Liver Cancer

Drug-eluting Beads in the Treatment of Cirrhosis-related Hepatocellular Carcinoma

a report by
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Hepatocellular carcinoma (HCC) is among the 10 most common neoplasms worldwide and the third highest cause of cancer-related deaths,1 with geographical variation in incidence and risk factors.2 Surgical methods remain the gold standard for the treatment of HCC. However, this is feasible in only 25–30% of patients because of tumour stage or the severity of underlying cirrhosis.

Transarterial chemoembolisation (TACE) is generally accepted as an effective palliative treatment for patients with unresectable HCC and adequate preservation of liver function. The justification of chemoembolisation as a palliative treatment for HCC has been strengthened by recent randomised trials and meta-analysis of previous smaller randomised trials, while a significant survival benefit has been shown compared with no treatment or systemic chemotherapy.3–6 TACE has been shown to reduce systemic toxicity and increase local effects and thus improve therapeutic results.

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Drug-eluting Bead as an Embolic Material
DC Bead is a soft deformable material of spherical shape composed of a polyvinyl alcohol macromer that has been modified with sulphonate groups, as described by Gonzalez et al.7,8 The microspheres are stored in phosphate packing solution and, when admixed with a solution of doxorubicin, the chemotherapeutic agent is incorporated into the bead, which initially increases in size. Upon completion of loading with doxorubicin heparin cofactor I (HCO), the beads undergo a slight decrease in diameter. This diameter reduction allows unobstructed delivery of all sizes of microspheres through microcatheters as small as 2.7F.8

Pre-clinical studies with DC Bead demonstrate a sustained continuous release of doxorubicin for a period of 14 days after injection.1,3,5 Additionally, pre-clinical and clinical studies have shown that the systemic...
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Increased tumour concentration and low peripheral blood levels are desirable to achieve good results and minimum toxicity.

These properties of DC Beads are not present in other embolisation materials used in chemoembolisation; as shown in other studies, polyvinyl alcohol particles or the gelatine-coated tri-acryl embospheres do not have the capability to transfer the doxorubicin molecules internally and, in addition, suspensions are unstable.12 In vitro measurements have also shown that when lipiodol was used as a doxorubicin carrier – such as in conventional TACE – local release was very rapid.8

Antitumoral Effects of the Device

Initial in vivo studies in a rabbit Vx-2 model showed that at concentrations per liver weight planned for clinical trials the concentration of doxorubicin in the peripheral blood was low and the fraction of non-viable tumour was higher compared with the intra-arterial injection.9 In addition, in the same model Hong et al. found that intra-tumoral doxorubicin levels at 72 hours after embolisation were about 400% higher than those after conventional TACE.7 Imaging and pathological correlations in an animal series with Yucatan pigs in which blunt beads and doxorubicin-eluting beads were compared showed that necrosis was more profound and more severe with the DC Beads.8,10 Tumour necrosis was greatest 7–14 days after treatment, while for this period the combined damaged and necrotic cells approached 100%. Compared with necrosis induced in controls with intra-arterial injection of doxorubicin followed by embolisation with unloaded DC Bead, there was a statistically significant advantage with the loaded beads. In the animal study of Hong et al., tumour necrosis in the Vx-2 animal model approached 100% at seven days, while plasma concentration of doxorubicin was minimal.9

Comparative Results of Transarterial Chemoembolisation and DC Bead

Results of non-DC Bead (conventional) TACE vary significantly between different studies, not only because of the different techniques used, but also because of the lack of homogeneity of patient and tumour samples. TACE results in the randomised trial conducted by Lo et al. reported one-, two- and three-year survival rates of 57%, 31% and 26%, respectively, with 32%, 11% and 3%, respectively, in the control group.4 In the randomised trial of Llovet et al., survival rates at one and two years were 82% and 63%, respectively, compared with 63% and 27%, respectively, with symptomatic treatment.3 The French multicentre trial on patients with advanced HCC showed survival rates with TACE of 64% and 38% at one and two years, respectively, compared with 18% and 6%, respectively, in the untreated control arm.13

Conventional TACE results from previous studies applied in relatively small cancers – which today are mostly directed to radiofrequency catheter ablation (RFA) – report a three-year survival of 34–77%,3–6,14 while in a paper in which TACE was applied prospectively to potential RFA candidates survival was 80%, 43% and 23% at one, three and five years, respectively.15 Local recurrence rates after a single conventional TACE were 33.2% at one year and 33.2% and 37.8% at two and three years, respectively, in the study by Takayasu et al., while survival rates at this study at one, two and three years were 93.3%, 77.1% and 77.1%, respectively, for tumours less than 5cm in diameter. Brown et al. demonstrated 61%, 42% and 32% survival rates at one, two and three years, respectively.16

Cumulatively, TACE achieves a partial response in 15–55% of patients with a delay in tumour progression.
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4. Lo CM, Ngan H, Tso WK, et al., Randomized controlled trial of DC Beads were used.10 A more profound transient increase in liver enzymes has been observed in animal studies when small DC Beads were used.10

In their recent study, Varella et al. showed that the treatment was well tolerated without impairment of liver function.11 Likewise, Malagari et al.20 observed transient liver enzyme increase with return to baseline at one month after each procedure. Bilirubin levels remained relatively constant, with no statistically significant changes compared with baseline.

Liver Function

A common observation in all TACE procedures is a transient rise of liver enzymes peaking at 24–36 hours and returning to baseline after five to six days. Previous studies with DC Bead showed that similar increases also develop with a more prolonged elevation, which may remain high over a 14-day period. This may be attributed to the sustained release of doxorubicin causing a cytotoxic effect.9,10 A more profound transient increase in liver enzymes has been observed in animal studies when small DC Beads were used.10

Complications

TACE-related mortality is less than 4%.21 The most common serious adverse events are liver abscess or liver infarction, each of which occur in approximately 2% of patients; 30-day mortality is 1%.3,4,7,10 In the study by Varella et al., two cases of liver abscess were observed out of 27 patients, each of which was lethal.11 In the study by Malagari et al., procedure-related mortality was 0%.20 In this study, all patients suffered from post-embolisation syndrome; the maximum duration of pain was three days. Fever was observed in 83%, 80% and 95% of the patients after the first, second and third procedure, respectively. Serious complications, including liver abscess and cholecystitis, developed in 3.2% of their patients.

Early clinical results show that doxorubicin-eluting DC Bead presents higher percentages of necrosis and tumour response in short-term follow-up. Randomised trials of DC Bead TACE and conventional TACE are currently taking place that will provide more solid conclusions.

Conclusion

Published data show that TACE is an effective method of treatment for HCC. Early clinical results show that doxorubicin-eluting DC Bead presents higher percentages of necrosis and tumour response in short-term follow-up. Long-term follow-up is necessary in order for the existing DC Bead registries to define long-term survival rates, recurrence-free time length and percentage of new lesions occurring in non-embolised areas of the liver.
PRECISION TACE™ with DC Bead™ - Addressing the Challenge in HCC

The 1- and 2- year survival is 92.5% and 88.9%, respectively, with a mean follow-up of 27.6 months.

None of the patients presented alopecia, bone marrow toxicity, dyspnea or pulmonary embolism.

Chemoembolisation using DEBs is a safe and effective procedure with a favourable pharmacokinetic profile.

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References