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Defibrotide

Updated: December 27, 2017.

OVERVIEW

Introduction

Defibrotide is a complex mixture of single stranded polydeoxyribonucleotides derived from porcine intestinal mucosa that has antithrombotic and profibrinolytic activity and is used in the treatment of severe sinusoidal obstruction syndrome (SOS) after hematopoietic cell transplantation (HCT). Defibrotide is used in patients with severe liver injury and has not been associated with worsening of serum aminotransferase elevations during therapy and has not been linked to cases of clinically apparent, idiosyncratic liver injury.

Background

Defibrotide (de fib' roe tide) is a mixture of single stranded molecules of polydeoxyribonucleotides derived from porcine intestinal mucosa with molecular weights between 15,000 and 30,000 daltons. The short, single stranded DNA molecules have antithrombotic and profibrinolytic activities which suggested their use to treat SOS occurring after myeloablative regimens given in preparation of HCT. However, the pathophysiology of SOS involves destruction of sinusoidal endothelial centers in centrolobular (zone 3) regions along with stellate cell activation and deposition of collagen in sinusoids, and not thrombus formation. Thus, the mechanism of action of defibrotide in severe SOS is unknown, but it appears to act as an adenosine receptor agonist and as a stimulus to the production of endogenous prostaglandins, both of which modulate thrombogenesis and fibrinolysis. Defibrotide also binds to endothelial cells and may have cytoprotective activities on sinusoid cells or modulating effects on stellate cells. In multiple open label clinical trials, defibrotide was found to improve recovery of serum bilirubin elevations in SOS, but only in comparison to historical controls. Despite the lack of prospective, randomized controlled trials, defibrotide was approved for use in the United States in 2016 for severe SOS accompanied by evidence of renal or pulmonary failure occurring after myeloablation in preparation for HCT. Defibrotide is available as a solution for injection in single use vials of 200 mg/2.5 mL (80 mg/mL) under the brand name Defitelio. The recommended dose is 6.25 mg/kg every 6 hours for at least 21 days. Side effects include bleeding, hypotension, diarrhea, nausea and abdominal pain, but the typical patient receiving defibrotide is often critically ill with multiorgan failure and severe liver injury. Thus, minor and even fairly major side effects of defibrotide would be difficult to link to this therapy as opposed to the underlying severe, acute injury.

Hepatotoxicity

Defibrotide therapy has not been linked to serum aminotransferase elevations or with instances of clinically apparent liver injury separate from the features of SOS for which it is given. In a trial of defibrotide as prophylaxis against SOS conducted in 356 children undergoing HCT, rates of severe adverse events such as

hemorrhage, gastrointestinal complaints and liver injury were similar in those receiving defibrotide as in untreated children.

Likelihood score: E (unlikely cause of clinically apparent acute liver injury).

Mechanism of Injury

Defibrotide consists of a mixture of porcine polydeoxyribonucleotides which are unlikely to have a direct toxic effect on the liver and also unlikely to cause idiosyncratic metabolic or immunoallergic injury.

Outcome and Management

No convincing instances of clinically apparent or severe acute liver injury have been linked to defibrotide in the published literature, and worsening of the underlying liver injury during therapy is generally considered due to the severity of the sinusoidal obstruction rather than drug induced injury. The appearance of excessive hemorrhage, however, is often a reason for early discontinuation of defibrotide.

Drug Class: Antithrombotic Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Defibrotide – Defitelio®

DRUG CLASS

Antithrombotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Defibrotide	83712-60-1	Unspecified	Deoxyribonucleic Acid

ANNOTATED BIBLIOGRAPHY

References updated: 27 December 2017

Abbreviations used: HCT, hematopoietic cell transplantation; SOS, sinusoidal obstruction syndrome (which was formerly called veno-occlusive disease: VOD).

Zimmerman HJ. Heparin. Drugs used in cardiovascular disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 641-3.

(Textbook of hepatotoxicity published in 1999 before availability of defibrotide).

Weitz JI. Blood coagulation and anticoagulant, thrombolytic, and antiplatelet drugs. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 849-76.

(Textbook of pharmacology and therapeutics).

Richardson PG, Elias AD, Krishnan A, Wheeler C, Nath R, Hoppensteadt D, Kinchla NM, et al. Treatment of severe veno-occlusive disease with defibrotide: compassionate use results in response without significant toxicity in a high-risk population. Blood 1998; 92: 737-44. PubMed PMID: 9680339.

(Among 19 patients with severe SOS after HCT [bilirubin 11.7 to 54.4 mg/dL] who were treated with defibrotide, 8 had an initial response and 5 were long term survivors; side effects included nausea, hypotension, bleeding, and abdominal cramping, and serious adverse events were common, but "a causative temporal relationship to any grade 3 or 4 toxicity with defibrotide could not be shown).

Chopra R, Eaton JD, Grassi A, Potter M, Shaw B, Salat C, Neumeister P, et al. Defibrotide for the treatment of hepatic veno-occlusive disease: results of the European compassionate-use study. Br J Haematol 2000; 111: 1122-9. PubMed PMID: 11167751.

(Among 40 patients with SOS after HCT treated with defibrotide [10 to 40 mg/kg daily] for 2-53 [median=14] days, 22 [55%] had complete resolution and 17 [43%] were long term survivors, response not correlating with daily or total dose; "defibrotide was safely administered with no significant side effects").

Richardson PG, Murakami C, Jin Z, Warren D, Momtaz P, Hoppensteadt D, Elias AD, et al. Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome. Blood 2002; 100: 4337-43. PubMed PMID: 12393437.

(Among 88 patients with severe SOS after HCT treated with defibrotide [5 to 60 mg/kg/day for 1-139 days], complete resolution occurred in 36% and therapy was "without significant toxicity").

DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). Seminars Liver Dis 2002; 22: 27-41. PubMed PMID: 11928077.

(Review of the clinical features, pathophysiology and management of SOS, formerly known as veno-occlusive disease, which appears to be due to toxic injury to sinusoidal endothelial cells which undergo necrosis, detachment and release into sinusoids with subsequent obstruction, collagen formation and obliteration of central [hepatic] veins).

Kornblum N, Ayyanar K, Benimetskaya L, Richardson P, Iacobelli M, Stein CA. Defibrotide, a polydisperse mixture of single-stranded phosphodiester oligonucleotides with lifesaving activity in severe hepatic veno-occlusive disease: clinical outcomes and potential mechanisms of action. Oligonucleotides 2006; 16: 105-14. PubMed PMID: 16584299.

(Review of the clinical features, pathogenesis and therapy of SOS focusing upon defibrotide, its structure, proposed mechanisms of action, clinical efficacy and safety: "in general no significant side effects occurred").

Richardson PG, Soiffer RJ, Antin JH, Uno H, Jin Z, Kurtzberg J, Martin PL, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. Biol Blood Marrow Transplant 2010; 16: 1005-17. PubMed PMID: 20167278.

(Among 149 patients with severe SOS after HCT treated with defibrotide [25 or 40 mg/kg/day] for 2-85 [median = 19] days, resolution occurred in 49% and 43%, and adverse events were common [~90%] but only 3% were attributed to therapy [hypotension, hemorrhage], none of which were liver related).

Richardson PG, Ho VT, Giralt S, Arai S, Mineishi S, Cutler C, Antin JH, et al. Safety and efficacy of defibrotide for the treatment of severe hepatic veno-occlusive disease. Ther Adv Hematol 2012; 3: 253-65. PubMed PMID: 23606935.

(Review of safety and efficacy of defibrotide as therapy of severe SOS; mentions that in most studies there was "no significant toxicity").

Corbacioglu S, Cesaro S, Faraci M, Valteau-Couanet D, Gruhn B, Rovelli A, Boelens JJ, et al. Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. Lancet 2012; 379 (9823): 1301-9. PubMed PMID: 22364685.

(Among 356 children undergoing myeloablation and HCT who were given prophylaxis with defibrotide or were not treated, SOS rates were somewhat less with treatment [12% vs 20%], but overall survival was the same; adverse event rates were also similar in the two groups including hemorrhage and gastrointestinal complaints; no mention of ALT elevations or hepatotoxicity).

Richardson PG, Riches ML, Kernan NA, Brochstein JA, Mineishi S, Termuhlen AM, Arai S, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. Blood. 2016 Mar 31; 127 (13): 1656-65. PubMed PMID: 26825712.

(Among 102 adults with severe SOS after HCT treated with defibrotide [25 mg/kg] for 1-58 [median = 21.5] days, resolution by 100 days occurred in 25.5% compared to 12.5% in a matched, historical control group and adverse event rates were also similar).

Strouse C, Richardson P, Prentice G, Korman S, Hume R, Nejadnik B, Horowitz MM, et al. Defibrotide for treatment of severe veno-occlusive disease in pediatrics and adults: an exploratory analysis using data from the Center for International Blood and Marrow Transplant Research. Biol Blood Marrow Transplant 2016; 22: 1306-12. PubMed PMID: 27108694.

(In a retrospective analysis of 8341 patients who underwent HCT between 2008 and 2011 enrolled in an international database, 3.2% developed SOS, which was severe in 1.2% and included 41 defibrotide treated patients who were compared to 55 untreated subjects and had slightly, but not statistically significantly better survival [39% vs 31%], lower rates of graft-vs-host disease [23% vs 38%], but no differences in engraftment rates or other measures of safety).

Corbacioglu S, Carreras E, Mohty M, Pagliuca A, Boelens JJ, Damaj G, Iacobelli M, et al. Defibrotide for the treatment of hepatic veno-occlusive disease: final results from the International Compassionate-Use Program. Biol Blood Marrow Transplant 2016; 22: 1874-82. PubMed PMID: 27397724.

(Among 710 patients treated with defibrotide in an international compassionate use study, the 100+ day survival rate was 54% and adverse events were those largely due to multiorgan failure and graft vs host disease, while severe bleeding events occurred in 55 patients [8%] and were fatal in 37 [5%]).

Richardson PG, Riches ML, Kernan NA, Brochstein JA, Mineishi S, Termuhlen AM, Arai S, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. Blood 2016; 127: 1656-65. PubMed PMID: 26825712.

(Among 102 patients with severe SOS after HCT treated with defibrotide, the 100+ daily survival was 38% which compared favorably to historical control rates [25%] while adverese event rates, including bleeding, were similiar).