Clinical Commissioning Policy (Revised)
Use of defibrotide in severe veno-occlusive disease following stem cell transplant (all ages) [210401P]

Commissioning position

Summary

Defibrotide is recommended to be available as a treatment option through routine commissioning for severe veno-occlusive disease following stem cell transplant within the criteria set out in this document.

Executive summary

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain language summary

Severe veno-occlusive disease (VOD) of the liver is an uncommon complication of stem cell transplantation caused by the chemotherapy and / or radiotherapy that patients receive as part of preparation for transplant. It is most likely to affect patients with certain risk factors or underlying conditions. Severe VOD is associated with a high risk of death and can cause multi-organ failure requiring long stays in hospital, often in intensive care. A drug called defibrotide can be given to adults or children with severe VOD to treat the condition.

What we have decided

NHS England has carefully reviewed the evidence to treat severe VOD following stem cell transplant with defibrotide. We have concluded that there is enough evidence to make the treatment available at this time.

Links and updates to other policies

This document updates B04/P/c Clinical Commissioning Policy: Use of defibrotide in severe veno-occlusive disease following stem cell transplant published January 2015.

Committee discussion

See the committee papers (https://www.england.nhs.uk/publication/defibrotide-for-severe-veno-occlusive-disease-following-stem-cell-transplant/) for full details of the evidence.

The condition

Veno-occlusive disease of the liver (VOD) occurs as a result of the conditioning treatment administered prior to haemopoietic stem cell transplantation, otherwise known as BMT. The condition is also known as sinusoidal obstruction syndrome in view of the associated characteristic histopathological findings (De Leve et al, 1999). The terms veno-occlusive disease and sinusoidal obstruction syndrome are used interchangeably in this document.

The mean prevalence of VOD is in the range of 14% (range 0-60%) depending upon the risk factors present (Coppell et al, 2010). The condition causes considerable morbidity and mortality and severe VOD is associated with a mortality of over 80% by day + 100 following haematopoietic stem cell transplantation (HSCT) (McDonald et al, 1993; Carreras et al, 1998).

Defibrotide:

- Is indicated in severe VOD following HSCT in adults and in adolescents, children and infants over 1 month of age.
- Was granted Orphan Drug Status by the European Marketing Authority (EMA) in 2004 and has been supplied in the UK and in more than 40 countries on a named patient basis since 2009.
- Is a Hospital only product due to the specialised nature of this disease and mode of delivery of the prescription medicine.
- Does not change the pathway of care, therefore the only changes to the budget are drug acquisition costs and cost avoidance as a result of reduced ICU/HDU use.

Epidemiology and needs assessment

The mean prevalence of VOD is in the range of 14% (range 0-60%) depending upon the risk factors present (Coppell *et al*, 2010)In 2018, 1,679 allogeneic transplants were performed and reported to British Society for Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT), of which 1,648 were registered with BSBMTCT. There were some repeat transplants, therefore there were 1,511 unique patients who received allografts, of whom 318 were paediatric patients and 1,263 adults. Of these patients, 890 adult and 30 paediatric patients had reduced intensity conditioning and would be unlikely to develop VOD. The remaining are the risk group for VOD, 300 adults and 260 paediatric patients had full intensity conditioning, according to NHS England and Improvement prior approvals database in 2018, 66 patients received defibrotide after HSCT allografts (approx. 11%).

Alternative treatment strategies

There is no standard alternative treatment strategy for severe VOD. Agents such as N-acetylcysteine and tissue plasminogen activators have been investigated but have not been found to be beneficial. High dose methylprednisolone may be helpful in some patients. The mainstay of supportive care in patients with VOD is management of fluid balance. Renal replacement therapy may be required in severe cases. Patients with multi-organ failure will require management in a high-dependency or intensive care environment. Early discussion with a specialist hepatology unit is advised regarding further therapeutic options.

Prostaglandin E1, pentoxyfylline and heparin (unfractionated and low molecular weight) have been investigated for use in the prophylaxis of VOD and have not been found to be helpful.

Evidence summary

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of this treatment for the indication.

Defibrotide is a single-stranded polydeoxyribonucleotide which has anti-thrombotic, anti-inflammatory and anti-ischaemic properties. This agent appears to have a protective effect against endothelial cell injury by cytotoxic agents and down regulates protein concentrations, gene expression and the activity of endothelial cell triggers such as heparanase (Eissner *et al*, 2002). Defibrotide has not been associated with an increased bleeding risk despite reducing pro-coagulant activity and increasing fibrinolysis (Echart *et al*, 2009; Falanga *et al*, 2003). Following reports of the success of defibrotide in the treatment of VOD, several studies have focused on the role of this agent in prophylaxis.

Several studies in both adults and children have reported on the efficacy of defibrotide in the treatment of veno-occlusive disease. Richardson *et al* reported on 19 patients who had received defibrotide for the management of severe veno-occlusive disease in a compassionate use study (Richardson *et al*, 1998).

Intravenous defibrotide was administered in doses ranging from 5 mg/kg per day to 60 mg/kg per day. Patients were included if they had a clinical diagnosis of VOD (bilirubin > 34.2 µmol/L and two of the following: hepatomegaly and/or right upper quadrant pain, ascites or greater than 5% weight gain above admission weight) or a positive biopsy result. In addition, patients who presented within 16 days of transplant had a predicted risk score of 40% defined by the Bearman model or, if presenting after day + 16, VOD constituted their main clinical problem. Eight patients (42%) had resolution of VOD as defined by resolution of bilirubin to < 34.2 µmol/L and improvement of other symptoms and signs of VOD.

An additional 69 patients received defibrotide on an emergency use basis based on the emergent data. Patients were enrolled prospectively from 8 transplantation centres and received a dose ranging from 5 to 60 mg/kg/day. Patients were included based on a clinical diagnosis (bilirubin ≥ 34.2 µmol/L, hepatomegaly and/or right upper quadrant pain, and ≥ 5% weight gain from admission, with or without ascites) or two clinical criteria and positive hepatic biopsy. Patients had to have a predicted risk score of 30% as defined by the Bearman model or, if presenting after day +16, VOD was considered their main clinical problem and organ failure was present in at least one organ system. Complete response was defined as in the pilot

study. The complete response rate in 88 patients (including the 19 patients in the pilot study) was 36% and survival at day +100 was 35% (Richardson et al, 2002).

A randomised phase II dose-finding study was subsequently conducted by the same group. Adult or paediatric patients were included if they had a clinical diagnosis of VOD by day +35 post-HSCT or biopsy proven VOD. Patients were also included if they had portal vein flow reversal on ultrasound, jaundice and one other clinical criterion. Patient eligibility was also defined by the severity criteria from the previous study (Richardson et al, 2002). Patients were randomised to receive lower dose defibrotide (25 mg/kg/day, n = 75) or higher dose defibrotide (40 mg/kg/day, n = 74) administered intravenously every 6 hours for ≥ 14 days or until complete response, progression of VOD or unacceptable toxicity was observed (Richardson et al, 2010). Complete response was defined as total serum bilirubin < 34.2 µmol/L with resolution of VOD-related multi-organ failure. The overall complete response rate was 46% and there was no significant difference between the two arms. The day +100 post HSCT survival rates were 42% and again there was no significant difference between the two arms. There was a slightly higher rate of adverse events in the higher dose arm (10% v 7%) but this difference did not achieve statistical significance.

The lower dose of defibrotide was subsequently selected for phase III trials in VOD as there was no difference in efficacy or toxicity in the phase II randomised study. The results of a phase III study comparing the use of defibrotide in the treatment of severe VOD to an historical control group have been presented in abstract form (Richardson et al, 2009). Patients were included if they met the Baltimore criteria for VOD and complete response was assessed as bilirubin < 34.2 µmol/L and resolution of multi-organ failure. One hundred and two patients received defibrotide intravenously at a dose of 6.25 mg/kg four times daily and were compared to 32 historical control patients. The day + 100 complete response rate was 24% in the treatment arm compared to 9% in the historical control group (p=0.015). The day + 100 mortality rate was 62% in the treatment arm compared to 75% in the control group (p=0.051). Haemorrhagic adverse events were similar in the two groups.

Following completion of the above trial, the protocol was continued and patients were included if they met the eligibility for the trial or if they had non-severe VOD or had developed VOD after chemotherapy rather than after haematopoietic stem cell transplantation. The results of this expanded access programme have been reported in abstract form (Richardson et al, 2011, Richardson et al, 2012). 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 complete response 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. (Richardson et al, 2012).

The role of defibrotide in the treatment of VOD has also been investigated by other groups. Corbacioglu et al reported a retrospective analysis of 45 patients aged between 0.2 and 20 years who received defibrotide intravenously at an average dose of 40 mg/kg/day. VOD was diagnosed using the Baltimore criteria. Complete response was defined as resolution of VOD and multi-organ failure-related symptoms and a bilirubin of < 34.2 µmol/L. Twenty-two patients had severe disease and 23 had moderate or mild disease. The overall complete response (CR) rate was 76% with a survival rate of 64% at day + 100 (Corbacioglu et al, 2004). Bulley et al have also reported a retrospective series of the use of defibrotide in paediatric patients. In this series of 14 patients, 60% stopped defibrotide due to clinical improvement and the survival rate to day + 100 was 79% (Bulley et al, 2007). The European compassionate-use study included 40 patients who fulfilled either the Baltimore or Seattle criteria for VOD and received intravenous defibrotide (10 to 40 mg/kg daily). Twenty-two patients (55%) showed a complete response as defined by bilirubin < 34.2µmol/l and resolution of signs/symptoms of VOD and end-organ dysfunction. The survival rate at day + 100 was 43%. The complete response rate in the 10 poor-risk patients was 36% (Chopra et al, 2000).

In a post hoc analysis of 1000 patients (both adults and children) who had had defibrotide as part of an expanded access treatment programme, Kernan et al (2018) reported the outcomes of treatment in a subgroup of patients analysed by the timing of VOD/SOS onset (≤21 or >21 days). There was no difference in the day 100 post-transplant survival rates in these two groups with the survival in the 264 (26%) late-onset VOD/SOS patients assessed to be 52.8% and that in the overall HSCT population as 58.9%.

Use of defibrotide in preventing VOD

Whilst there is randomised control data supporting use of defibrotide in prevention of VOD in a small group of children undergoing allogeneic stem cell transplantation with high risk factors, this use is not licensed.

Treatment

VOD is a potentially life-threatening post-HSCT complication that is reported to be severe is approximately 33% of cases (Carreras et al, 2011). Severe VOD can be fatal in more than 80% of cases (Coppell et al, 2010). Severe VOD is frequently associated with multi-organ failure and the necessity for prolonged hospital admission including the need for intensive care support.

Post-HSCT complications are a significant contributor to the costs of HSCT. VOD has been shown to be one of the costliest complications (Svehen 2006) post-transplant. Five-year post-transplant, VOD patients cost 63% more compared with patients that didn’t develop VOD. After one-year post HSCT, the cost for patients with VOD is nearly double that of patients that don’t develop VOD. Most of this excess cost is incurred within the inpatient setting shortly after transplant.

Without treatment patients with severe VOD may die within days or weeks of an expensive transplant procedure, often in an intensive care setting. Defibrotide has been shown to be effective in the treatment of severe VOD in several studies, with

complete response rates of 24% to 49%, and with a significant improvement in survival of 52% at day 100.

There is no published QALY data for the UK but the consideration of cost utility for treatment of severe VOD are set out in the Scottish Medicines Consortium advice (May 2014). The factors affecting the cost of defibrotide are set out in Table 2. Paediatric patients will cost less than adult patients based on weight and dosing.

Table 2: Factors affecting average cost per course of treatment with defibrotide

Parameter
Average body weight at baseline (kg)
Average daily dose (mg/kg/day) of defibrotide
Length of defibrotide treatment (mean, in days)
Costs per 200mg vial (expected list price)
Mg per vial
Wastage (maximum number of vials wasted)

Source: Jazz Pharmaceuticals

Defibrotide treatment needs to be compared with costs of severe VOD not treated with defibrotide and are based on extended lengths of stay in these patients.

In summary, treatment with defibrotide reduces mortality compared with historical controls. Defibrotide can reduce the length of stay avoiding extended use of ICU or HDU beds.

Safety

Defibrotide is well tolerated with few adverse events. An increased risk of haemorrhage has not been associated with use of this agent.

Rationale behind the policy statement

Severe VOD is a condition with a high rate of morbidity and mortality. It is uncommon in the majority of patients undergoing allogeneic transplantation, but several high risk groups have been identified.

Defibrotide is well tolerated with minimal toxicity. This policy therefore recommends defibrotide for the treatment of severe VOD when it occurs following stem cell transplantation.

Implementation

Criteria

Patients eligible to receive treatment with defibrotide would include:

- Adults who have a diagnosis of severe veno-occlusive disease following BMT based on clinical criteria (modified Seattle or Baltimore i.e. classic criteria) or histopathological findings:
- Adults with late onset VOD who exhibit signs and symptoms consistent with veno-occlusive disease after 21 days based on the European BMT diagnostic criteria as described by Mohty *et al.* 2016.
- Children who have a diagnosis of severe veno-occlusive disease following European BMT (EBMT) paediatric criteria with no limitation (modified Seattle or Baltimore i.e. classic criteria) or histopathological findings as described by Corbacioglu *et al* 2018

Adults:

Classical SOS/VOD	Late onset SOS/VOD

• In the first 21 days after HSCT
• Bilirubin ≥2 mg/dL and two of the following criteria must be present:
  ○ Painful hepatomegaly
  ○ Weight gain >5%
OR
  ○ Ascites
	• ≥21 Days after HSCT
	• Classical VOD/SOS beyond day 21
	OR
	• Histologically proven SOS/VOD
	OR
	• Two or more of the following criteria must be present:
	  ○ Bilirubin ≥2 mg/dL (or 34 µmol/L)
	  ○ Painful hepatomegaly
	  ○ Weight gain >5%
	  ○ Ascites
	AND
	• haemodynamical or/and ultrasound evidence of SOS/VOD

Abbreviations: EBMT = European Society for Blood and Marrow Transplantation; SOS = sinusoidal obstruction syndrome; VOD = veno-occlusive disease. These symptoms/signs should not be attributable to other causes.	

Children (0-18 years)
EBMT paediatric criteria:

No limitation for time of onset.
Children who have 2 or more of the following:

- Bilirubin ≥34 µmol/L within 72 h, or rising bilirubin from a baseline value on 3 consecutive days
- A weight gain >5% above baseline value or otherwise unexplained weight gain on 3 consecutive days despite the use of diuretics
- Hepatomegaly (best if confirmed by imaging) above baseline value*
- Ascites (best if confirmed by imaging) above baseline value*
- Unexplained consumptive and transfusion-refractory thrombocytopenia (≥1 Weight-adjusted platelet substitution per day to maintain institutional transfusion guidelines).

*Suggested: imaging (ultrasonography, computed tomography or magnetic resonance imaging) immediately before HSCT to determine baseline value for both hepatomegaly and ascites.

Starting criteria

- Patients requiring **treatment** would receive 6.25 mg/kg of defibrotide intravenously four times daily from the onset of clinical signs of veno-occlusive disease.

Stopping criteria

- Defibrotide should be administered for a minimum of 21 days and continued until the symptoms and signs of severe VOD resolve.

Exclusions

Defibrotide will **not be routinely commissioned** in the following scenarios:

- In patients with active bleeding
- Prevention of VOD in either paediatric or adult patients
- For treatment of graft versus host disease.

Where clinicians consider prescribing defibrotide for patients not covered in the circumstances above, an Individual Funding Request may be considered where the patient's case is exceptional.

Patient pathway

Patients for HSCT will normally be referred to a transplant centre as per the local referral policy. The transplant team will be responsible for the authorisation and administration of defibrotide for patients requiring this intervention. In the event of a patient being admitted to a non-transplant centre then an appropriate pathway under the governance of the transplant centre would be needed for authorisation and administration including transfer back to the transplant centre or care under formal shared care transplant arrangements.

Governance arrangements

Consent, patient evaluation and investigations prior to the commencement of defibrotide must be carried out by the transplant centre in accordance with relevant transplant centre policy.

No additional investigations are required for the provision of defibrotide. All processes involved in HSCT must fulfil Human Tissue Authority (HTA) requirements and must meet JACIE standards in line with accreditation standards.

All centres should have a local standard operating procedure detailing the use of defibrotide.

Provider organisations must register all patients on defibrotide, using a prior approval process and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

NHS England is responsible for funding defibrotide in line with this policy as part of and consistent with existing, agreed local contract currencies.

Audit requirements

Regular audit should be carried out on the use of defibrotide. Audit criteria will encompass the following:

- The % of patients undergoing allogeneic transplantation who receive defibrotide treatment and outcomes.
- Patients receiving defibrotide to demonstrate compliance with commissioning criteria.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Documents which have informed this policy

BCSH/BSBMT Guideline: Diagnosis and Management of Veno-occlusive Disease (Sinusoidal Obstruction Syndrome) following Haematopoietic Stem Cell Transplantation 2013 (submitted to British Journal of Haematology).

BMT: Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in paediatric patients: a new classification from European society for blood and marrow transplantation (EBMT criteria for diagnosis and severity of SOS/VOD in children) 2018 (submitted to Nature.com/bmt)

Definitions

Conditioning	This is the term used to describe the preparative regimen of chemotherapy and / or radiotherapy that patients receive prior to stem cell transplant.
Autologous stem cell transplant	This is the process of high dose chemotherapy followed by infusion of the patient's own stem cells which will repopulate the bone marrow and allow the recovery of the patient's blood counts.
Allogeneic stem cell transplant	This is the process of high dose chemotherapy followed by infusion of donor stem cells.

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Change form for published Specifications and Products developed by Clinical Reference Group (CRGs)

Product name: Clinical commissioning policy: use of defibrotide in severe veno-occlusive disease following stem cell transplant

Publication number: Formerly B04-P-C and P200804P

Description of changes required

Describe what was stated in original document	Describe new text in the document	Section/Paragraph to which changes apply	Describe why document change required	Changes made by	Date change made
Stated adult or children.	Removed children.	Implementation Criteria (in first and second bullet point).	To bring policy into line with diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in paediatric patients classification from the European society for blood and marrow transplantation. This change will take into account the difference between paediatric and adult patients.	Pharmacy Lead	18/01/21

			This is a non-material change as paediatrics was included in the original review and we do not expect this to change the numbers.		
Adult and children's VOD criteria in same bullet points as same.	Add third bullet point including the children criteria (separated from adult criteria).	As above Added third bullet point.	As above.	Pharmacy Lead	18/01/21
Table for Criteria for early and late onset VOD.	Existing criteria headed as for adults.	Implementation table Added header of adults.	Children's VOD is described by a different set of criteria as set out by eBMT.	Pharmacy Lead	18/01/21
Missing paediatric VOD criteria which is different from adults as paediatric do not have early/late VOD.	Added new paragraph to include paediatric EBMT VOD criteria for paediatric patients (Age 0-18 years). Reference for this added.	Implementation Criteria below table for adult VOD criteria.	As above.	Pharmacy Lead	18/01/21
No paediatric criteria guideline/paper.	Added BMT paper which informed paediatric eBMT VOD criteria.	Documents which have informed this policy.	Reference required.	Pharmacy Lead/Lead Commissioner	18/01/21

Missing paediatric VOD paper which informs this policy of paediatric criteria.	Added paediatric VOD paper reference.	References.	Reference required.	Pharmacy Lead/Lead Commissioner	18/01/21