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BRIEF COMMUNICATION

Low, fixed dose defibrotide in management of hepatic veno-occlusive disease post stem cell transplantation

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KEYWORDS
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Abstract
Objective/background: Hepatic veno-occlusive disease (VOD) is well recognized potentially serious regimen-related toxicity seen after stem cell transplantation. Severe VOD is associated with poor long-term outcomes with very high mortality. Besides supportive care, only defibrotide has been found to be effective in the management of VOD. The recommended dose of defibrotide is 25 mg/kg/d but there has been no classical dose finding study done for this drug. A higher dose of defibrotide is associated with increased risk of bleeding and this drug is prohibitively expensive. We report our experience of using fixed low dose of defibrotide in patients with VOD.
Methods: We retrospectively evaluated 511 patients who underwent stem cell transplant at our center from November 2007 and December 2015. All patients received ursodeoxycholic acid as VOD prophylaxis. Modified Seattle criterion was used for diagnosis and severity grading of VOD. Patients developing VOD were initially treated with furosemide and adequate analgesia. Defibrotide was started within 12 to 24 hours of diagnosis of VOD. All adult patients received defibrotide at a fixed dose of 200 mg twice daily while two children were given dose of 100 mg and 50 mg twice daily.

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Results: Nine (1.7%) of our patients developed VOD. Daily dose of defibrotide ranged from 5 mg/kg/d to 20 mg/kg/d till resolution of VOD. All patients had complete resolution of VOD. None of our patients required ventilator support or dialysis. No episodes of bleeding were observed. No dose response relationship was observed between defibrotide dose and time to resolution of VOD.

Conclusion: Low fixed dose defibrotide initiated early seems to be effective and safe in treatment of VOD. This is relevant in a resource limited setting and warrants prospective evaluation.

Introduction

Hepatic veno-occlusive disease (VOD) is well recognized potentially serious regimen-related toxicity seen after stem cell transplantation (SCT). VOD post SCT is triggered by high dose conditioning chemotherapy causing damage to hepatic sinusoidal endothelium. Damaged endothelial cells break free from the basement membrane and embolize to center of lobule. Later stages are characterized by sub endothelial fibrin deposition and platelet thrombi formation in sinusoid and central veins of liver causing blockage of sinusoidal outflow. These pathological event leads to typical clinical features of VOD such as weight gain, ascites and tender hepatomegaly followed by jaundice, liver dysfunction and secondary renal, respiratory and circulatory compromise leading to multiorgan dysfunction syndrome (MODS) in severe cases [1]. VOD incidence varies from 10% to 60% after SCT. Recent studies reported decline in incidence reflecting change in type and dose of conditioning chemotherapy [2]. VOD after SCT is divided into 3 risk groups. Mild VOD is associated with symptoms that do not require specific treatment and VOD resolves spontaneously, moderate VOD manifests as symptoms requiring treatment, but resolves before day 100 post SCT while severe VOD requires treatment and does not resolve by day 100 or results in death of patient [3]. Severe VOD is associated with poor long-term outcomes with mortality in up to 80% of cases [4]. Thus management of severe VOD clearly is an unmet medical need.

Treatment of VOD includes supportive care in form of management of fluid retention, control of sepsis and renal, respiratory and circulatory support. Of the numerous specific therapies tried for treatment of VOD, only defibrotide (DF) has been found to be effective in the management of VOD. DF is the sodium salt of complex single-stranded deoxyribonucleotide derived from porcine mucosa. It stabilizes and protects endothelial cells and balances the procoagulant and fibrinolytic pathways at local level. Initial study by Richardson et al used DF doses from 5 mg/kg/d with escalation to 60 mg/kg/d. Clinical response in that study was seen at doses lower than 25 mg/kg/d in all 8 responding patients and no dose-response relationship was observed with higher doses [5]. A dose finding study compared 25 mg/kg/d to 40 mg/kg/d of DF. A lower dose of 25 mg/kg/d was found to be equally effective and hence became standard of care in patients with VOD [6]. Though the dose of 25 mg/kg/d has been adopted as standard dose, there has been no classical dose finding study done for this drug. Higher doses of DF have been found to increase risk of bleeding [7]. DF is a prohibitively expensive drug, out of reach for patients in many parts of world. High cost has forced transplant physician to change their practice for more restrictive use of this active drug [8]. This may lead to delay in initiation of DF which may be counterproductive as delay in initiation of DF has been associated with poor outcomes [9,10]. As there is no typical dose response effect with this drug, we used a fixed low dose of DF in our patients with VOD. This report is our experience of using fixed low dose of DF in patients who developed VOD.

Method

We did a retrospective analysis of records all patients who underwent a SCT at our centre between November 2007 and December 2015. A total of 511 patients (280 autologous and 231 allogeneic; 374 males and 137 females) underwent SCT in this period were included in this analysis. Median age of study population was 31 years (range 2—63 years) and 65 patients were pediatric (age less than 14 years). Diagnosis was acute leukemia in 153 patients, aplastic anemia in 24 patients, chronic myeloid leukemia in 33 patients, lymphoma in 160 patients, multiple myelomas in 92 patients, MDS and other myeloproliferative neoplasm in 25 patients, neuroblastoma in 16 patients, thalassemia in 1 patient, Ewing's sarcoma and non-seminomatous germ cell tumor in remaining 7 patients. All patients received ursodeoxycholic acid as prophylaxis for VOD at a dose of 10 mg/kg/d. Patients were started on ursodeoxycholic acid at least two days before the start of conditioning therapy till day +28 post transplant for autologous transplant and till day 100 post allogeneic transplant. Conditioning regimens used for allogeneic transplant patients were either myeloablative (Cy-TBI or BuCy-2) or reduced intensity regimens which included fludarabine plus busulfan (8 mg/kg) or melphalan (140 mg/m^2) or cyclophosphamide (120 mg/kg). We used cyclosporine and methotrexate or mycophenolate mofetil (CSA+MTX/MMF) as GVHD prophylaxis for sibling matched allogeneic SCT, cyclosporine with post-transplant cyclophosphamide for haplo-SCT and ATG in addition to CSA+MTX/MMF for MUD SCT. Autologous transplant patients received BEAM or LACE conditioning for lymphoma while patients with multiple myelomas received standard melphalan conditioning. Bu (130 mg/m^2)-Mel (90 mg/m^2) conditioning is used for patients with neuroblastoma and Ewing sarcoma and carboplatin-etoposide in Non-seminomatous germ cell patients.

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