Defibrotide (Defitelio) for hepatic veno-occlusive disease in haematopoietic stem cell transplantation – first line

August 2011

This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.
Defibrotide (Defitelio) for hepatic veno-occlusive disease in haematopoietic stem cell transplantation – first line

Target group

- Hepatic veno-occlusive disease (VOD): patients receiving haematopoietic stem cell transplantation (HSCT) – prophylaxis and/or treatment, first line, monotherapy.

Background

VOD of the liver is a rare but potentially life-threatening complication of HSCT therapy. The intensive high-dose conditioning regimens used as part of stem-cell transplantation (SCT) damages the sinusoidal endothelium and small hepatic venules. This endothelial damage can induce activation of the coagulation cascade leading to local hypercoagulation and blockage of these small hepatic vessels. The occlusion causes significant hepatic dysfunction, which can lead to liver failure and damage to other organs such as the kidneys and lungs (severe VOD).1

Technology description

Defibrotide (Defitelio) is the sodium salt of a complex mixture of single-stranded oligodeoxyribonucleotides derived from porcine mucosal DNA. Pre-clinical studies suggest defibrotide targets heparanase and reduces endothelial stress, with no protective effect on tumours seen either in vitro or in vivo. The agent has demonstrated effects on vascular endothelial cells; respectively enhancing and suppressing factors involved with fibrinolysis and coagulation, and enhancing the action of plasmin and the anticoagulant effect of heparin. Defibrotide is thought to have multiple pharmacological actions, however the main therapeutic effects are believed to be primarily due to its anti-thrombotic, anti-inflammatory and anti-ischaemic properties. Defibrotide is administered by intravenous (IV) infusion at 6.25mg/kg every 6 hours for 21 days or until VOD symptoms resolve.

Defibrotide is available to patients in the EU for this indication on a named patient basis. Defibrotide is currently in phase II development for multiple myeloma.

Innovation and/or advantages

If licensed, defibrotide would present a new treatment option for this group of patients. Current management of VOD is limited to supportive care such as diuretics, analgesia, haemodialysis and mechanical ventilation.

Developer

Gentium SpA.

Availability, launch or marketing dates, and licensing plans

Defibrotide is available as a treatment investigational new drug in the USA and pre-licence sales in the rest of the world, including the UK. An application for a Marketing Authorisation with the EMA was made in May 2011, with a final licence anticipated in Q1 2012. The licence has been granted an accelerated review.

NHS or Government priority area

None identified

---

a Expert personal communication
Relevant guidance

- NICE cancer service guideline. Improving outcomes in haematology-oncology cancer. 2003³.

Clinical need and burden of disease

Hepatic VOD is one of the most serious complications associated with SCT⁴. Figures on the incidence of VOD vary depending on the type of transplant, diagnostic criteria and conditioning regimes, however a recent systematic review suggested an incidence of 13.7%⁴. Expert opinion suggests this figure is likely to be an over-estimate, with many cases of diagnosed VOD being attributable to cyclosporine toxicity⁵. VOD is more common following allogeneic than autologous SCT⁴ and the risk is further increased in patients receiving busulphan containing conditioning regimens⁶. Prognosis for severe VOD is poor, with mortality rates estimated to be 84.3%⁴.

In 2009, a total of 2,823 HSCTs were performed in the UK. 57.6% of these were autologous, the remainder being allogeneic, either related or unrelated⁵. As the use of HLA-matched⁷ siblings for donors remains an option for only 30% of patients, the use of stem cells from unrelated donors has increased in recent years⁸. In 2009, 749 unrelated donor HSCTs were performed (including 88 using cord blood), compared with 301 transplants in 2001⁶. In 2009-2010 there were 7 admissions for hepatic VOD in England, resulting in 93 bed days and 10 finished consultant episodes⁷. In England and Wales, only 2 deaths due to hepatic VOD were registered in 2009⁹ (ICD10 K76.5).

Existing comparators and treatments

There are currently no approved therapies for the prophylaxis or treatment of hepatic VOD in the EU or USA. Current management of VOD is limited to supportive care, including diuretics, analgesia, haemodialysis and mechanical ventilation². Treatments with systemic anti-coagulant and thrombolytic therapies, such as heparin, low-molecular weight heparin and tissue plasminogen activator (t-PA), have no proven benefit and may lead to significant haemorrhage².

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00272948, 2004-000592-33, EBMT-PD-200601; paediatric; defibrotide; phase III.</th>
<th>NCT00358501, DF 2005-01; adult and paediatric; defibrotide; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors</td>
<td>European Group for Blood and Marrow Transplantation.</td>
<td>Gentium SpA.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (inc. UK) and Israel.</td>
<td>Canada and USA.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=360; paediatric &lt;18 years; undergoing HSCT at risk of VOD. Randomised to prophylactic IV defibrotide 25mg/kg/day from conditioning until day 30 post HSCT or therapeutic defibrotide 25mg/kg/day beginning at day of VOD diagnosis.</td>
<td>n=34; adult and paediatric &lt;16 years; severe hepatic VOD following HSCT. Patients received IV defibrotide 25mg/kg/day for 21 days.</td>
</tr>
</tbody>
</table>

⁶ Expert personal communication
⁷ Human leukocyte antigen-matched.
<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Day 180 following HSCT.</th>
<th>Day 100 following HSCT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>VOD by day 30 post-HSCT.</td>
<td>Complete resolution (CR) of severe VOD by day 100 post-HSCT.</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td>Composite scoring system for assessment of VOD severity (multi-organ failure (MOF) and mortality by day 100); incidence and severity of graft-versus-host disease (GvHD).</td>
<td>Mortality by day 100 post-HSCT.</td>
</tr>
<tr>
<td>Key results</td>
<td>For defibrotide prophylaxis vs control respectively: VOD at day 30, intention to treat analysis, 12% vs 20% (p=0.049), per-protocol analysis, 11% vs 20% (p=0.022). Composite score for morbidity and mortality was in favour of defibrotide prophylaxis arm (p=0.034); renal failure experienced in 1% vs 6% (p=0.017). GvHD by day 100, 45% vs 63% (p=0.004), and severity in defibrotide prophylaxis arm lower than control (p=0.003).</td>
<td>For defibrotide vs historical control respectively: CR rate, 24% vs 9% (difference 15%, 95% CI: 3 to 30%; p=0.015) Mortality by day 100, 62% vs 75% (difference -13%, 95% CI: -32 to 3%; p=0.051).</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>Serious adverse events (SAEs) were experienced by 61% vs 59% of defibrotide prophylaxis vs control patients respectively.</td>
<td>Haemorrhagic adverse events (any grade) were similar between the two groups (65% vs 69%); 18% of defibrotide patients experienced drug-related toxicity that led to discontinuation.</td>
</tr>
</tbody>
</table>

**Trial**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00628498, defibrotide 2006-05; adult and paediatric; defibrotide; phase III.</th>
<th>NCT00003966, 9918, DFCl-99118, CDR0000067166, CHNMC-02118, DFCl-1999-P-010076/14; adult and paediatric; defibrotide; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Gentium SpA.</td>
<td>Dana-Farber Cancer Institute.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Abstract”.</td>
<td>Publication”.</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
<td>USA.</td>
</tr>
<tr>
<td>Design</td>
<td>Non-randomised, historically-controlled.</td>
<td>Randomised, dose-finding.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=104; adult and paediatric; clinical diagnosis of hepatic VOD. Patients received IV defibrotide 25mg/kg/day for 21 days. 69 participants that would have met entry criteria for NCT00358501 were compared to historic controls from that trial.</td>
<td>n=149; adult and paediatric; severe hepatic VOD post-HSCT. Patients received IV defibrotide 25mg/kg/day or 40mg/kg/day for a minimum of 14 days or until CR, progression of VOD or unacceptable toxicity.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Day 100 following HSCT.</td>
<td>Day 100 following HSCT.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>CR of severe VOD by day 100 post-HSCT.</td>
<td>CR of severe VOD.</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td>Survival to day 100 post-HSCT for subset of patients who would have been eligible for NCT00358501.</td>
<td>Survival to day 100 post-HSCT; safety and tolerability; AEs; effect of defibrotide on plasminogen activator inhibitor-1 (PAI-1).</td>
</tr>
</tbody>
</table>
August 2011

Key results

For defibrotide vs historical control respectively:
CR rate, 34% vs 9% (difference 25%, 95% CI: 6 to 36.6%; p=0.0064).
Survival by day 100, 34% vs 25% (p=0.0463).

Overall CR and survival by day 100 post-HSCT were 46% and 42%, respectively, with no significant difference reported between treatment arms.

Expected reporting date

Estimated primary completion date June 2012.

Adverse effects (AEs)

AEs included pulmonary haemorrhage, gastro-intestinal haemorrhage, hypotension, rectal haemorrhage, cerebral haemorrhage and pulmonary haemorrhage.

Incidence of treatment-related AEs:
8% overall, 7% in 25mg/kg/day arm and 10% in 40mg/kg/day arm (p>0.05).

Estimated cost and cost impact

The final cost of defibrotide has not yet been confirmed. Pre-licence sales are on the basis of ‘cost recovery’ and the company report that the price per 200mg vial is currently €137 (approximately £123).

Claimed or potential impact – speculative

Patients

☑️ Reduced mortality or increased length of survival
☐ Other:

☑️ Reduction in associated morbidity or improved quality of life for patients and/or carers
☐ Quickier, earlier or more accurate diagnosis or identification of disease
☐ None identified

Services

☑️ Increased use – daily IV therapy.
☐ Service organisation
☐ Staff requirements

☑️ Decreased use – potential for shorter length of stay.
☐ Other:
☐ None identified

Costs

☐ Increased unit cost compared to alternative
☑️ New costs: new therapeutic option.

☐ Increased costs: more patients coming for treatment
☑️ Savings: reduced stay in intensive care unit and reduced costs associated with MOF and VOD management.

☐ Increased costs: capital investment needed
☐ Other:

Other issues

☐ Clinical uncertainty or other research question identified:
☑️ None identified

References


The National Institute for Health Research National Horizon Scanning Centre Research Programme is funded by the Department of Health.
The views expressed in this publication are not necessarily those of the NHS, the NIHR or the Department of Health

The National Horizon Scanning Centre,
Department of Public Health and Epidemiology
University of Birmingham, 90 Vincent Drive, Edgbaston, Birmingham, B15 2SP, England
Tel: +44 (0)121 414 7831 Fax +44 (0)121 414 2269
www.haps.bham.ac.uk/publichealth/horizon