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DEFIBROTIDE: A MAJOR BREAKTHROUGH TO FIGHT VENOOCCLUSIVE DISEASE (VOD) OF HEMATOPOIETIC STEM CELL TRANSPLANTATION

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ABSTRACT
Venoocclusive disease (VOD) is a serious drawback of the standard Hematopoietic stem cell transplantation (HSCT) therapy. Day+ 100 survival of VOD patients after HSCT is very low (about 20%).[1] Previously the standard treatment for VOD was prophylactic and supportive which showed low evidence of effectiveness and high risk of adverse effects.[5] Recently, FDA approved the first therapy, Defibrotide for the treatment of this severe, rare and life-threatening hepatic VOD on March 30, 2016. Defibrotide was approved for the treatment of adult and pediatric patients suffering from hepatic veno-occlusive disease (VOD) with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation (HSCT).[10] Defibrotide increases tissue plasminogen activator (t-PA) and increases protection of activated endothelial cells from being damaged by chemotherapy, tumor necrosis factor-α (TNF-α), serum starvation and perfusion.[11]

KEYWORDS: Defibrotide, Venoocclusive.

INTRODUCTION
Hematopoietic stem cell transplantation (HSCT) is a standard treatment for many malignant and non-malignant diseases. Drawback for this standard therapeutic modality is that severe morbidity and mortality may result from HSCT. One of the major complications of HSCT is hepatic veno-occlusive disease (VOD) which is also known as hepatic sinusoidal obstruction syndrome.[1] Hepatic VOD can result after autologous or allogeneic HSCT, usually before day +30 after transplantation. Less than 2 percent of patients suffer from severe hepatic VOD after HSCT but almost 80 percent of patients who develop severe hepatic VOD do not survive. The complication can occur regardless of the underlying disease, stem cell source, or type of pre-transplant conditioning.[2] Hepatic VOD is characterized by increased serum bilirubin concentration, tender hepatomegaly, fluid retention and weight gain. Most commonly used diagnostic criteria for VOD are Baltimore criteria (Jones' criteria) and modified Seattle criteria.[3] The diagnosis by Baltimore criteria requires hyperbilirubinaemia (total bilirubin ≥ 34.2µmol/L) and the presence of at least 2 of the symptoms before day +21: hepatomegaly, ascites and weight gain >5% over baseline.[4] Diagnosis by the modified Seattle criteria require the presence of at least 2 criteria before day +20: hyperbilirubinaemia (total bilirubin ≥ 34.2µmol/L), hepatomegaly with right upper quadrant pain, ascites and unexplained weight gain >2% over baseline.[5] Complicated by VOD after HSCT, patients can suffer complications ranging from mild, reversible disease to a severe syndrome associated with multiorgan failure (pulmonary and renal dysfunction and encephalopathy) and death.[6] The standard treatment for hepatic VOD is mostly supportive like diuresis, fluid restriction and avoidance of hepatotoxic medications, transfusion and renal replacement therapy. Intensity conditioned regimens and individualization of chemotherapy dose are approached for prevention of VOD but found unsuitable for chemoresistant hematologic malignancies.[7] Prophylactic medication with low molecular weight heparin, danaparoid, ursodeoxycholic acid, prostaglandin E1, glutamine and fresh frozen plasma has been associated with decreased incidence of VOD. Another medication like prostaglandin E1, tissue plasminogen activator (t-PA), heparin and antithrombin III has been used to treat severe VOD.[8] But these prophylactic and standard treatments failed to show high evidence of significant effectiveness and safety for VOD.[9]

Now the first FDA-approved therapy for treatment of this severe, rare and life-threatening hepatic VOD has come out. On March 30, 2016, Defibrotide was approved for the treatment of adult and pediatric patients suffering from hepatic veno-occlusive disease (VOD) with renal or pulmonary dysfunction following hematopoietic stem-

cell transplantation (HSCT).[10] This drug Defibrotide is a major breakthrough in transplantation community to treat this frequently fatal VOD in patient receiving chemotherapy and HSCT.

MECHANISM OF ACTION

In vitro studies show that Defibrotide binds to multiple sites on vascular endothelium which are involved in cell regulation and increases protection of activated endothelial cells from being damaged by chemotherapy, tumor necrosis factor-α (TNF-α), serum starvation and perfusion.[11] It increases tissue plasminogen activator (t-PA) and thrombomodulin expression and decreases von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1) expression. Therefore it reduces endothelial cell activation and increases endothelial cell-mediated fibrinolysis[12]. Defibrotide also enhances the enzymatic activity of plasmin to hydrolyze fibrin clots. Though the mechanism of action of Defibrotide has not been fully elucidated, these *in vitro* studies support the role of Defibrotide in endothelial cell protection and restoration of thrombosis and fibrinolysis balancing.[13]

PHARMACOKINETICS

At the end of intravenous infusion, maximum plasma concentration peaked and then declined with rapid clearance. Plasma concentration does not accumulate with multiple dose infusion up to 4-fold of therapeutic dose.[14] Defibrotide is highly bound to plasma proteins (average 93%) and volume of distribution is around 10 L. An average of 9.48% of total dose administered is excreted unchanged in urine within 24 hours. The estimated total clearance of Defibrotide is 3.4 to 6.1 L/hr. Elimination half-life is less than 2 hours.[15] *In vitro* studies showed that Defibrotide is not markedly metabolized by human hepatocyte cells. Defibrotide has no CYP450s enzyme inhibition or induction.[14]

DRUG INTERACTION

Defibrotide has profibrinolytic activity and may enhance the activity of antithrombotic/fibrinolytic drugs like alteplase and heparin.[15] Therefore, concomitant use of Defibrotide with antithrombotic or fibrinolytic drugs is contraindicated as it can increase the risk of hemorrhage. Recombinant t-PA enhances the antithrombotic activity of Defibrotide and increases the risk of hemorrhage when co-administered and so it also is contraindicated.[16]

CLINICAL TRIALS

Approval of Defibrotide was based on the results of three main studies: two prospective clinical trials and one expanded access study. The efficacy of Defibrotide was assessed in treatment of 528 patients in three studies. All these patients had been diagnosed of hepatic VOD with liver or kidney abnormalities after HSCT. Efficacy of Defibrotide was based on Day+ 100 survivals after HSCT.[17]

CLINICAL TRIAL 1

The 102 adult and pediatric patients were administered Defibrotide at a dose of 6.25 mg/Kg infusion every 6 hours for at least 21 days and continued till patient was discharged from hospital. Patients in this study group were not permitted to receive concomitant treatment like heparin, warfarin or alteplase as they could increase the risk of bleeding. The survival rate was 38% (95% Confidence Interval: 29%, 48%) at 100 days after transplantation.[18]

CLINICAL TRIAL 2

The 75 adult and pediatric patients were treated with Defibrotide at a dose of 6.25 mg/Kg infused every 6 hours for at least 14 days. The treatment could be given until the signs of hepatic VOD disappeared. The survival rate was 44% (95% Confidence Interval: 33%, 55%) at100 days after transplantation.[18]

EXPANDED ACCESS STUDY

The 352 adult and pediatric patients were treated with Defibrotide at a dose of 6.25 mg/Kg infused every 6 hours. The Day+ 100 survival was 45% (95% Confidence Interval: 40%, 51%).[19]

Other studies showed that in patients with hepatic VOD with renal or pulmonary dysfunction who were treated with supportive care or medications other than Defibrotide, the Day+ 100 survival rates are 21% to 31%.[20]

ADVERSE EFFECTS AND CONTRAINDICATIONS

The most common adverse effects are hypotension, diarrhea, vomiting, nausea and epistaxis. The most common adverse reactions that can lead to permanent discontinuation are pulmonary alveolar hemorrhage, gastrointestinal hemorrhage, sepsis, graft versus host disease and lung infiltration. The use of Defibrotide is contraindicated in concomitant use with systematic anticoagulant or fibrinolytic therapy and in patients with known hypersensitivity to Defibrotide or its excipients.[21]

SPECIAL POPULATIONS

Pregnant women should be warned of potential risk of miscarriage and lactating mother should be advised to stop breastfeeding during treatment with Defibrotide. There are no identified differences in responses between elderly and younger patients. Efficacy and safety outcomes are almost the same for pediatric and adult patients. Dose adjustment is not recommended for patients with renal and hepatic impairment.[20]

PRESENT STATUS

Defibrotide is available in a quantity of 200mg in 2.5 mL vial (80 mg/mL). It is given by infusion by diluting in 5% Dextrose Injection or 0.9% Sodium Chloride Injection to a concentration of 4 mg/mL to 20 mg/mL and administered over 2 hours. The diluted solution

should be used within 4 hours if it is stored at room temperature and within 24 hours if stored in refrigerator. The recommended dose is 6.25 mg/Kg body weight every 6 hours for at least 21 days and continued until the signs and symptoms of VOD disappear.[21]

CONCLUSION

Hepatic veno-occlusive disease (VOD) is a life-threatening complication of hematopoietic stem cell transplantation (HSCT). Therapeutic modalities for severe VOD have limitations and dismal outcomes.[21] Defibrotide is the first drug approved by FDA for treatment of severe VOD. Defibrotide increases the expected survival rates of patients with severe hepatic VOD and it can significantly fill the gap needed for transplantation community.

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