Doxorubicin-eluting beads (DC Bead, DC Bead M1 and Radiopaque DC Bead) for hepatocellular carcinoma

LAY SUMMARY

Hepatocellular carcinoma is the most common type of liver cancer. Most cases of hepatocellular carcinoma are caused by cirrhosis, a condition associated with damage and scarring to the liver. This is often caused by excessive alcohol intake or having long term infections with hepatitis B or C. It is more common in men than women and typically affects older people.

DC Bead consists of beads that are designed to release doxorubicin, a chemotherapy drug, at a slow rate at the site of the cancer. This is delivered directly to the hepatic artery, a blood vessel that supplies blood to the liver. Studies have shown that DC Bead delivers doxorubicin to the tumour without the drug spreading to healthy tissue.

DC Bead is already used to treat hepatocellular carcinoma in the UK.

NIHR HSRIC ID: 7219 (and 11780)
TARGET GROUP

- Hepatocellular carcinoma (HCC): doxorubicin delivered using transarterial chemoembolisation (TACE).

TECHNOLOGY

DESCRIPTION

Doxorubicin-eluting beads (DC Bead, DC Bead M1 and radiopaque DC Bead) are used during TACE therapy for the treatment of HCC. The majority of the blood supply to the normal liver parenchyma comes from the portal vein, whereas blood flow to the tumour typically comes mainly from the hepatic artery. Furthermore, HCC tumours are generally hypervascular compared with the surrounding normal parenchyma. TACE involves the intra-arterial injection of polyvinyl alcohol beads or particles loaded with a chemotherapeutic agent around a tumour. The blood supply to the tumour is then reduced or ceases altogether, causing it to shrink or die. The reduced blood supply also allows the chemotherapeutic agent to remain at the site of the tumour longer, exposing the tumour cells to higher levels of the chemotherapeutic and reducing the peak systemic plasma levels. DC Bead can be loaded with a dose of up to 37.5mg doxorubicin per ml. A maximum total dose of 150mg of doxorubicin per procedure is recommended. DC Bead also comes in a smaller version, DC Bead M1, and a radiopaque version of DC Bead.

DC Bead has already received a CE mark and has been available in the UK since 2004. The use of doxorubicin in TACE is an established procedure for the treatment of HCC. DC Bead loaded with doxorubicin is sometimes referred to as DEBDOX, which was trademarked by Bio UK in December 2009.

INNOVATION and/or ADVANTAGES

Doxorubicin-eluting beads offer an additional approach to TACE therapy for patients with hepatocellular cancer.

DEVELOPER

Biocompatibles UK Limited, a wholly owned subsidiary of BTG.

AVAILABILITY, LAUNCH OR MARKETING

- DC Bead was first CE Marked by Biocure Inc in 2003. The company was then taken over by Bio UK in 2004, and DC Bead is available and used in the UK.
- Radiopaque DC Bead - a radiopaque embolic drug eluting bead.
- DC Bead is currently registered with CE Mark as a Class IIb product.

* Company comment.
PATIENT GROUP

BACKGROUND

HCC is a malignant tumour arising from liver cells (hepatocytes) and occurs mainly in cirrhotic livers\(^4\). It is sometimes known as hepatoma and is usually confined to the liver, although occasionally it spreads to other organs\(^5\). The liver plays an important role in the storage of nutrients, the production of bile and protein, and the breakdown of harmful and waste products\(^6\). HCC affects more men than women and the incidence increases with age\(^6\). HCC almost always develops from chronic liver disease, mainly alcoholic or viral (hepatitis B or C) and presents with cirrhosis in about 90% of cases\(^6\). Other risk factors include insulin resistance associated with non-alcoholic steatohepatitis, diabetes, and obesity\(^7\), as well as smoking, infections and alcohol consumption\(^6\).

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

CLINICAL NEED and BURDEN OF DISEASE

Liver cancer is the 18\(^{th}\) most commonly diagnosed cancer in the UK, accounting for 1% of all new cases of cancer\(^8\), a figure that is continuing to rise. In 2013, there were 4,387 new cases of liver cancer in England, 2,799 (64%) in males and 1,588 (36%) in females\(^5\). HCC is the main type of primary liver cancer, accounting for about 85% of cases\(^10\). Most cases of HCC are secondary to either a viral infection (hepatitis B or C) or cirrhosis\(^11\). The incidence of HCC has increased in recent years as a result of the rising prevalence of infection with hepatitis C virus and increased alcohol consumption\(^11,12\). Approximately 40-50% of HCCs in Europe can be attributed to excessive alcohol consumption\(^13\).

In 2013-14 there were 10,184 admissions for HCC (ICD-10 C22.0) in England, resulting in 61,415 bed days and 14,408 finished consultant episodes\(^14\). During 2014, there were 4,452 registered deaths from HCC in England and Wales\(^15\).

\(^b\) Company comment.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE interventional procedure guidance. Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer (IPG488). May 2014.

Other Guidance

- European Society for Medical Oncology. Hepatocellular Carcinoma: ESMO-ESDO Clinical Practice Guidelines. 2012\textsuperscript{16}.
- American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: An Update. 2011\textsuperscript{17}.

CURRENT TREATMENT OPTIONS

For the majority of patients with HCC, treatment is palliative rather than curative. The only potentially curative options for HCC are surgery or ablation in selected patients. Treatments include:

- Sorafenib – considered the standard of care for advanced HCC with well-preserved liver function by some authorities\textsuperscript{16}, but is not recommended by NICE\textsuperscript{7}.
- Chemotherapy – doxorubicin is a commonly used chemotherapy drug and may help to shrink the size of the tumour in HCC\textsuperscript{18}. Other chemotherapy drugs that may be used include cisplatin, fluorouracil and gemcitabine\textsuperscript{18}.
- Chemoembolisation – TACE used with doxorubicin or cisplatin\textsuperscript{18,19}. TACE is the most widely used primary treatment for HCC not amenable to curative treatment by excision or ablation\textsuperscript{c}. TACE is recommended for patients with BCLC\textsuperscript{d} stage B (intermediate), or those with an excellent liver function and multinodular asymptomatic tumours without macroscopic vascular invasion or extra hepatic spread, however, it cannot be used as a single modality treatment to cure intermediate HCC\textsuperscript{16}. Studies with DEBDOX suggest

\textsuperscript{c} Company comment.
\textsuperscript{d} Barcelona Clinic Liver Cancer (BCLC) staging system.
there is less leakage of chemotherapy into the systemic circulation than conventional TACE, resulting in fewer side effects, with at least the same activity in randomised phase II trials.\textsuperscript{16}

- Hepatic resection – surgery is the most effective treatment for primary liver cancer.\textsuperscript{18} and the standard treatment for HCC\textsuperscript{20}.
- Liver transplantation – to be eligible, the tumour size must be \(\leq 5\)cm (single tumour), or a single tumour between 5-7cm for at least 6 months or two to three tumours that are \(<3\)cm.\textsuperscript{18}
- Radiofrequency ablation – more effective for treating small HCCs (\(\leq 5\)cm in diameter). In certain scenarios, it has also demonstrated clinical effectiveness equal to surgical resections.\textsuperscript{19}

### Efficacy and Safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
<th>Schedule</th>
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<tbody>
<tr>
<td>V, NCT00261378, CA1008; DC Bead with doxorubicin vs conventional TACE therapy; phase II.</td>
<td>Biocompatibles UK Ltd.</td>
<td>Biocompatibles UK Ltd.</td>
<td>Publication\textsuperscript{21,22}, trial registry\textsuperscript{23}.</td>
<td>Austria, France, Germany and Switzerland.</td>
<td>Randomised, active-controlled.</td>
<td>n=212; aged (\geq 18) years; HCC not suitable for resection or percutaneous ablation, or patients eligible for resection or percutaneous ablation but the treatment is unfeasible or the patient declines; no prior chemotherapy, radiotherapy or TACE (with or without chemotherapy); eligible for chemoembolisation prior to transplantation and the expected transplant waiting time exceeds 6 months; if received previous potentially curative treatment (resection and percutaneous ablation), then must demonstrate recurrence with clearly measurable disease according to RECIST or EASL (European Association for the Study of the Liver); must have bilobar disease that can be treated superselectively in a single session or both lobes able to be treated within 3 weeks; Eastern Cooperative Oncology Group performance status 0 and 1 and preserved liver function (Child Pugh Class A or B).</td>
<td>Randomised to receive 4mL of DC Bead with doxorubicin at 37.5mg/mL for a total of 150mg doxorubicin per treatment, or 50-70mg/m(^2) to a maximum of 150mg doxorubicin with conventional TACE (cTACE). Patients received chemoembolisation at baseline, 2 and 4 months for a maximum of three procedures.</td>
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<td>I; DC Bead; phase I/II.</td>
<td>Biocompatibles UK Ltd.</td>
<td>Published.</td>
<td>Publication\textsuperscript{24}.</td>
<td>Spain.</td>
<td>Non-randomised, uncontrolled.</td>
<td>n=27; patients with asymptomatic, untreated HCC, Child Pugh A cirrhosis without vascular invasion or extra hepatic spread. The pharmacokinetic profile was performed in 13 of the 27 patients in the DC Bead group and 5 patients were in the cTACE group.</td>
<td>Patients received 2 episodes of TACE therapy using DC Bead loaded with doxorubicin, separated by 2 months. Dose of doxorubicin ranged from 25mg/m(^2) to 100mg/m(^2). In a subset group that received only cTACE, participants were administered 50mg or 75mg of doxorubicin and obstruction was done with injections of gelfoam fragments</td>
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<td>Follow-up</td>
<td>Follow-up up to 6 months.</td>
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<td><strong>Primary outcome/s</strong></td>
<td>Objective response rate according to RECIST and EASL.</td>
<td>Safety and pharmacokinetics.</td>
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<td><strong>Secondary outcome/s</strong></td>
<td>Toxicity, change in alpha foetal protein, time to hospital discharge, safety, other procedures or interventions required, cardiotoxicity, local tumour response, health care resource use, patient quality of life and time to progression.</td>
<td>Tumour response.</td>
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<td><strong>Key results</strong></td>
<td>The DC Bead group had higher rates of complete response, objective response, and disease control compared with the cTACE group (27% vs. 22%, 52% vs. 44%, and 63% vs. 52%, respectively). Superiority hypothesis was not met (one-sided p=0.11). Objective response was p=0.038 compared to cTACE in patients with Child-Pugh B, ECOG 1, bilobar disease, and recurrent disease. DC Bead resulted in reduced serious liver toxicity (p&lt;0.001) and a significantly lower rate of doxorubicin-related side effects (p=0.0001). The mean maximum post chemoembolisation alanine transaminase and aspartate transaminase increase in the DC Bead group was 50% (p=0.001) and 41% (p&lt;0.001) less than in the cTACE group, respectively. The mean total length of hospital stay for all procedures and serious AEs (SAEs) was 12 ± 9 days in both treatment groups. At six months, mean levels of alpha foetal protein were 25.62 ± 890.28IU/mL (geometric mean ± coefficient of variance) at baseline and 16.59 ± 1237.54IU/mL at 6 months or early withdrawal in the DC Bead group and 27.54 ± 2400.19IU/mL and 13.49 ± 1008.98IU/mL, respectively in the cTACE group. There was a small but statistically significant difference in mean change from baseline in LVEF between the DC Bead and cTACE groups of 4% (95% CI, 0.71–7.3; p=0.018).</td>
<td>During the first treatment session, 89% (24 of 27 patients) of cases achieved arterial blood flow obstruction (complete obstruction in 21). Of the remaining 3 patients, 2 obtained complete obstruction during the second treatment session, whereas in the third patient, obstruction was unfinished because the HCC tumour was fed by multiple small arteries. Obstruction was maintained in 4 of the 21 patients that had achieved a total occlusion during the first DC Bead TACE. Of these 4, 3 had a second TACE session due to newly developed collaterals. Based on RECIST criteria there were zero complete responses, and 12 partial responses (&gt;30% reduction was registered in 12 patients, 44%). In the remaining cases, 7 were classed as stable disease and 5 as disease progression. Objective response rate increased to 66.6% (intention-to-treat); 26% had complete response; 41% had partial response. The pharmacokinetic profile was performed in 13 of the DC Bead group and 5 in the cTACE group. Doxorubicin Cmax and AUC were significantly lower in the DC Bead group (78.97 ± 38.3ng/mL and 662.6 ± 417.6ng/mL min) than in the cTACE group (2341.5 ± 3951.9ng/mL and 1812.2 ± 1093.7ng/mL min, p=0.00002 and p=0.001, respectively). After a median follow-up of 27.6 months, 1- and 2-year survival is 92.5% and 88.9%, respectively.</td>
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<td><strong>Adverse effects (AEs)</strong></td>
<td>Treatment emergent AEs affecting the liver occurred in 16.1% of the DC Bead group compared with 25% of the cTACE group. Treatment emergent cardiac AEs occurred in 4.3% of DC Bead group and 7.4% of the cTACE group. SAEs included 1 death due to cardiomegaly (DC Bead), 1 life-threatening acute cardiac failure and 1 coronary artery occlusion, (both cTACE).</td>
<td>After the first TACE, 37% presented a clinically relevant post-TACE syndrome but did not require prolonged hospital stay; 6 (22%) patients presented with mild fever and 4 (15%) with nausea and vomiting. Two patients were diagnosed with liver abscess – one was completely healed with antibiotics while the other developed progressive liver decompensation and died at 3 months. After the second procedure (n=22), 4 patients (18%) presented with post-TACE syndrome, 7 (32%) with mild pain, and 3 (14%) with nausea and vomiting. All</td>
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minor secondary effects disappeared within the first week. None of the patients presented alopecia, bone marrow toxicity, dyspnoea or pulmonary embolism.

ESTIMATED COST and IMPACT

COST

The cost of DC Bead is unknown. A 50mg vial (powder for reconstitution) of doxorubicin hydrochloride encapsulated in liposomes costs £456.13\(^\text{25}\). A 10mL vial (2mg/mL) of pegylated doxorubicin hydrochloride encapsulated in liposomes costs £360.23\(^\text{25}\).

IMPACT - SPECULATIVE

Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- No impact identified

Impact on Health and Social Care Services
- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- None identified

Impact on Costs and Other Resource Use
- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs:
- None identified

Other Issues
- Clinical uncertainty or other research question identified:
- None identified

REFERENCES


