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Defibrotide for the Treatment of Severe Hepatic Veno-Occlusive Disease and Multiorgan Failure after Stem Cell Transplantation: A Multicenter, Randomized, Dose-Finding Trial

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Therapeutic options for severe hepatic veno-occlusive disease (VOD) are limited and outcomes are dismal, but early phase I/II studies have suggested promising activity and acceptable toxicity using the novel polydisperse oligonucleotide defibrotide. This randomized phase II dose-finding trial determined the efficacy of defibrotide in patients with severe VOD following hematopoietic stem cell transplantation (HSCT) and identified an appropriate dose for future trials. Adult and pediatric patients received either lower-dose (arm A: 25 mg/kg/day; n = 75) or higher-dose (arm B: 40 mg/kg/day; n = 74) i.v. defibrotide administered in divided doses every 6 hours for ≥14 days or until complete response, VOD progression, or any unacceptable toxicity occurred. Overall complete response and day +100 post-HSCT survival rates were 46% and 42%, respectively, with no significant difference between treatment arms. The incidence of treatment-related adverse events was low (8% overall; 7% in arm A, 10% in arm B); there was no significant difference in the overall rate of adverse events between treatment arms. Early stabilization or decreased bilirubin was associated with better response and day +100 survival, and decreased plasminogen activator inhibitor type 1 (PAI-1) during treatment was associated with better outcome; changes were similar in both treatment arms. Defibrotide 25 or 40 mg/kg/day also appears effective in treating severe VOD following HSCT. In the absence of any differences in activity, toxicity or changes in PAI-1 level, defibrotide 25 mg/kg/day was selected for ongoing phase III trials in VOD.

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INTRODUCTION

Hepatic veno-occlusive disease (VOD) is one of the more common and important nonhematologic toxicities following high-dose cytoreductive therapy for hematopoietic stem cell transplantation (HSCT) [1,2]. Diagnosis of hepatic VOD is based on clinical criteria, including the presence of painful hepatomegaly,

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jaundice, ascites, fluid retention, and weight gain [2,3]. The condition usually develops before day +30 post-HSCT, although it can occur later [1,2,4]; its reported incidence varies from ~5% to 60%, and it is typically associated with the conditioning regimen used as well as the donor source, being more common after allogeneic HSCT than after autologous HSCT [4-7]. The presentation of VOD ranges from mild, reversible disease to a severe syndrome associated with multiorgan failure (MOF) and death [4-6]. Severe VOD is one of the most frequent causes of early death in the HSCT setting, with a mortality rate of up to 98%–100% by day +100 post-HSCT in adults, and marginally lower mortality in children [5,6,8].

Hepatic VOD is also known as sinusoidal obstruction syndrome (SOS) or VOD/SOS, reflecting the primary injury typically caused by cytoreductive agents to sinusoidal endothelial cells in zone 3 of the hepatic acinus [9,10]. Secondary events include sinusoidal hemostasis leading to elevated sinusoidal pressure and dilatation, subendothelial edema within small hepatic venules, and deposition of fibrinogen and factor VIII in both sinusoids and within hepatic venules [9,11]. These events are followed by ischemia, hepatocyte necrosis, collagen deposition, and sinusoidal fibrosis, leading to sinusoidal obstruction followed by sclerosis and occlusion of hepatic venules [9-11]. As these processes progress, widespread intrahepatic zonal disruption leads to portal hypertension, worsening liver dysfunction, and ascites, eventually resulting in MOF (characterized by pulmonary and renal dysfunction, as well as encephalopathy) and death [10,11].

Current standard treatments for hepatic VOD are supportive, including diuresis, transfusion, renal replacement therapy, and analgesia. There are few effective options that target the underlying cause. Reduced-intensity conditioning regimens, individualized chemotherapy dosing, and avoidance of cyclophosphamide (Cy) are currently experimental approaches to prevention, but these strategies often are not suitable for chemoresistant hematologic malignancies [1]. Administration of intravenous busulfan and pharmacokinetic (PK) monitoring of busulfan and Cy have been shown to reduce the frequency of VOD [12]. Prophylactic ursodeoxycholic acid use has been associated with decreased incidence of VOD in some studies, although the relative effects on cholestatic versus sinusoidal injury per se are unclear [13]. Currently, there is no proven effective therapy for either prevention or treatment of hepatic VOD. Interventional studies that have investigated prostaglandin E1, tissue-plasminogen activator (t-PA), heparin, and antithrombin III (ATIII) for treating severe VOD have demonstrated neither significant effectiveness nor safety in this setting [14-16]. Indeed, the use of t-PA in patients with severe VOD and MOF has been associated with markedly excessive toxicity, precluding its use in this population [14].

Defibrotide is a polydisperse oligonucleotide with local antithrombotic, anti-ischemic, and anti-inflammatory activity. It binds to the vascular endothelium, modulates platelet activity, promotes fibrinolysis, decreases thrombin generation and activity, and reduces circulating levels of plasminogen activator inhibitor type 1 (PAI-1) [17-21]. Defibrotide has selective and protective effects on the small vessels, but not macrovascular, endothelium [22,23]. Experimental models suggest that it may enhance endothelial cell survival and stabilize microvasculature [24]. Defibrotide has no protective effect on tumors, and in fact was found to enhance the antitumor activity of various agents in preclinical studies [25]. In adult and pediatric patients with VOD, defibrotide treatment has been associated with complete response (CR) rates of 36%–76%, with day +100 post-HSCT survival rates of 32%–79% and no substantial defibrotide-associated toxicity [26-30]. Multicenter phase I/II trials of defibrotide have included intrapatient dose escalation from 10 mg/kg/day to 60 mg/kg/day [26-28]. In the largest study published to date, the majority of CRs occurred at doses of 20-40 mg/kg/day [28].

The objectives of our dose-finding trial were to (1) determine the CR rate in patients with severe VOD following HSCT treated with defibrotide at 25 or 40 mg/kg/day, (2) assess the safety profile of defibrotide at these doses in this population, and (3) determine the dose for use in phase III and other future trials in VOD. The trial also aimed to generate preliminary descriptive PK data for defibrotide in a limited subset of patients.

MATERIALS AND METHODS

Patients

Adult or pediatric patients with a clinical diagnosis of hepatic VOD, defined as the presence of jaundice (total serum bilirubin ≥2 mg/dL) and at least 2 associated signs, including ascites, weight gain >5% from baseline, hepatomegaly, or right upper quadrant pain, by day +35 post-HSCT were considered eligible. Abdominal Doppler ultrasound was performed at trial entry to identify the presence/absence of portal vein blood flow reversal and confirm diagnostic findings. Patients with jaundice and portal vein blood flow reversal on Doppler examination and only one other diagnostic criteria were eligible for the trial. For patients with preexisting hepatomegaly, confirmation of liver size increase after admission by physical examination or imaging was required. Patients who did not meet all criteria but had biopsy-proven VOD were also eligible. In patients with concurrent confounding causes of liver dysfunction, positive biopsy findings or a wedged transhepatic venous pressure gradient ≥10 mm Hg was required to confirm