Executive Summary

Background
Veno-occlusive disease severity ranges from mild to severe, with severe defined by the presence of multi-organ failure which is associated with more than 85% mortality by 100 days. VOD can occur in approximately 20% of patients undergoing stem cell transplant.

Defibrotide has recently been granted a marketing authorisation via the centralised procedure of the EMA for the treatment of severe hepatic veno-occlusive disease in adults and children. It is anticipated that defibrotide will be launched in the UK during quarter 1 of 2014.

A joint BCSH and BSBMT guideline recommends defibrotide 6.25mg/kg QDS for the prevention of VOD in children undergoing allogeneic stem cell transplantation. The guideline suggests defibrotide at the same dose for prevention of VOD in adults and recommends defibrotide for the treatment of VOD in adults and children.

Epidemiology
The total number of stem cell transplantations in the U.K (allogeneic and autologous) in 2010 was 3191. This gives an approximate transplantation rate of 5 per 100,000 population.

Published data

Prophylaxis
Children
An open label, phase 3, randomised control trial for prophylaxis of hepatic VOD (n=356) has been fully published. The authors reported that 22 (12%) of 180 patients in the defibrotide group had veno-occlusive disease by 30 days after HSCT compared with 35 (20%) of 176 controls (risk difference -7.7%, 95% CI -15.3 – -0.1%) (P= 0.0488).

Adults
Two articles were found reviewing the use of prophylactic defibrotide in adult patients undergoing HSCT; a retrospective review of 58 patients where no patients met the Baltimore criteria for VOD and no patients died of suspected VOD within 100 days of transplantation; and a prospective study of 52 patients in a single centre compared with 52 historical controls which reported that none of the defibrotide patients and 10 of the control patients developed VOD.

Treatment
Children
A prospective cohort study reviewed the use of high dose defibrotide (60mg/kg/day) in combination with antithrombin III (ATIII) replacement in 91 patients with VOD. These patients were compared with 71 historical controls who did not receive any specific anti-VOD therapy. Complete remission occurred in 46% of patients in the control group and 100% of patients in the treatment group. Survival at day +100 was 46% of patients in the control group and 93% of patients in the treatment group.
Defibrotide for the prophylaxis or treatment of hepatic veno-occlusive disease in adults or children undergoing haematopoietic stem-cell transplantation

Background

Hepatic veno-occlusive disease is a potentially life-threatening complication that mainly occurs after myelo-ablative conditioning therapy and haematopoietic stem-cell transplantation (HSCT), usually occurring before day +30 after transplantation. Hepatic veno-occlusive disease (VOD) is more common after allogeneic stem cell transplantation (SCT) than after autologous SCT. The disease can affect about 20% of such patients and is characterised clinically by increased serum bilirubin concentrations, tender hepatomegaly, fluid retention, and weight gain. The diagnostic criteria for hepatic VOD have been standardised by two groups of investigators. The Baltimore criteria require hyperbilirubinaemia (total bilirubin of 34.2µmol/L or more) and the presence of at least 2 of the following symptoms before day +21: hepatomegaly, ascites, and weight gain >5% over baseline. The modified Seattle criteria require the presence of at least two of the following before day +20: hyperbilirubinaemia (total bilirubin of 34.2µmol/L or more), hepatomegaly with right upper quadrant pain, ascites or unexplained weight gain >2% over baseline (1). VOD is thought to be caused by damage to sinusoidal endothelial cells and hepatocytes in zone 3 of the liver acinus, the area surrounding the central veins (15). About half of the patients with VOD develop multiple organ dysfunction. Veno-occlusive disease severity ranges from mild to severe, with severe defined by the presence of multi-organ failure which is associated with more than 85% mortality by 100 days (4).

Defibrotide is a single-stranded polydeoxyribonucleotide derived from porcine tissue, which has anti-thrombotic, thrombolytic, anti-inflammatory, and anti-ischaemic properties (7). It has recently been granted a marketing authorisation via the centralised procedure of the EMA for the treatment of severe hepatic veno-occlusive disease in adults and children (17). It is anticipated that defibrotide will be launched in the UK during quarter 1 of 2014.

Two retrospective studies have also been published which reported similar results in favour of defibrotide.

Adults

One retrospective analysis was found which looked at data from 14 patients diagnosed with VOD treated with defibrotide in a single centre. A CR was obtained in 78.57% of patients. All complete responders were alive at 100 days after transplantation.

The results of an expanded access programme have been reported in abstract form. The latest interim analysis reported on 333 patients. The overall complete response rate was 30% with a 50% survival rate at day +100 in HSCT patients.

Safety

There is limited published information on the safety profile of defibrotide. The studies included in this review state that toxicity appears to be low and most adverse event rates were similar to the control group.

Cost

If we assume that patients require 100 vials whether used for treatment or prophylaxis and each vial costs £396 (including VAT) then the average cost per patient treated will be £39,600. Assuming 20% of stem cell transplant patients receive defibrotide, the cost per 100,000 population would be expected to be approximately £39,600.
The European Society for Blood & Marrow Transplantation also recommend defibrotide as the only specific treatment for VOD and for use in the prophylaxis of patients at risk of developing this complication. (EBMT Handbook 6th edition 2012) (21).

This review is looking at evidence for using defibrotide for both prophylaxis and treatment of hepatic VOD in adults and children.

**Epidemiology**

The total number of stem cell transplantations in the U.K (allogeneic and autologous) in 2010 was 3191 (15). The U.K population in 2010 was 62.3 million (16). This gives a 2010 epidemiology figure for allogeneic and autologous stem cell transplantations of 5 per 100,000 population.

**Published data**

**Prophylaxis**

Children

Four papers were identified reviewing the use of defibrotide for prophylaxis of hepatic VOD in children, one of which was an open label, phase 3, randomised control trial (4).

Children under 18 years old were enrolled at 28 university hospitals or academic medical centres in Europe. Eligibility criteria included patients who had undergone myeloablative conditioning before allogeneic or autologous HSCT, and had one or more risk factors for veno-occlusive disease. These risk factors were pre-existing liver disease (including any hepatic complications before transplantation, doubling of transaminase concentrations, and previous abdominal irradiation), second myeloablative HSCT, allogeneic HSCT for leukaemia beyond the second relapse, conditioning with busulfan and melphalan, previous treatment with gemtuzumab ozogamicin, and diagnoses of inherited haemophagocytic lymphohistiocytosis, adrenoleukodystrophy, or osteopetrosis.

Randomisation was computer-generated and was stratified by centre and diagnosis of osteopetrosis. Patients were randomised to receive either intravenous defibrotide 6.25mg/kg four times daily given over 2 hours starting the day of transplantation and continuing for 30 days after transplantation (or at least 14 days if patients were discharged from hospital before 30 days after HSCT), or no prophylaxis for veno-occlusive disease (control group). Patients in either group who developed veno-occlusive disease received treatment with defibrotide at 25mg/kg per day until complete recovery or death.

Treatment with systemic tissue-plasminogen activator, therapeutic-dose heparin (apart from central venous catheters), or other antithrombotics was not permitted. Use of ursodeoxycholic acid was permitted.

The primary endpoint was incidence of veno-occlusive disease by 30 days after HSCT by modified Seattle criteria; veno-occlusive disease was defined as the presence of two or more of increased bilirubin concentration (>34µmol/L), hepatomegaly, ascites, and unexplained weight gain of more than 5% from baseline (modified from >2% weight gain in original Seattle criteria). Secondary endpoints were incidence and severity of graft-versus-host disease by 100 days and 180 days after HSCT, and multi-organ failure and mortality by 100 days after HSCT. Adverse events were recorded until 180 days after HSCT.

The intention to treat population consisted of 180 patients who were randomly assigned to receive defibrotide prophylaxis (treatment group) and 176 patients assigned to the control group. Patients were followed for a median of 180 days after transplantation (range 28–1108). Baseline characteristics were evenly distributed between the two arms. The median age was 5.1 years in the defibrotide group and 4.6 years in the control group.

The main results were as follows:

- 22 (12%) of 180 patients in the defibrotide group had veno-occlusive disease by 30 days after HSCT compared with 35 (20%) of 176 controls (risk difference -7.7%, 95% CI -15.3 – -0.1%) (the P value from competing risk analysis was 0.0488).
- Patients who received defibrotide prophylaxis had a lower incidence and severity of acute graft-versus-host disease by 30 days and 100 days than did those in the control group.
- Incidence of chronic graft-versus-host disease did not differ between groups by 180 days (16 [9%] of 180 patients in the defibrotide group compared to 17 [10%] of 176 patients in the control group (p=0.8022)).
- Rates of veno-occlusive disease-associated mortality at 100 days after HSCT did not differ between the defibrotide group (four [2%] of 180 patients) and the control group (ten [6%] of 176 controls); p=0.10. This may have been influenced by the fact that the protocol permitted all patients irrespective of the initial treatment arm to receive defibrotide treatment after the onset of VOD.
Defibrotide for the prophylaxis or treatment of hepatic veno-occlusive disease in adults or children undergoing haematopoietic stem-cell transplantation

- The incidence of veno-occlusive disease-associated organ failures were reduced in the defibrotide arm compared with the control arm. The incidence of renal failure was 1% in the defibrotide arm and 6% in the control arm; p=0.0169. Incidences of adverse events, serious adverse events, and events leading to study discontinuation were similar between groups. 207 serious adverse events were reported in 108 patients in the defibrotide group and 231 adverse events were reported in 103 control patients. The cumulative incidence of haemorrhage was similar between the groups (39 [22%] of 177 in defibrotide group versus 37 [21%] of 176 control patients; p=0.8176).

A second retrospective analysis reviewed 9 children with malignant infantile osteopetrosis who received defibrotide prophylaxis for veno-occlusive disease (7). These 9 children were compared with 11 historic controls who did not receive defibrotide. Routine low dose heparin (100IU/kg/day) was used for all patients. If VOD was not diagnosed, defibrotide was discontinued on day +30 post SCT. The median age was 5 months (range 1–21 months).

 Conditioning before HSCT was variable. Busulfan (either oral or IV) was used in all patients, but cyclophosphamide, fludarabine, and thiotepa were given in different combinations. Thiotepa was omitted in patients transplanted after March 2001 (which included all patients in the defibrotide group). Patients with and without defibrotide prophylaxis were not significantly different concerning age at diagnosis, time to transplant, weight, sex, type of graft and donor, and the disease status reflected in the haematopoietic status at SCT.

 Defibrotide was administered for a median of 42 days (range 31–74 days), including one patient with therapeutic defibrotide. The median dose of defibrotide was 40mg/kg/day.

 The incidence of VOD was 63.6% (7/11) in the historical control group and 11.1% (1/9) in the defibrotide prophylaxis group. The overall mortality was 18.2% (2/11) in the historical control group and 11% (1/9) in the defibrotide prophylaxis group. No adverse events were observed for defibrotide.

 Another retrospective analysis reviewed 47 children in a single unit who received prophylactic defibrotide 20mg/kg/day from the start of conditioning until day 28 post stem cell transplantation (8). This group was compared retrospectively to a historical control group of 56 children transplanted in the same centre. High risk patients in the control group (those receiving busulfan conditioning regimens and children with deranged baseline transaminase levels) received ursodeoxycholic acid (15mg/kg once daily and tinzaparin 50 units/kg once daily). VOD was diagnosed according to modified Seattle criteria.

 In the defibrotide group 4/47 patients developed clinical VOD (although subsequent liver biopsy did not confirm VOD in 2 of these patients). The defibrotide dose was increased in these 4 patients to a treatment dose of 40–60mg/kg/day. All symptoms resolved fully within 14 days in the 4 patients.

 In the historical control group, 4/56 patients (7%) developed VOD. One of these patients received defibrotide once VOD was confirmed. Two of the four patients died in intensive care 30 days post-transplant, with VOD a major contributory factor to their deaths.

 The final article found which reviewed the use of prophylactic defibrotide in children undergoing HSCT was a retrospective analysis of 57 children at a single centre (6). The children were affected by beta thalassemia and were considered at very high risk for developing VOD (liver fibrosis, iron overload, hepatitis C virus infections, busulfan-based conditioning, methotrexate and ciclosporin). All patients received a busulfan-based conditioning regimen, either orally (four HSCT) or intravenously (59 HSCT). All patients received oral defibrotide (10mg/kg daily increased to 40mg/kg daily) as VOD prophylaxis from median day -9 to median day +29. Veno-occlusive disease was diagnosed according to the Seattle criteria. The median age at HSCT was 8 years.

 Five patients discontinued defibrotide early due to platelet refractoriness not responsive to dedicated platelet transfusions and the consequent high risk of haemorrhage. One of these five patients (who discontinued defibrotide on day 5 post HSCT) developed VOD. No other cases of VOD were noted. The authors reported that none of the patients treated with oral defibrotide experienced haemorrhagic complications or other side effects that could probably be related to defibrotide.

**Adults**

Two articles were found reviewing the use of prophylactic defibrotide in adult patients undergoing HSCT.

One of the articles was a retrospective review of defibrotide prophylaxis in 58 patients during allogeneic SCT at a single centre (10). The majority of the patients received alemtuzumab as part of the conditioning regimen. The median age was 45 years (range 16–62 years). 37 out of 58 patients received a reduced intensity conditioning regimen.
Patients received 5mg/kg defibrotide twice daily intravenously from day +1 to +21. No patient received heparin or ursodeoxycholic acid as VOD prophylaxis. Patients were followed up for 100 days post transplant and the Baltimore criteria were used to diagnose VOD.

No patients met the Baltimore criteria for VOD and no patients died of suspected VOD within 100 days of transplantation. The dose of defibrotide was increased to 10mg/kg four times daily in three patients in whom VOD formed part of differential diagnosis for deranged liver function tests, but who did not meet the Baltimore criteria for VOD.

Patients tolerated defibrotide well and there were no drug discontinuations or cases of haemorrhagic complications attributable to defibrotide.

The second study was a prospective study looking at the use of defibrotide prophylactically in allogeneic stem cell transplant in 52 patients in a single centre setting (11). These patients were compared with 52 historical controls who received heparin alone as prophylaxis. VOD prophylaxis with defibrotide 200–400mg intravenously four times daily was initiated the day before the conditioning regimen was started and continued until day +20 post transplantation. Low dose heparin was given to all patients (5000 IU IV continuously for 24 hours if weight <70kg or 10000 IU if weight > 70kg).

The Baltimore criterion was used to diagnose VOD. The median age of patients in the defibrotide group was 36.5 years (range 5–60) and the median age in the control group was 37 years (range 4–60). The two groups were similar with respect to primary disease, conditioning regimen, risk factors for VOD, and haemoglobin level. There were some differences which included type of transplant (more unrelated donors in the defibrotide group).

There was no grade 3 or 4 toxicity related to defibrotide or any worsening of clinical bleeding.

None of the patients in the defibrotide group developed VOD. 10 out of 52 patients in the control group developed VOD (3 patients died as a result of VOD).

**Treatment**

**Children**

Following the literature search, 3 articles were found assessing the use of defibrotide as treatment of children with VOD following HSCT.

Corbacioglu S. et al report on a retrospective analysis of 45 children between 0.2 and 20 years (median age 8.2 years) who were treated with defibrotide for hepatic VOD after HSCT (3). The data were collected from 12 unselected European centres on patients diagnosed with VOD (based on the Baltimore criteria) treated with defibrotide without forehand knowledge of their clinical outcomes. A standardised questionnaire was used to collect the data.

The severity of VOD was defined as follows:

- Mild disease is clinically obvious VOD without intervention.
- Moderate disease is VOD that requires treatment but resolves completely.
- Severe VOD was defined on the presence of multi-organ failure (MOF) in addition to VOD. Multi-organ failure (MOF) was defined as either an oxygen requirement with an oxygen saturation of <90% on room air and/or ventilator dependent, and/or renal dysfunction (doubling of baseline creatinine and/or dialysis dependent) and/or encephalopathy. In order for multi-organ failure to be VOD related, it had to be present within 28 days after the diagnosis of VOD.

Complete response (CR) was defined as resolution of VOD- and MOF-related symptoms together with a bilirubin decrease to less than 34.2µmol/L. Patients who did not achieve CR were defined as no responders (NR).

Defibrotide was administered i.v. as four divided doses per day over 2–4 hours. Doses were increased according to response and tolerability.

84% of patients received a busulfan-based chemotherapy conditioning regimen, 73% were treated with cyclophosphamide, 44% received melphalan, 9% of patients received fludarabine, and two were treated with total body irradiation. 13% of patients had a mismatched related and 9% a mismatched unrelated donor.

80% of patients received prophylaxis for VOD. 64% of patients received low dose heparin (100U/kg/day), 14% received heparin and ursodiol, 11% received heparin and ATIII, 5.5% received heparin and L-glutamine, and 5.5% received ursodiol mono-therapy.

The median day of VOD diagnosis was day +12 post transplant (range 0–58). In 22% of patients, VOD was mild. 29% of patients had moderate disease and 49% of patients had severe VOD with MOF.

The median duration of treatment with defibrotide was 17 days (range 1–83 days). The median dose of defibrotide was 40mg/kg/day (range 10–110mg/kg/day). Prophylactic drugs were not discontinued after defibrotide was initiated.
The main results were as follows:

- The overall CR rate was 76% with 64% of patients surviving beyond day +100.
- The CR rate in the group of patients with severe VOD was 50% with 36% of patients surviving beyond day +100.
- The CR rate of patients who were treated with defibrotide only was 75% and in patients receiving additional treatment it was 76%.
- The median age of patients with a CR was not different from patients with NR (9.6±2.4 vs 6.8±3.6 years).
- The average defibrotide dose in the CR group was 45±7mg/kg/day and in the NR group 27±10mg/kg/day (P<0.01).
- The average delay from diagnosis of VOD to start of defibrotide was 1±0.5 day in the CR group and 5.5±2 days in the NR group (P<0.01). This was also observed in the group of patients with severe disease (1.3 vs. 5.5 days; P<0.01).
- A maximum delay of 1 day to start of treatment vs. more than one day delay from the diagnosis of VOD remained the only significant predictor of CR.

The following adverse events were observed:

- 35% of patients suffered coagulation abnormalities. However, coagulopathy was present prior to the administration of defibrotide.
- In 7% (n=3) defibrotide was discontinued:
  1. One critically ill patient with severe VOD and an average defibrotide dose of 25mg/kg/day developed intracranial haemorrhage and suffered severe gastrointestinal bleeding. This patient suffered from consumptive coagulopathy needing replacement therapy prior to the onset of VOD.
  2. Another patient suffered convulsions on day +16 as a result of parenchymal and ventricular haemorrhage of the left parieto-temporal region. The patient received defibrotide for 6 days and the average dose was 40mg/kg/day.
  3. The third patient discontinued defibrotide due to diarrhoea.
- No other grade 3 or 4 toxicity attributable to the defibrotide was reported.

Another retrospective study reports the use of defibrotide treatment in paediatric patients with hepatic VOD following hematopoietic stem cell transplant (1). Analysis was performed in 14 patients with a median age of 10.2 years (0.4–18.1). The Baltimore and modified Seattle diagnostic criteria were applied retrospectively to each case; cases where a clinical diagnosis of hepatic VOD had been made though the diagnostic criteria were not met were noted.

All patients had received high dose antineoplastic therapy for conditioning prior to hematopoietic stem cell transplant and 13 of the 14 patients received a conditioning regimen that included cyclophosphamide. Eight of the patients (57%) received transplants from matched unrelated donors. No prophylaxis medication was given to any of the patients. 11 patients were diagnosed with hepatic VOD within 3 weeks of transplant and so the diagnostic criteria for VOD could be applied to these patients only.

The median delay between diagnosis of hepatic VOD and initiation of defibrotide was 1 day (range 0–33 days). The median duration of defibrotide treatment was 16 days (range 4–37 days). The median maximum defibrotide dose was 38.5mg/kg/day (range 11–81mg/kg/day).

Two patients developed a gastrointestinal bleed while receiving defibrotide. One patient developed an intracranial bleed on the 36th day of defibrotide therapy which was likely to be cause by a disseminated fungal infection that was discovered post mortem. This patient and two others died while receiving defibrotide. The primary cause of death in these three cases was: disseminated aspergillosis, pneumonitis due to cytomegalovirus, and multi-organ failure. All other patients survived to day +100 (79%).

There are no details in this study about response rates to the defibrotide treatment.

The third prospective cohort study reviewed the use of high dose defibrotide (60mg/kg/day) in combination with antithrombin III (ATIII) replacement (aimed at maintaining the ATIII activity at 100% or above) in 91 patients with VOD (2). These patients were compared with 71 historical controls who did not receive any specific anti-VOD therapy.

VOD was diagnosed according to the modified Seattle criteria (extended until day +30).

Complete remission of VOD was defined as resolution of VOD- and multiorgan dysfunction- related symptoms as well as a bilirubin decrease to less than 34µmol/L. Survival was defined as being alive without signs of VOD beyond day +100.

The onset of VOD occurred on a median of day +12 (4–29) after HSCT in the treatment group and day +12.5 (1–28) after HSCT in the control group. The median duration of combined therapy in the treatment group was 16 days (5–65 days).
The following results were obtained:

- The total VOD incidence was 18% in the control group and 15% in the treatment group.
- The median age at HSCT was 7.9 years in the control group and 8.2 years in the treatment group.
- Complete remission occurred in 46% of patients in the control group and 100% of patients in the treatment group.
- Survival at day +100 was 46% of patients in the control group and 93% of patients in the treatment group.
- The patient death in the treatment group was caused by idiopathic pneumonitis.
- Combined anti-VOD therapy with ATIII and defibrotide had a significant impact on complete remission and day +100 survival (OR 3.0 and 16.4; p=0.003 and 0.006). The lack of a group receiving defibrotide alone prevented analysis of the additional effect of ATIII beyond the effect of defibrotide.
- Three of the 14 VOD patients experienced non life-threatening bleeding complications: two had bladder haemorrhage and one had haemorrhage after drainage of a pleural effusion.

Adults

One retrospective analysis was found which looked at data from 14 patients diagnosed with VOD based on the Seattle criteria and treated with defibrotide in a single centre (9).

Evidence of multiorgan failure was recorded if there was documented dysfunction of 1 or more organs in addition to the liver. Renal dysfunction was defined as a doubling of the baseline serum creatinine level or dialysis dependence; pulmonary dysfunction was defined as the need for supplemental oxygen and/or documentation of hypoxemia by arterial blood gas determination or oxygen saturation by oximetry or the need for mechanical ventilation; central nervous system dysfunction was defined as documentation of confusion, lethargy, delirium, and/or coma. All patients received low-dose heparin (100 U/kg/day), ursodeoxycholic acid (750mg/day), and N-acetyl-L cysteine (600mg/day) as prophylaxis for VOD. Low dose heparin infusion was discontinued at least 6 hours before defibrotide was initiated.

The main results are as follows:

- The median age of patients was 40.5 years (range 16–46 years).
- The median duration of treatment with defibrotide was 21.5 days (range 4–39 years).
- 42.85% of patients had severe VOD.
- Defibrotide was initiated at a dose of 10mg/kg/day in all patients and increased to 25mg/kg/day in 4 patients. Two patients responded to dose escalation and 2 patients died of VOD despite the increased dose.
- A CR was obtained in 78.57% of patients. All complete responders were alive at 100 days after transplantation. With a median follow-up of 416.5 days (range 80–753 days), 7/11 defibrotide responder patients (63.63%) died of disease relapse among whom all were heavily pretreated, poor-risk patients.

Adults and children

Three studies were found reviewing the use of defibrotide as treatment of VOD which did not distinguish between adults and children (i.e. the studies contained patients from both age populations). One of the studies was a cohort study in 88 patients treated with defibrotide for VOD (13). The results of this study are comparable to other studies discussed in this review and so this cohort study is not discussed in more detail.

Richardson PG et al conducted a multi centre, phase II, randomised, dose-finding trial (14). Adult or paediatric patients with a clinical diagnosis of hepatic VOD, defined as per modified Baltimore criteria (addition of right upper quadrant pain as an additional symptom, and the time frame extended to +35 days post HSCT) were eligible. Abdominal Doppler ultrasound was performed at trial entry to identify the presence/absence of portal vein blood flow reversal and confirm diagnostic findings. Patients with jaundice and portal vein blood flow reversal on Doppler examination and only one other diagnostic criterion were eligible for the trial. For patients with pre-existing hepatomegaly, confirmation of liver size increase after admission by physical examination or imaging was required. Patients who did not meet all criteria but had biopsy-proven VOD were also eligible.

Patients had to have a predicted ≥30% risk of severe VOD according to the Bearman model. Patients not assessed by the Bearman model were eligible if they had concomitant multi-organ failure (presence of renal, pulmonary, and/or central nervous system dysfunction).

Exclusion criteria included significant uncontrolled acute bleeding; haemodynamic instability requiring multiple vasopressors; grade B-D graft-versus-host disease (excluding grade B skin-only GVHD); the treatments that the historical control patients received for the treatment of VOD.
Defibrotide for the prophylaxis or treatment of hepatic veno-occlusive disease in adults or children undergoing haematopoietic stem-cell transplantation

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Defibrotide was administered for documented intrinsic lung disease (excluding intubation secondary to a mechanical barrier to ventilation in the presence of adequate oxygenation parameters); grade 4 neurotoxicity (excluding confusion and/or delirium); previous or concomitant systemic t-PA therapy; concomitant use of heparin or other anticoagulants (excluding use for routine central venous line (CVL) management, fibrinolytic instillation for CVL occlusion, intermittent dialysis, or ultrafiltration); concomitant treatment with antithrombin III or other antithrombotics, nonsteroidal anti-inflammatory drugs, or ursodiol was not permitted (although ursodiol could be used in specific circumstances).

Randomisation was stratified by whether or not the conditioning regimen included cyclophosphamide and by age (adult ≤18 years vs paediatric <18 years). For both treatment arms, the defibrotide starting dose was 10mg/kg/day. This initial dose was then increased to 25mg/kg/day in arm A and 40mg/kg/day in arm B. Patients were treated for a minimum of 14 days or until achievement of CR, or until progression of VOD, unacceptable toxicity, or co morbidities precluded further treatment.

The primary endpoint was CR which was defined as resolution of hyperbilirubinaemia with resolution of VOD-related multiorgan failure. Secondary endpoints included safety and tolerability of defibrotide, effect of defibrotide on plasminogen activator inhibitor-1 (PAI-1), and relationship between defibrotide dose and response, day +100 mortality, and/or PAI-1 level.

All randomised patients who received one or more doses of defibrotide were included in baseline, survival, and safety analyses. All randomised patients who received 3 or more days of defibrotide therapy were included in response analyses.

151 patients were randomised, of whom 149 received one or more doses of defibrotide (arm A: n=75; arm B: n =74) and 141 were evaluable for response (arm A: n= 72; arm B: n=69). Patient demographic and baseline characteristics were well balanced between the 2 arms. The characteristics of VOD did not differ between the two arms.

The main results were as follows:

- The median duration of therapy was 19 days (range 2–82 days) in arm A and 20 days (range 2–65 days) in arm B.
- Reasons for ending treatment were resolution of VOD (33% in arm A and 30% in arm B), VOD progression (15% and 19%), death (13% and 16%), patient discharge (12% and 11%), withdrawal of care (13% and 9%), alternative diagnosis (5% and 3%), and adverse events (8% and 12%, of which 3% and 5%, respectively, were considered defibrotide-related toxicity).
- The overall CR rate in the evaluable population was 46%, with 49% (95% CI 37–69%) in arm A and 43% (95% CI 32–55.2%) in arm B. The difference between the arms was not statistically significant (p=0.613).
- Overall 42% of the patients in the treated population were alive at day +100 post HSCT.
- In the patients who died by day +100 post-HSCT, the most common cause of death was progressive VOD (29% in arm A and 28% in arm B).
- The most common grade 3–5 adverse events overall were renal failure, hypotension, hypoxia, and other pulmonary events. Defibrotide-related adverse events leading to discontinuation of treatment occurred in only 4% of patients.
- A daily dose of 25mg/kg/day can be used safely in adults and children after HSCT, and higher doses were probably not more effective.

Another study, which has been published in abstract form only, was a trial comparing defibrotide (25mg/kg/day) in the treatment of VOD/ multi-organ failure (MOF) post HSCT to a historical control (12). The historical control was created by reviewing medical charts starting 6 months prior to the use of defibrotide at each centre. There is no indication as to Eligibility criteria included meeting the Baltimore criteria for VOD by day +21 and either renal and/or pulmonary failure by day +28. Exclusion criteria included severe graft-versus-host disease (GvHD) involving the liver or gut, clinically significant bleeding, or the need for >1 vasopressors to control blood pressure.

The primary endpoint was CR (defined as bilirubin < 2mg/dL and resolution of MOF. The data was stratified according to the following variables: allogeneic/autologous HSCT, adult/paediatric, 1 or 2+ HSCTs, and ventilator/dialysis dependence. A secondary endpoint was mortality at day +100.
The study compared 102 defibrotide patients with 32 historical controls. Baseline characteristics were similar for both groups. The median age was 21 years in the defibrotide group and 18 years in the control group (43% and 44% respectively were paediatric in the two groups). 88% of patients in the defibrotide group received an allogeneic transplant compared with 84% in the control group. 13% of patients in the defibrotide group had received a prior stem cell transplant compared with 3% in the historical control group. The median time after transplant until VOD diagnosis was 13 days in the defibrotide group compared with 11 days in the historical control group. 
The median duration of defibrotide therapy was 22 days (range 1–60 days), with a median daily dose of 19mg/kg/day.

For the primary efficacy analysis, the day +100 CR rate was 24% for the defibrotide group and 9% for the historical control (95% CI difference in CR rate 3–30%; p=0.015).

The secondary endpoint (day +100 mortality rate) was 62% in the defibrotide group and 75% in the historical control group (95% CI difference in rate -32–3%; p=0.051). 
For patients receiving autologous HSCT (n=12 and 5 patients in defibrotide and historical control arms), the CR rate was 75% versus 0% respectively (p=0.005). 
Haemorrhagic adverse events (any grade) were similar between the two groups (65% in the defibrotide group versus 69% in the control group). 18% of patients in the defibrotide experienced a drug-related toxicity that led to treatment discontinuation.

The results of an expanded access programme have been reported in abstract form. Patients were included if they met the eligibility criteria for the trial described above (reference 12) or if they had non-severe VOD or developed VOD after chemotherapy rather than HSCT. The latest interim analysis reported on 333 patients (305 who had undergone HSCT with 274 undergoing an allogeneic transplant). Two hundred and twenty patients had severe disease at study entry. The overall complete response rate was 30% with a 50% survival rate at day + 100 in HSCT patients. In the patients with non-severe VOD the CR rate was 39% and the day + 100 survival rate was 65%. The 155 patients who met the original trial criteria had a CR rate of 29% compared to 9% in the historical control group (p=0.0019) and superior survival at day + 100 (49% versus 25%, p=0.0016). The main toxicities were haemorrhage in 18% and hypotension in 4% of patients with 2% of patients experiencing life-threatening haemorrhage. A low incidence (8%) of all grades of acute graft vs. host disease was also noted (18).

There is limited published information on the safety profile of defibrotide. The studies included in this review state that toxicity appears to be low and most adverse event rates were similar to the control group. The trials used a small number of patients and were not powered to detect all adverse events of defibrotide. Haemorrhage and coagulation abnormalities are potentially the most significant of the adverse events associated with defibrotide use. More evidence is required to properly assess the toxicity of defibrotide in the prophylaxis and treatment of HSCT.

Cost

If we assume that patients require 100 vials whether used for treatment or prophylaxis and each vial costs £396 (including VAT) then the average cost per patient treated will be £39,600.

Using the figure of 5/100,000 population who received an allogeneic or autologous stem cell transplant in 2010, and assuming 20% of stem cell transplant patients receive defibrotide, the cost per 100,000 population would be expected to be approximately £39,600.

Points for consideration

The trials reported here used different eligibility criteria for the trial and different risk factors for the development of VOD. Different criteria between studies were used to diagnose VOD (e.g. Baltimore criteria, Seattle criteria, or a modification of either of these criteria). Also, different medications were permitted during the trials and this also varied between studies (e.g. heparin, ursodeoxycholic acid). It is therefore not possible to directly compare results between the studies.

Prophylaxis

The best evidence available to support the use of defibrotide for VOD is for prophylaxis (where data from a phase III randomised control trial are published). The authors reported that 22 (12%) of 180 patients in the defibrotide group had veno-occlusive disease by 30 days after HSCT compared with 35 (20%) of 176 controls (risk difference -7.7%, 95% CI -15.3 – -0.1%) (the P value from competing risk analysis was 0.0488). Also, patients who received defibrotide prophylaxis had a lower incidence and severity of acute graft-versus-host disease by 30 days and 100 days than did those in the control group.
Defibrotide for the prophylaxis or treatment of hepatic veno-occlusive disease in adults or children undergoing haematopoietic stem-cell transplantation

A joint working group established by the Haematology subgroup of the British Committee for Standards in Haematology (BCSH) and the British Society for Bone Marrow Transplantation (BSBMT) has produced a guideline for the diagnosis and management of veno-occlusive disease of the liver following haematopoietic stem cell transplantation (HSCT). The guideline recommends defibrotide 6.25mg/kg QDS for the prevention of VOD in children undergoing allogeneic stem cell transplantation with the following risk factors: pre-existing hepatic disease, second myeloablative transplant, allogeneic transplant for leukaemia beyond second relapse, conditioning with busulfan containing regimens, prior treatment with gemtuzumab ozogamicin, diagnosis of primary haemophagocytic lymphohistiocytosis, adrenoleukodystrophy or osteopetrosis (19).

No standard dose of defibrotide was used for prophylaxis of VOD; although the phase III randomised control trial in children used intravenous 25mg/kg/day (4). The randomised dose finding trial for adults and children suggested that defibrotide 25mg/kg/day intravenously can be used safely in adults and children after HSCT and higher doses were probably not more effective (14).

Treatment
The evidence to support the use of defibrotide for the treatment of hepatic VOD in both children and adults is limited to cohort studies and retrospective analyses due to the fact that it has been impossible to conduct randomised studies since there are no other effective treatments. It is also important to note that a placebo-controlled trial of defibrotide in the treatment of VOD would not be ethical. It is therefore difficult to assess the benefit of defibrotide for the treatment of hepatic VOD. Defibrotide has been licensed for the treatment of severe VOD and is recommended in the BCSH/BSBMT VOD guidelines.

References
5. Supplementary webappendix accompanying reference 4
7. Corbacioglu S et al. Stem cell transplantation in children with infantile osteopetrosis is associated with a high incidence of VOD, which could be prevented with defibrotide. Bone Marrow Transplantation. 2006; 38:547–553
Defibrotide for the prophylaxis or treatment of hepatic veno-occlusive disease in adults or children undergoing haematopoietic stem-cell transplantation


Details of Search Strategy

1. EMBASE; DEFIBROTIDE/ [Limit to: Human]; 689 results.
2. EMBASE; LIVER VEIN OBSTRUCTION/; 1164 results.
3. EMBASE; 1 AND 2 [Limit to: Human]; 58 results.
4. MEDLINE; HEPATIC VENO-OCCCLUSIVE DISEASE/ [Limit to: Humans]; 910 results.
5. MEDLINE; defibrotide.ti,ab [Limit to: Humans]; 219 results.
6. MEDLINE; 4 AND 5 [Limit to: Humans]; 61 results.
7. EMBASE,MEDLINE; Duplicate filtered: [1 AND 2 [Limit to: Human]], [4 AND 5 [Limit to: Humans]]; 119 results.

Also, reference lists of articles obtained were searched to see if any further relevant articles could be found.

Please direct any comments to Angela Bell, London & South East Medicines Information Service, Guy’s Hospital, Great Maze Pond, London SE1 9RT
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