying from 5% to 72% because the definition and criteria of ES are not described precisely. Diagnostic definition suggested by Spitzer contains major and minor criteria: a temperature of ≥ 38°C without a defined infectious etiology, erythrodermic rashes not related to any drug covering a body area over 25%, non-cardiogenic pulmonary edema accompanying with hypoxia and diffuse pulmonary infiltrates are major criteria, hepatic dysfunction with either bilirubin of ≥ 2 mg/dL or transaminase levels of ≥ 2 times normal, renal failure, weight gain of ≥ 2.5% of baseline body weight and a transient encephalopathy unexplained by other causes are considered as minor criteria. For diagnosis, all three major criteria or two major criteria and one or more minor criteria, within 96 hours of engraftment is sufficient.

Chang L, et al. characterized that recipients at younger age and male, male-male donor-recipient combinations, unrelated donors, cord blood as a stem cell source, ABO major incompatibility, myeloablative conditioning, and TBI (1200 cGy) are risk factors. Ak et al. stated that some agents used in acute GVHD prophylaxis may have a role in the etiology.

It was detected that immunosuppressive therapy consisting of tacrolimus/methotrexate/ATG had lower ES risk than the use of cyclosporine alone. Major treatment is systemic corticosteroid dose of 1.5 mg/kg/day or > 1.5 mg/kg/day depending on the condition of patient. In addition, it was reported that grade II-IV acute GVHD, and NRM were decreased with > 1.5 mg/kg/day of corticosteroid dose.

4. Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH) is a syndrome developing in the presence of hypoxia, multi-lobar pulmonary infiltrates, symptoms of pneumonia and progressively hemorrhagic bronchoalveolar lavage (BAL). DAH is generally seen in the first 30 days after allo-HSCT with the incidence of 2-14% and the mortality rates of over 60%.

DAH etiology is not elucidated in the context of transplantation. While infections, cardiac causes including heart failure, toxicity from pre-transplant thoracic radiation, chemotherapy and early marrow engraftment are the factors leading to DAH, no definite cause could be detected in 20% of patients. Although the etiology of DAH is still unclear, it is believed that GVHD, inflammatory cytokine release and lung tissue injury may play roles in the pathogenesis of DAH.

Gupta S et al. has mentioned four criteria in their study for diagnosis of DAH:

1) Symptoms (dyspnea, cough, fever) and signs (tachypnea, tachycardia) related with pneumonia
2) Multilobar pulmonary infiltrates that can be observed in chest radiographs as indicator of widespread alveolar injury
3) Absence of laboratory and clinical signs of cardiogenic pulmonary edema
4) Presence of 20% or more hemosiderin-laden macrophages in BAL or progressively bloodier return on BAL from three separate subsegmental bronchi.

Conventional therapy of DAH contains corticosteroids and supportive care. Predictably, supportive therapy includes oxygen and ventilation support, transfusion of blood products and antimicrobial therapy. Rathi NK et al. classified the cases of post transplant DAH in three groups according to methylprednisolone doses in the treatment: (1) low dose: < 250 mg/day, (2) medium dose: 250–1000 mg/day and (3) high dose: ≥ 1000 mg/day. Authors concluded that intensive care unit and hospital mortality significantly low only in low-dose steroid group and stated that treatment strategies may need to be reanalyzed in order to avoid potential unnecessary therapies.

5. Thrombotic microangiopathy

Transplant-associated thrombotic microangiopathy (TA-TMA), which is similar to thrombotic thrombocytopenic purpura (TTP), is a rare complication following transplant in which hemolytic anemia
and thrombocytopenia accompanies to this process. In the etiology of TA-TMA, drugs -such as cyclosporin, tacrolimus, sirolimus- GVHD, infections including viral -especially CMV- and fungal pathogens, high dose chemotherapy, radiotherapy, unrelated donor and HLA mismatch transplants can be considered as leading factors. TA-TMA generally emerges within first 100 days of post transplant period. According to the literature, the prevalence varies between 0% and 74% because it is often not recognized sufficiently. TA-TMA has a high mortality rate reaching almost 100%. Unlike classical TMA, it is quite difficult to determine a common reason for small vessel injury in transplant recipients. Especially busulfan, fludarabine, platinum-based chemotherapy and total body irradiation are blamed. Various fungal factors, especially Aspergillus, and various viral factors, especially CMV and Adenovirus, may cause endothelial damage by causing an increase in soluble fms-like tyrosine kinase or thrombomodulin, PAI-1, and inflammatory cytokines. Other potential infectious causes include parvovirus B19, HHV-6, and, most recently, BK virus. Endothelial injury developing due to the use of calcineurin inhibitors such as cyclosporine and tacrolimus is related to direct cytotoxic damage, platelet aggregation, elevated VWF and thrombomodulin, altered complement regulator proteins, and decreased production of prostacyclin and nitric oxide. It is supposed that sirolimus, an inhibitor of mammalian target of rapamycin (mTOR) causes TA-TMA by preventing repair of injured endothelium and by decreasing local VEGF production. In allo-HSCT recipients, it is considered that higher VEGF levels are associated with less endothelial injury, better survival, and less severe GVHD. The relationship between GVHD and TA-TMA is not a surprising condition because donor T lymphocytes primarily encounter with recipient endothelial cells during engraftment process. However, not only direct damaging effect

**Table 1. Diagnostic Criteria of TMA**

<table>
<thead>
<tr>
<th>BMT-CTN diagnostic criteria:</th>
<th>IWG diagnostic criteria:</th>
<th>Overall-TMA diagnostic criteria suggested by Cho BS et al.:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistocytes: ≥ 2 per high-power field in peripheral blood,</td>
<td>Schistocytes: &gt; 4% in peripheral blood,</td>
<td>Schistocytes: ≥ 2 per high-power field in peripheral blood,</td>
</tr>
<tr>
<td>LDH: Increased above institutional baseline,</td>
<td>LDH: Sudden and persistent increase,</td>
<td>LDH: Increased,</td>
</tr>
<tr>
<td>Renal function: Doubling of serum creatinine or 50% decrease in creatinine clearance from baseline before transplantation,</td>
<td>Thrombocytopenia: &lt; 50 X 10^9/L or a ≥ 50% decrease in platelet count,</td>
<td>Thrombocytopenia: &lt; 50 X 10^9/L or a ≥ 50% decrease in platelet count,</td>
</tr>
<tr>
<td>Central nervous system: Unexplained neurologic dysfunction,</td>
<td>Red cells: Decreased hemoglobin or increased red blood cell transfusions,</td>
<td>Red cells: Decreased hemoglobin</td>
</tr>
<tr>
<td>Coombs test: Negative direct and indirect.</td>
<td>Haptoglobin: Decreased,</td>
<td>Coombs test: Negative,</td>
</tr>
<tr>
<td>Other: No coagulopathy.</td>
<td></td>
<td>Haptoglobin: Decreased,</td>
</tr>
</tbody>
</table>

and thrombocytopenia accompanies to this process. In the etiology of TA-TMA, drugs -such as cyclosporin, tacrolimus, sirolimus- GVHD, infections including viral -especially CMV- and fungal pathogens, high dose chemotherapy, radiotherapy, unrelated donor and HLA mismatch transplants can be considered as leading factors. TA-TMA generally emerges within first 100 days of post transplant period. According to the literature, the prevalence varies between 0% and 74% because it is often not recognized sufficiently. TA-TMA has a high mortality rate reaching almost 100%. Unlike classical TMA, it is quite difficult to determine a common reason for small vessel injury in transplant recipients. Especially busulfan, fludarabine, platinum-based chemotherapy and total body irradiation are blamed. Various fungal factors, especially Aspergillus, and various viral factors, especially CMV and Adenovirus, may cause endothelial damage by causing an increase in soluble fms-like tyrosine kinase or thrombomodulin, PAI-1, and inflammatory cytokines. Other potential infectious causes include parvovirus B19, HHV-6, and, most recently, BK virus. Endothelial injury developing due to the use of calcineurin inhibitors such as cyclosporine and tacrolimus is related to direct cytotoxic damage, platelet aggregation, elevated VWF and thrombomodulin, altered complement regulator proteins, and decreased production of prostacyclin and nitric oxide. It is supposed that sirolimus, an inhibitor of mammalian target of rapamycin (mTOR) causes TA-TMA by preventing repair of injured endothelium and by decreasing local VEGF production. In allo-HSCT recipients, it is considered that higher VEGF levels are associated with less endothelial injury, better survival, and less severe GVHD. The relationship between GVHD and TA-TMA is not a surprising condition because donor T lymphocytes primarily encounter with recipient endothelial cells during engraftment process. However, not only direct damaging effect
of cytotoxic T lymphocytes but also activation of coagulation pathway, circulating cytokines and low VEGF levels support the situation.\textsuperscript{71} It was claimed that complement dysregulation has also effect on the disease pathogenesis.\textsuperscript{70}

In the historical process, Cho BS et al recently suggested a new guideline by restocking previous guidelines in addition to diagnostic criteria defined by Bone Marrow Transplant Clinical Trials Network (BMT-CTN) and International Working Group (IWG) (Table-1).\textsuperscript{83-85}

TA-TMA treatment can be separated into two groups; supportive treatments and treatments targeting directly the disease. First, it is essential to remove underlying causes which trigger the disease. Immunosuppressive treatments have a major role among these. When these drugs used in GVHD prophylaxis, dose reduction or discontinuation may not be always possible based on the clinical condition of patient. Because of the role of complement dysregulation in the disease pathogenesis, there are some clues showing that the monoclonal anti-C5 component antibody, eculizumab, may be beneficial. In the retrospective analysis of the patients diagnosed with TA-TMA and treated with eculizumab in France between 2010 and 2013, it was reported that monoclonal anti-C5 treatment provided better results compared to therapeutic plasma exchange (TPE).\textsuperscript{86} The most practical and fastest approach for treatment of TA-TMA is TPE. However, the median response rate was 36.5\% with the use of TPE in patients with TA-TMA between 1991 and 2003 with a mortality rate of 80\% [70]. Successful results have been obtained via using anti-CD20 monoclonal antibody, rituximab, treatment alone or with TPE/defibrotide treatment. Although the mechanism of action of Rituximab is not known, it is considered that it displaces the precursors of CD20 + B cells and represses T cell activation and functions by decreasing cytokine release.\textsuperscript{87} In a study which was conducted by Corti et al. it was shown that response was detected in 8 of 12 TA-TMA patients including 5 full responses with the use of defibrotide.\textsuperscript{88}

In summary, non-infectious early complications of allogeneic HSCT are still a challenging issue. Despite improvements in this field during the last decade, treatment of these early complications are still putting an important burden on both patients and physicians treating these patients. Early complications are still an important cause of mortality of Allo-HSCT. For practising hematologists and oncologists in this field awareness and early diagnosis of the acute complications remain to be an important key factor in order to obtain an optimal outcome in this patient population undergoing the early complications of Allo-HSCT.

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