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Does defibrotide prophylaxis decrease the risk of acute graft versus host disease following allogeneic hematopoietic cell transplantation?

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ABSTRACT

There is some preliminary evidence, that veno-occlusive disease prophylaxis with defibrotide (DF) may also have a role in decreasing risk of acute graft-versus-host disease (aGvHD) by preventing tissue damage. In this study, we aimed to investigate the role of DF prophylaxis on the development of aGvHD at D + 180. One hundred ninety-five consecutive adult patients receiving allogeneic HCT were retrospectively evaluated in 3 groups: no DF, DF/post-HCT (DF D + 1 to D + 14) and DF/pre-HCT (DF for 14 days concurrently with conditioning). The total (p: 0.057) and grades III/IV (p: 0.051) aGvHD rates at D + 180 were 46.5%, 40%, 25.5% and 15.5%, 11.2%, 0% in patients on no DF, DF/post-HCT and DF/pre-HCT. DF may have a role in decreasing incidence and severity of aGvHD, especially if used concurrently with conditioning regimen.

1. Introduction

Acute graft versus host disease (aGvHD) and hepatic veno-occlusive disease (VOD) are important early complications after hematopoietic cell transplantation (HCT) decreasing overall survival and quality of life. Both diseases share some important features from a pathophysiological point of view. Conditioning regimen-induced damage to endothelial cells of the liver, skin and gastrointestinal mucosa contributes to the development of aGvHD [1]. On the other hand, pathogenesis of VOD relates to damage to sinusoidal endothelial cells and hepatocytes as a result of conditioning regimen dependent injury [2]. Defibrotide (DF) is the established treatment of VOD. At the same time, the use of DF has been found useful in decreasing incidence of VOD in pediatric patients, who are considered to have high risk for development of VOD [3]. Therefore, the use of DF in terms of VOD prophylaxis in high-risk settings is increasing. There is also some preliminary evidence, that DF prophylaxis may also have a role in decreasing risk of aGvHD by preventing tissue damage [3]. In this study, we aimed to investigate the role of DF prophylaxis on the development of aGvHD.

2. Methods

2.1. Time frames according to availability of DF for VOD prophylaxis

Between January 2009 and October 2011 (first period) the drug was unavailable for treatment and/or prophylaxis

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in Turkish market. Nowadays, DF can be used as an off-label drug for prevention of VOD for special indications and following case-by-case approval by Turkish Drug and Pharmacy Agency (TDFA). Between November 2011 and January 2014 (second period), we were able to access the drug for high-risk patients, who actually received HCT and therefore DF could be used only after infusion of hematopoietic progenitor cells. Between February 2014 and January 2015 (third period), TDFA enabled access to DF for VOD prophylaxis in high-risk patients concurrently with administration of conditioning regimens.

2.2. Definition of high-risk states for DF prophylaxis

The following indications were accepted as high-risk settings for development of VOD by TDPA:

a) Abdominal radiotherapy involving liver
b) Biopsy proven liver fibrosis, cirrhosis or hemochromatosis
c) HBV or HCV infection
d) Previous HCT with myeloablative conditioning
e) Busulphan based conditioning regimen
f) Gemtuzumab ozagomycin treatment in the last 3 months
g) Matched unrelated donor-HCT
h) HCT before 7 years of age

2.3. Patients and treatment arms

The study included all consecutive patients who received allogeneic HCT (allo-HCT) between January 2009 and January 2015 in Ankara Oncology Hospital Stem Cell Transplantation Clinic. We used our HCT database, which was prospectively collected during study period. Patients were retrospectively analyzed in three time frames according to availability of DF for VOD prophylaxis. In the first period of the study (no DF arm), patients received only low molecular weight heparin (LMWH), ursodeoxycholic acid (UDCA) and N-acetyl cysteine (NAC) in terms of VOD prevention, what we called conventional approach. Conventional regimen for prevention of VOD consisted enoxaparin 0.4 mL (as long as they had platelet count ≥30,000/mm^3 and in the absence of bleeding), 750-mg/day po UDCA and 600-mg/day po NAC. Patients on no-DF arm were unable to receive DF in the case of VOD diagnosis, because the drug was unavailable in our country at that time period, when these patients were treated with allo-HCT. They only received supportive care following diagnosis of VOD. Patients who were transplanted on the second time frame received DF prophylaxis in addition to conventional prevention approach (DF/post-HCT arm). Patients on DF/post-HCT arm received 10 mg/kg/day IV DF for 14 days (from D + 1 to day D + 14). If the patients on DF/post-HCT arm were diagnosed as VOD, the dose of DF was increased to 25 mg/kg/day. During the third time period, patients received 10 mg/kg/day IV DF for 14 days beginning on the first day of conditioning regimen in addition to aforementioned conventional approach (DF/pre-HCT arm).

2.4. Risk factors, diagnosis and grading of aGvHD

All patients were evaluated according to known risk factors for aGvHD: HLA match, stem cell source (bone marrow or peripheral blood), intensity of preparative regimen (myeloablative or reduced-intensity conditioning), use of total body irradiation (TBI), sex mismatch (male patient-female donor), donor age and recipient seropositivity for CMV [4,5]. Patients presenting with both classic and non-classic (persistent, recurrent, late-onset) forms of aGvHD were included [6]. We used consensus criteria for grading aGvHD [7]. The frequency and severity of aGvHD were evaluated on the sixth month of the HCT procedure.

2.5. Definitions of HLA match and conditioning intensities

Donor HLA assessment and matching categorization of patients were made according to standard definitions defining minimum requirements [8]. Donors were grouped as matched related (MRD), one antigen mismatched related (MMRD), matched unrelated (MUD), one antigen mismatched unrelated (MMUD), haploidentical-related (haploid) and umblical cord blood (UCB). Conditioning regimes were chosen according to the standard policy of our HCT center taking into account the primary disease, remission status, age and comorbidities of patients. The definition of the conditioning intensity (myeloablative-MA or reduced-intensity conditioning-RIC) is made according to widely accepted criteria [9].

2.6. Conditioning regimens and aGvHD prophylaxis

All patients received predetermined conditioning and aGvHD prophylaxis according to our written institutional policy. Regardless of preparative regimen, graft source and HLA-match, all participants were treated with standard short-term methotrexate (MTX) and cyclosporine-A (CsA) based GvHD prophylaxis (MTX/CsA). Briefly, MTX/CsA regimen consisted IV methotrexate (MTX) (D + 1 15 mg/m^2, D + 3 and D + 6 10 mg/m^2) and cyclosporine-A (CsA) (from D − 1 to D + 180 with targeting through blood levels 150–350 ng/mL; tapering of CsA begun on day 100). The aGvHD prophylaxis regimen in RIC setting from MRD/MMRD, consisted ATG-Fresenius® (total dose 10 mg/kg) in addition to above-mentioned MTX/CsA regimen. In RIC/MUD setting, we used ATG-Fresenius® (total dose 30 mg/kg) plus MTX/CsA. Patients who received haploid-HCT, were treated with ATG-Fresenius® (total dose 10 mg/kg), IV cyclophosphamide 50 mg/kg at D + 3 plus MTX/CsA in terms of aGvHD prophylaxis.

All patients had a follow-up period until death or post-HCT D180, whichever occurred first. For patients, who received second HCT, we used only the data regarding the first HCT procedure. All participants gave written informed consent for all aspects of HCT procedure. Institutional review board approved the study.

2.7. Statistics

All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 21.0. (Armonk, NY: IBM Corp)