NEW DRUGS

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Defibrotide

Approved indication: hepatic veno-occlusive disease

Defitelio (Link Medical)
vials containing 200 mg/2.5 mL concentrate for dilution

Haematopoietic stem cell transplants can improve survival in patients with certain cancers, such as acute leukaemia. However, the procedure has many risks. One of the complications of haematopoietic stem cell transplantation is hepatic veno-occlusive disease, also known as sinusoidal obstruction syndrome. This results from damage to the endothelial cells in the liver. In addition to liver dysfunction, there may be failure of other organs. If untreated, the mortality rate in severe cases exceeds 80%.

Although the mechanism of action is uncertain, defibrotide has antithrombotic and anti-inflammatory effects. It may protect endothelial cells from damage.

Defibrotide is a mixture of oligonucleotides derived from the intestinal mucosa of pigs. It is supplied as a concentrate which has to be diluted before being given as an intravenous infusion over two hours. The dose is determined by the patient's weight.

After the infusion, defibrotide is rapidly cleared and will no longer be detectable within 3.5 hours. The infusion has to be repeated every six hours for a minimum of 21 days. Most of the dose is metabolised then excreted in the urine. Although plasma concentrations will be increased in patients with renal impairment, no dose adjustment is recommended.

A phase II trial studied two dosing regimens in 151 patients with severe hepatic veno-occlusive disease. They were given infusions every six hours for a median duration of approximately 20 days. Among the 72 patients who received 25 mg/kg/day there was a decrease in bilirubin and resolution of organ dysfunction in 49%. There were 44% who survived for at least 100 days after their stem cell transplant.[1]

The 25 mg/kg/day regimen was used in a phase III trial of severe veno-occlusive disease and multiorgan failure in 102 adults and children. Defibrotide was infused for a median of 21.5 days. There was a complete response in 25.5% of the patients, which was greater than the 12.5% response rate in a group of historical controls. The median time to a complete response to defibrotide was 34.5 days. At 100 plus days after their stem cell transplant 38.2% of this group was alive compared with 25% of the historical controls.[2]

An analysis of 573 patients treated in an expanded access program supported the clinical trial results. In the 387 patients with veno-occlusive disease and multiorgan dysfunction the survival rate was 45% at 100 plus days after transplant. This post hoc analysis suggested earlier treatment increased the chance of survival.[3]

In patients with severe veno-occlusive disease following stem cell transplantation, adverse events are common and so it can be difficult to be certain which are caused by treatment. During the phase III trial approximately 11% of the patients stopped defibrotide because of possible toxicity. Common adverse events include hypotension, vomiting, diarrhoea, fever, peripheral oedema and respiratory failure. The antithrombotic and fibrinolytic effects of defibrotide may contribute to cases of bleeding including epistaxis, haematuria and pulmonary alveolar haemorrhage. There is likely to be an interaction with other drugs that affect clotting.

There are difficulties in conducting clinical trials in seriously ill patients with veno-occlusive disease. The phase III trial was open label and not randomised. There were only 32 patients in the historical control group. While more patients given defibrotide survived for 100 plus days, there was little difference from the historical controls at 180 plus days (32.4% vs 25%).[2] Despite these methodological limitations, it does appear that defibrotide can improve short-term survival in patients with severe hepatic veno-occlusive disease after haematopoietic stem cell transplant.

[X] manufacturer did not respond to request for data

REFERENCES

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

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