AML17 Advice on Gemtuzumab Ozogamicin (Mylotarg)

Introduction

Various groups have reported an increased incidence of veno-occlusive disease (VOD) with Mylotarg, particularly in combination with other chemotherapy. This advice is for Investigators in the NCRI AML17 trial and is intended to aid recognition, diagnosis and treatment of VOD in the context of the trial.

Veno-occlusive disease

VOD, also known as sinusoidal obstruction syndrome (SOS), is a serious hepatic disorder characterised by jaundice, tender hepatomegaly, ascites and ascites. Historically occurring mainly in the transplant setting, it is increasingly recognised as a side effect of Mylotarg. The primary event is thought to be hepatocellular damage resulting in sloughing, obstruction of hepatic sinusoids and venules and portal hypertension.

Diagnosis

VOD is largely a clinical disease requiring a high index of suspicion. The cardinal features are:

- Hyperbilirubinaemia
- Ascites
- Weight gain (fluid retention)
- Hepatomegaly

Patients presenting with 3 or 4 of these features after receiving Mylotarg should be referred for an urgent Doppler ultrasound of the liver to assess hepatic blood flow. The diagnosis is confirmed in patients with sluggish or reversed hepatic blood flow.

Treatment

Defibrotide is a single-stranded polyribonucleotide with fibrinolytic, antithrombotic and anti-ischaemic properties. Between 30-40% of patients with VOD will achieve complete remission in the transplant setting (refs 170-173) and improved survival. The illness associated with Mylotarg appears to be a milder illness, but the AML Working Group recommends the use of Defibrotide for patients with proven or strongly suspected cases of VOD in the AML17 trial.[1-3]

The recommended dose for VOD is 10mg/kg in 4 divided doses[2;3] in a solution of 4g/L in 100ml saline given intravenously. It remains unclear as to the necessary duration of treatment in VOD. The Trial Co-ordinators recommend 7 days defibrotide, but to continue until the liver function is clearly improving.

Supply of Defibrotide

Defibrotide is available from IDIS; the price is £1273 for 10 x 200mg vials, but the Trial Co-ordinators are looking to supply this centrally from St. Mary's as with Mylotarg. Currently, the company says it will be on site on the next working day if in stock. Contact details: telephone 01932824100, e-mail: Jacqueline Teale, jteale@idispharma.com.

Prevention

The concomitant use of hepatic toxic drugs should be discouraged. Paracetamol is unnecessary prophylaxis against the infusional syndrome seen with Mylotarg; antihistamines may be used. Azole fungal prophylaxis should also be avoided in patients entering the trial until 5 days after Mylotarg.

Investigators should also be aware that Mylotarg frequently causes a transient elevation of liver function around 8-10 days following infusion. This usually settles within 2-3 days and is not indicative of VOD.

Reference List

1. Richardson PG, Murakami C, Jin Z 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;100:4337-4343.

2. Richardson PG, Elias AD, Krishnan A 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;92:737-744.

3. Chopra R, Eaton JD, Grassi A et al. Defibrotide for the treatment of hepatic veno-occlusive disease: results of the European compassionate-use study. British Journal of Haematology 2000;111:1122-1129.