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Escalation to High-Dose Defibrotide in Patients with Hepatic Veno-Occlusive Disease

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A B S T R A C T

Hepatic veno-occlusive disease (VOD) is a serious complication of high-dose chemotherapy regimens, such as those used in hematopoietic cell transplantation recipients. Defibrotide is considered a safe and effective treatment when dosed at 25 mg/kg/day. However, patients who develop VOD still have increased mortality despite the use of defibrotide. Data are limited on the use of doses above 60 mg/kg/day for persistent VOD. In this prospective clinical trial 34 patients received escalating doses of defibrotide. For patients with persistent VOD despite doses of 60 mg/kg/day, doses were increased to a maximum of 110 mg/kg/day. Increased toxicity was not observed until doses rose beyond 100 mg/kg/day. Patients receiving doses between 10 and 100 mg/kg/day experienced an average of 3 bleeding episodes per 100 days of treatment, whereas those receiving doses >100 mg/kg/day experienced 13.2 bleeding episodes per 100 days ($P = .008$). Moreover, dose reductions due to toxicity were needed at doses of 110 mg/kg/day more often than at lower doses. Defibrotide may be safely escalated to doses well above the current standard without an increase in bleeding risk. However, the efficacy of this dose-escalation strategy remains unclear, because outcomes were similar to published cohorts of patients receiving standard doses of defibrotide for VOD.

INTRODUCTION

Hepatic veno-occlusive disease (VOD) or sinusoidal obstruction syndrome may occur after high-dose chemotherapy regimens, like those used in hematopoietic cell transplantation (HCT), and severe cases are associated with a poor prognosis [1]. VOD is the result of sinusoidal endothelial cell damage in the liver and occurs in up to 12% of autologous and 40% of allogeneic HCT [2]. Additionally, plasminogen activator inhibitor-1 is recognized as a main contributor to the pathogenesis of VOD by preventing fibrinolysis by tissue plasminogen activator, thereby promoting clot formation [3,4]. This ultimately leads to sinusoidal obstruction, hepatic veno-occlusion, severe portal hypertension, and diminished liver function [5]. Classical signs and symptoms include hepatomegaly, right upper quadrant abdominal pain, hyperbilirubinemia, refractory thrombocytopenia, ascites, and weight gain [6,7].

Therapies for VOD are mostly supportive, with diuretics and fluid restriction. Many patients with VOD are able to recover fully with supportive care. In retrospective studies these cases are defined as mild or moderate VOD, whereas those who died or with persistent VOD for longer than 100 days are classified as severe VOD [8,9]. Clinically, severe cases manifest as progressive hepatorenal syndrome and multiorgan failure (MOF) and carry a 100-day mortality rate in excess of 75% [2,8,10]. Systemic anticoagulants and thrombolytic therapies carry substantial risk of life-threatening hemorrhage [11,12].

Defibrotide, initially named fraction P because of its phosphate-rich content, is a low-molecular-weight, single-stranded DNA adenosine receptor agonist that has fibrinolytic, antithrombotic, and anti-ischemic properties [12,13]. It selectively binds to damaged endothelium and up-regulates the release of prostacyclin, prostaglandin E_2, thrombomodulin, and tissue plasminogen activator [5]. Defibrotide may also decrease plasma levels of plasminogen activator inhibitor-1, allowing fibrinolysis [14]. The resulting vasodilation and clot breakdown reverses the pathophysiology of VOD. Defibrotide has also been shown to be a safer alternative to therapeutic heparin, antithrombin, or tissue plasminogen activator [15]

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and was associated with improved mortality in patients with VOD and MOF in at least 1 series [16].

Although defibrotide is generally considered to be an effective treatment, the mortality rate in patients with severe VOD remains high. With defibrotide treatment, complete response rates of 36% to 76% and 100-day survival rates of 32% to 64% have been observed in various populations with VOD [12,13,17-19]. Therefore, further optimization of VOD therapy is needed. In the studies published to date defibrotide has been dosed from 25 mg/kg/day to a maximum of 60 mg/kg/day [13,16,17,20,21]. One study found that the average defibrotide dose in responders was significantly higher than in nonresponders [22]. More recently, however, Richardson et al. [12] performed a randomized trial demonstrating no significant differences between complete response rates, 100-day survival, or toxicity in patients receiving 25 mg/kg/day versus 40 mg/kg/day. Defibrotide has been dosed as high as 110 mg/kg/day in 1 patient, with complete resolution of VOD without hemorrhage or toxicity [22].

It remains unclear if treatment of severe VOD at doses above 60 mg/kg/day is safe and effective. The purpose of this study was to evaluate the safety and efficacy of defibrotide escalated up to 110 mg/kg/day in patients with persistent VOD at 60 mg/kg/day.

METHODS

Patient Selection

This single-center, prospective study received institutional review board approval and was performed at St. Jude Children's Research Hospital between January 2004 and September 2009 (clinicaltrials.gov identifier: NCT00143546). All participants (or respective legal guardians) gave written informed consent. Defibrotide was available under US Food and Drug Administration–approved Investigational New Drug application 68012.

Patients were eligible if they met diagnostic criteria for VOD, using either (1) Jones criteria, which are hyperbilirubinemia (≥2 mg/dL) and 2 of the following conditions: hepatomegaly, ascites, or weight gain (≥5% of baseline); or (2) McDonald criteria, which are at least 2 of the following by day +20: hepatomegaly or right upper quadrant pain, jaundice or hyperbilirubinemia (≥2 mg/dL), and ascites or sudden weight gain (>2% of baseline). Patients were excluded if observed symptoms could be attributable to a diagnosis other than VOD.

Laboratory and Clinical Evaluation

Monitoring during defibrotide therapy included daily physical examination, weekly abdominal ultrasound with liver Doppler measurement, and complete blood counts and chemistry panels at least 4 times a week. Data on weight gain, presence of right upper quadrant abdominal pain, hepatomegaly, and fluid retention were collected for each patient. Coagulation parameters (antithrombin III [ATIII], prothrombin time [PT], patial thromboplastin time [PTT], fibrinogen, and D-dimer) were measured at least weekly. Follow-up evaluations continued to day 14 after administration of the last dose of defibrotide. On completion of therapy a physical examination to document weight, liver size, and right upper quadrant abdominal tenderness was conducted. Onset of VOD was defined as the first day a patient met VOD criteria. Day 0 was defined as the date of cellular infusion in patients receiving HCT or the first day of the last chemotherapy cycle.

Renal insufficiency was defined as creatinine ≥3 times baseline, renal failure as receiving dialysis, pulmonary insufficiency as the need for supplemental oxygen for >24 hours, and pulmonary failure as receiving mechanical ventilation. Mild MOF was defined as VOD coexisting with either pulmonary or renal insufficiency. Severe MOF was defined as VOD in the presence of pulmonary or renal failure.

Treatment Design

Defibrotide was administered to patients intravenously in 1 of 2 dosing regimens. From 2003 to August 2006 patients were dosed at 10 mg/kg/day, divided every 6 hours, then escalated by 10 mg/kg/day, and plateaued at 60 mg/kg/day by day 6. A rapid escalation regimen was adopted starting late 2006; the initial dose was 6.25 mg/kg, the second dose was 7.5 mg/kg, the third dose was 10 mg/kg, the fourth dose was 12.5 mg/kg (total 36.25 mg/kg/day), and then the dose plateaued on the second day at 15 mg/kg/dose (60 mg/kg/day). In patients with rapidly progressing VOD, doses were allowed to be escalated faster at the discretion of the clinician. For patients with persistent VOD at 60 mg/kg/day, further escalation was allowed at increments of 10 mg/kg/day to a maximum of 110 mg/kg/day or until toxicity attributable to defibrotide was noted. Dosing was based on baseline weight, obtained before the start of transplant or chemotherapy. Therapy was continued until patients improved. Transfusions were used to keep platelets $\geq 20 \times 10^9$/L and hematocrit ≥30%, with clotting factors replaced as needed. Complete response was defined as evidence of complete resolution of VOD-related symptoms and a decrease in bilirubin to ≤2 mg/dL.

Adverse Events

All patients were monitored for the development of adverse events from the time of administration of the first dose of defibrotide until 14 days after the last dose, which were recorded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events v3.0. If significant toxicity attributable to defibrotide occurred, it was reduced by 50% or discontinued if the symptoms were life-threatening.

Statistical Analysis

Fisher exact test was used to compare the difference of 2 proportions of bleeding and hypotension events. The Kaplan-Meier method was used for overall survival (OS) estimates. OS was defined as the time from start of defibrotide treatment until death from any cause. Cumulative incidence of nonrelapse mortality (NRM) was defined from the start of defibrotide treatment until death due to treatment, with relapse as a competing risk. Univariate Cox proportional regression, Poisson regression, and Fine and Gray's regression analysis were used to test associations between factors and OS, bleeding events, and NRM, respectively [23,24]. Factors analyzed were time from transplant/chemotherapy to onset of VOD, bilirubin level at the time of VOD diagnosis, peak bilirubin level, receipt of dialysis, receipt of mechanical ventilation, and peak dose of defibrotide. All surviving participants were censored at the time of last follow-up date. All reported *P* values are 2-sided and are considered statistically significant at <.05. Statistical analyses were performed with R-3.1.0 [25].

RESULTS

Patient Characteristics

Thirty-five consecutive patients who received defibrotide were evaluated. One patient who received defibrotide for pulmonary VOD was excluded, leaving 34 patients in the final analysis (Table 1). Thirty-one patients developed VOD after transplantation, and 3 had received chemotherapy without transplantation. The median age was 8 years, 11 months (range, .5 to 21.6 years). Most patients (74%) had a hematologic malignancy. Twelve patients received total body irradiation, 10 patients received busulfan, 18 patients received cyclophosphamide, and 14 received melphalan in their preparative regimen. All 3 nontransplant patients had acute leukemia. Before developing VOD, 1 patient had received clofarabine, etoposide, and cyclophosphamide; 1 had received fludarabine, cytarabine, Mylotarg, and granulocyte colony-stimulating factor; and the third patient had received dexamethasone, etoposide, and cyclophosphamide. All transplant patients received continuous infusion of heparin for VOD prophylaxis.

Characterization of VOD and MOF

VOD developed at a median of 12 days after transplant/chemotherapy (range, −7 to 78). The median bilirubin level at the time of VOD diagnosis was 4.5 mg/dL (range, 2 to 19.7). Nineteen patients (56%) had MOF at enrollment, with another 10 patients developing MOF while on defibrotide treatment (5 within 1 day). Ultimately, MOF occurred in 29 patients (85%), with most (n = 22) being severe. Twenty-six patients had renal insufficiency; 17 received dialysis. Pulmonary insufficiency was documented in 29 patients; 20 received mechanical ventilation.

Defibrotide Administration

The median time from VOD diagnosis to start of defibrotide therapy was 0 days (range, 0 to 6), with 30 patients (88%) starting defibrotide within 1 day of VOD diagnosis. The median peak defibrotide dose was 60 mg/kg/day (range, 6.25 to 110).