REVIEW

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Chemoembolization with DC Bead™ for the treatment of hepatocellular carcinoma: an update

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Practice Points

- Chemoembolization with DC Bead™ (Biocompatibles UK Ltd) loaded with doxorubicin is indicated for hepatocellular carcinoma with Barcelona Center for Liver Cancer B stage of disease and Barcelona Center for Liver Cancer A when the patient is not suitable for curative treatments including surgery or local ablation.
- With drug-eluting beads, chemoembolization allows a standardized, precise and reproducible procedure in contrast with the conventional lipiodol-based chemoembolization.
- The pharmacokinetic profile of chemoembolization with DC Bead loaded with doxorubicin has been proven in animal and human studies, and is characterized by high concentrations of the chemotherapeutic locally into the tumor and very low systemic exposure to doxorubicin as plasma concentrations have shown.
- Safety studies have shown that drug-eluting chemoembolization has less liver toxicity and less doxorubicin-related side effects compared with conventional chemoembolization. Sizes below 70 µm in diameter have not been tested for safety in humans yet.
- The most common complication post-drug-eluting beads is postembolization syndrome; however, this occurs less frequently than with conventional chemoembolization.
- Efficacy studies have shown a high percentage of necrosis and good local response that is superior to conventional chemoembolization in more advanced disease (Child–Pugh B, ECOG 1, recurrent or bilobar tumors).
- The two studies with long-term follow-up show very high 5-year survival rates; however, there is no randomized study with survival as a primary end point.

SUMMARY In this review, DC Bead™ for the treatment of hepatocellular carcinoma is discussed. The embolic device and its mechanism of action is described, focusing on the clinical application and the preclinical background. Guidelines for patient selection and management, along with technical considerations for the appropriate use are provided. Clinical details including local response, comparison with conventional chemoembolization and bland embolization, survival and safety issues are also discussed in detail.

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Several embolic agents have been used over the last decade in conjunction with intra-arterial drug delivery. The intended purpose of embolization is twofold: to prevent washout of the drug from the tumor site, and to induce ischemic necrosis. Drug-eluting beads act at both of these levels achieving vessel blockade and delivery of the chemotherapeutic locally for several days after embolization (in a precise and predictable manner in accordance with the Higuchi equation from *in vitro* modeling), while at the same time the diffusion of the chemotherapeutic in the systemic circulation is negligible [1–5]. In contrast with the conventional lipiodol-based chemoembolization, the drug-eluting bead with chemoembolization is standardized, and reproducible. Today there are three platforms of drug-eluting beads including DC Bead™ (Bio-compatibles UK Ltd, a BTG group company), Hepasphere/Quadrasphere (Merit Medical Inc.) and Tandem (Celonova Biosciences Inc.). The drug-eluting platform of DC Bead is the most extensively studied at a preclinical and clinical level with data of 5-year survival and this review focuses on this drug-eluting device in the treatment of hepatocellular carcinoma (HCC).

Mechanism of action pharmacokinetics

The DC Bead is a drug-delivery embolization system, consisting of beads of polyvinyl alcohol – hydrogel modified by sulfonate groups [1–3]. The bead is biocompatible and is capable of being loaded with anthracycline derivatives such as doxorubicin, the most universal chemotherapeutic agent for chemoembolization by an ion-exchange mechanism [1–3]. The beads are formulated by inverse suspension polymerization into different categories of spherical maximal diameter, ranging in size from 70 to 900 μm [6,7]. Lewis *et al.* demonstrated that >99% of the targeted dose of doxorubicin is loadable in the beads, up to an approximate maximum of 40 mg of drug in a volume of 1 ml of hydrated beads [1,2]. This is achieved normally in the hospital pharmacy prior to a procedure by simple addition of the desired concentration of doxorubicin solution to the beads. The smaller the caliber of the bead the faster the loading time (for beads 100–300 μm , the loading time is 60 min but can be accelerated by use of agitation). The fastest loading is achieved with M1™ (Biocompatibles, BTG), which has a size range of between 70 and 150 μm . The loading with doxorubicin displaces a small amount of

water from the beads and their average diameter decreases by a factor of 10% for beads 100–300 μm , while the beads also become more rigid. Larger-sized (700–900 μm) beads show an approximate 35% decrease in average diameter when loaded with the maximum dose of drug [1,2]. Cross-sectional fluorescent microscopy of histological tissue sections reveals that the loaded beads release doxorubicin up to at least 600 μm from the surface of the beads at a level that is above IC_{50} for tumor cells and for at least 3 weeks postembolization [8]. Overall, the drug impregnates an area of at least 1.2 mm in diameter around the occluded vessel. The tissue concentration of the drug ranges from 5 μM at 8 h to 0.65 μM at 1 month [8].

Animal models of liver cancer showed that the concentration of doxorubicin within the tumor remains high up to 14 days post-transcatheter infusion, suggesting continuous release of doxorubicin from the microspheres, whereas systemic drug concentration is kept at minimal levels [2]. The doxorubicin C_{max} was approximately 15-times higher in the small-sized beads animal group versus the large beads group, despite that the relative dose administered was only approximately 1.5-times greater in the small bead group [2]. In addition, clinical studies have shown that TACE with DC Bead results in higher tumor concentrations and lower systemic concentrations of doxorubicin compared with intra-arterial doxorubicin and conventional TACE [4,5]; Varela *et al.* found that doxorubicin C_{max} and the area under the curve were significantly lower in DC Bead chemoembolization patients (78.97 ± 38.3 and 662.6 ± 417.6 ng/ml/min) than in conventional chemoembolization (2341.5 ± 3951.9 and 1812.2 ± 1093.7 ng/ml/min; $p = 0.00002$ and $p = 0.001$, respectively) [4]. Phase I/II studies in HCC have demonstrated promising efficacy with low toxicity [4,5]. A Phase II study from China showed a low peak plasma doxorubicin concentration (49.4 ± 23.7 ng/ml), and no systemic toxicity after DC Bead chemoembolization with doxorubicin [5].

Guidelines & technical recommendations: indications

Technical recommendations for the use of doxorubicin-loaded DC Bead in the treatment of HCC have been released by a consensus from a panel of experts [9]. According to these guidelines the target patient group includes patients with HCC of Barcelona Center for Liver Cancer

(BCLC) B or A stage unsuitable for curative treatments. Liver function parameters suitable for DC Bead are the same with conventional chemoembolization. Pretreatment imaging requires either multidetector computerized tomography or MRI with dynamic images at three different phases. Before loading with doxorubicin the supernatant should be extracted from the vial to allow the ionic exchange that is necessary for binding with the drug [1–3]. The loading of DC Bead with doxorubicin should be prepared using 50–75 mg doxorubicin for each vial of DC Bead (2 ml of beads; loading dose: 25–37.5 mg doxorubicin/ml of beads). For disease within the Milan criteria, the total dose of doxorubicin should not exceed 75 mg for the two vials of DC Bead, while for disease beyond the Milan criteria, the dose of doxorubicin should reach 150 mg for the two vials (75 mg per vial) in each embolization session. In bilobar tumors, a staged embolization is advisable treating each lobe separately with sessions 2–4 weeks apart in the absence of complications requiring a longer time interval between the two treatments.

As a general rule the smallest available DC Bead should be used especially in tumors below 6–7 cm in diameter paying attention to potential arteriovenous shunts. In the presence of arterioportal shunts a larger size of DC Bead should be used. Loaded DC Bead should be mixed with a nonionic contrast medium. At least 5–10 ml of nonionic contrast should be used per 1 ml of DC Bead (i.e., 10–20 ml are required to dilute one vial of DC Bead) before injection. The catheter used for the delivery should not be wedged but should be as close to the tumor as possible allowing inflow of blood that is necessary to push the beads into the tumor vasculature. The end point of embolization should be occlusion of the intratumoral vessels until near stasis (i.e., the contrast column in the feeding vessel should clear within 2–5 heartbeats). After the delivery of the two vials if there is additional inflow and visualization of intratumoral vessels no additional bland embolic is necessary but there is no general consensus over this. C-arm dual-phase cone-beam assists in predicting local response and correct positioning of the microcatheter [10]. Alternatively, contrast-enhanced ultrasound intraprocedurally can be of the same use [11].

Recently, the stability of elution kinetics after storage for up to 14 days has been performed [12]. It was found that the variance in doxorubicin concentration of the samples stored in the

syringes under refrigerated conditions was less than 10% over the 14-day period. The chromatographic purity of doxorubicin eluted from the DC Bead in their primary glass vial packaging was measured at 99.7%. The dissolution test showed that the elution rate and amount recovered from samples stored in vials were statistically similar between day 0 and day 14. The chromatographic purity of the doxorubicin loaded into DC Bead in the presence of non-ionic contrast medium was >99.0% for 7 days under refrigerated conditions. These findings indicate that doxorubicin-loaded DC Bead has adequate physicochemical stability over a period of 14 days when stored in syringes or vials under refrigerated conditions. The admixtures of doxorubicin-loaded beads with contrast medium are stable for up to 7 days under refrigerated conditions [12].

Local response

Local response results are summarized in [Table 1](#). Local response is evaluated 4 weeks postembolization with dynamic three-phase MRI or multidetector computerized tomography ([Figure 1](#)). The Barcelona Center for Liver Cancer (BCLC) reported midterm results of 27 Child–Pugh A cirrhotics (76% male; 59% hepatitis C virus) with large/multifocal HCC that received chemoembolization with doxorubicin-loaded DC Bead at doses adjusted for bilirubin and body surface (range: 47–150 mg) with a response rate of 75% (66.6% on intention to treat) [4]. Poon *et al.*, using modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria, and taking into account the extent of tumor necrosis, found that 63.3% patients had a partial response and 6.7% had a complete response [5]. The group of Geschwind *et al.* reported overall tumor response (including complete and partial response, as well as stable disease) of 100% when measured with both European Association for the Study of the Liver (EASL) and RECIST criteria (25% partial response and 75% stable disease) [13]. Similar results were observed in another single-center Phase II trial [14]. In a study with 62 HCC patients treated with DC Bead chemoembolization a complete response was observed in 4.8% after the first procedure, and 3.6 and 8.3% after the second and third procedures, respectively [15]. At 9 months a complete response was seen in 12.2%, an objective response in 80.7%, progressive disease in 6.8% and 12.2% showed stable disease. Mean

Table 1. Results of local response and survival in recent studies.

Study (year)	Local response (%)	Survival (%)	Comment	Ref.
Varela <i>et al.</i> (2007)	Response: 66 PR: 44.4 [†] SD: 25.9 [†] CR: 25.9 [‡]	At 12 months: 92.5 At 24 months: 88.9	On intention-to-treat	[4]
Poon <i>et al.</i> (2007)	CR: 6.7 PR: 63.3	At 12 months: 92.5 At 24 months: 88.9	Prospective study Results at 1 month	[5]
Malagari <i>et al.</i> (2008)	CR: 12.2 PR: 75.6 PD: 6.8 SD: 12.2	NA	At 9 months after three scheduled sessions Prospective study	[15]
Malagari <i>et al.</i> (2008)	CR: 16.1 OR: 72	At 18 months: 94.1 At 30 months: 88.2	After three scheduled sessions Prospective study	[16]
Kettenbach <i>et al.</i> (2008)	CR: 27 PR: 13 PD: 40 SD: 3	At 6 months: 93	Prospective study	[17]
Sacco <i>et al.</i> (2011)	CR: 51.5 [§] PR: 48.5 [§] PD: 17.9	At 24 months estimated: 86.8	Prospective–randomized study	[18]
Sycha <i>et al.</i> (2012)	OR: 89%	NA	NA	[20]
Dhanasekaran <i>et al.</i> (2010)	NA	At 6 months: 71 At 12 months: 58 At 24 months: 48 Median survival 610 days [§]	Retrograde study	[22]
Lammer <i>et al.</i> (2010)	CR: 27 [§] OR: 52 [§] DC: 63 [§]	NA	Prospective–randomized study	[24]
Malagari <i>et al.</i> (2012)	CR: 22.5–23.5 [¶] PR: 46.5–49 [¶] PD: 8.4–4.9 [¶] SD: 22.5 [¶]	At 12 months: 93.6 At 24 months: 83.8 At 3 years: 62.0 At 4 years: 41.0 At 5 years: 22.5 Mean overall survival: 43.8 months	Prospective study After three scheduled sessions and then on demand	[27]
Burrel <i>et al.</i> (2012)	NA	Median survival after censoring at the time of transplant/ sorafenib was 47.7 months	Prospective study	[28]

[†]Response Evaluation Criteria In Solid Tumors criteria.

[‡]WHO-modified criteria.

[§]In the DC Bead™ arm.

[¶]Range for Child–Pugh A and Child–Pugh B cirrhosis.

CR: Complete response; DC: Disease control (complete response plus partial response plus stable disease); NA: Not applicable;
OR: Objective response (complete response plus partial response); PD: Progressive disease; PR: Partial response; SD: Stable disease.

tumor necrosis ranged from 77.4 to 83.9% (range: 28.6–100) across three treatments [15].

In another study with 71 HCC patients with tumors of a mean diameter of 6.2 cm, sustained complete response was observed in 16.1%,

and objective response in 72%. Sustained partial response was seen in 72.05%. Survival at 18 months was 94.1% [16]. At 24-months follow-up survival was 91.1%. Sustained objective response was seen in 66.2% while sustained

complete response was 16.1%. At 30 months survival was 88.2% [16]. At 6-month follow-up Kettembach *et al.* achieved complete response in 27%, partial response in 13%, stable disease in 3%, and progressive disease in 40%, of patients, according to RECIST criteria [17]. In their randomized study between DC Bead and conventional chemoembolization Sacco *et al.* at 1 month achieved complete response and partial response rates of 70.6 and 29.4%, respectively, after conventional chemoembolization, and 51.5 and 48.5%, respectively, after DC Bead chemoembolization; the difference was not significant [18]. However, in this study the mean diameter of tumors treated was small (65% had BCLC stage A disease). Extrapolating from conventional chemoembolization, it has been proved that patients who underwent chemoembolization for HCC showed a response (with both EASL criteria and modified RECIST) and improved survival after the second chemoembolization treatment [19]. At least two chemoembolization procedures should be performed in the same targeted lesions before further treatment is abandoned [19]. Syha *et al.* reported an objective response in 89% with higher necrosis in patients that received more than one DC Bead chemoembolization [20]. Lencioni *et al.* combining DC Bead chemoembolization with radiofrequency ablation for lesions ranging from 3.3 to 7.0 cm in diameter found that induction of necrosis increased from $48.1 \text{ cm}^3 \pm 35.7$ (standard deviation [SD]) after ablation to $755 \text{ cm}^3 \pm 52.4$ achieving a confirmed complete response in 60% [21].

Comparison with C-TACE

Dhanasekaran *et al.* in their comparative study of DC Bead chemoembolization versus conventional chemoembolization included 71 patients retrospectively, with 63.4% receiving DC Bead and 36.6% conventional chemoembolization [22]. The median survival was 610 (range: 351–868) and 284 days (range: 4–563; $p = 0.03$), respectively. In Okuda stage I, survival in the respective groups was 501 (range: 421–528) and 354 days (range: 148–560; $p = 0.02$). In Child–Pugh classes A and B, survival in the respective groups was 641 (range: 471–810) and 323 days (range: 161–485; $p = 0.002$). Median survival in patients with Cancer of Liver Italian Program 3 score in the respective groups was 469 (range: 358–581) and 373 days (range: 195–551; $p = 0.03$). These results show a clear advantage of the DC Bead embolization, while they report that grade 5 toxicity was similar between the two groups. However, this study is retrospective, nonrandomized and the number of patients in each group is small. In another retrospective study, longer time to progression (TTP) with DC Bead chemoembolization was found compared with conventional chemoembolization (11.7 and 7.6 months, respectively; $p = 0.018$) [23].

Sacco *et al.* randomly assigned 67 HCC patients not suitable for curative treatments between c-TACE and drug-eluting bead chemoembolization in a 1:1 ratio with primary end points of safety, toxicity and tumor response at 1 month [18]. The lesions treated had a mean size

Figure 1. Hepatocellular carcinoma in a 58-year-old male with hepatitis B virus liver cirrhosis. Hepatocellular carcinoma (A) before and (B) after one session of drug-eluting chemoembolization.

($\pm$ SD) of 41.6 mm $\pm$ 23.2 (range: 10–130 mm). Secondary end points were the number of repeated chemoembolization cycles, time to recurrence and local recurrence, time to radiologic progression, and survival. At 1 month, complete and partial tumor response rates were 70.6 and 29.4%, respectively, in the conventional chemoembolization group and 51.5 and 48.5%, respectively, in the DC Bead chemoembolization group. No differences were observed between groups in time to recurrence and local recurrence, radiologic progression, and survival. In this study the dose of doxorubicin was 50–100 mg for both groups. Median expected time to recurrence was 12.8 months after conventional and DC Bead chemoembolization ($p < 0.99$), whereas median expected times to local recurrence were 12.8 months after conventional chemoembolization and 8.9 months after DC Bead chemoembolization ($p < 0.46$). Radiologic progression was recorded in 17.9%, with mean expected times of 24.2 months after conventional chemoembolization and 15.6 months after DC Bead chemoembolization ($p < 0.64$; median not reached). The estimated 24-month cumulative survival rates were 83.6 and 86.8% after conventional chemoembolization and drug-eluting bead chemoembolization, respectively ($p < 0.96$). However, the number of patients was small in each group, follow-up was short, while it also has to be pointed out that it was an open-label design and finally that the majority of the patients (65%) had BCLC A disease.

The PRECISION V study is the largest prospective, blinded, randomized trial comparing DC Bead chemoembolization with conventional TACE. In this study 212 patients with Child–Pugh A/B cirrhosis and large and/or multinodular, unresectable, N0, M0 HCCs were randomized according to Child–Pugh status (A/B), performance status (ECOG 0/1), bilobar disease (yes/no) and prior curative treatment (yes/no) [24]. The primary end point was tumor response (EASL) at 6 months with independent blinded MRI evaluation. The drug-eluting bead group showed higher rates of complete response, objective response and disease control compared with the conventional chemoembolization group (27 vs 22%, 52 vs 44% and 63 vs 52%, respectively). Although superiority was not proved ($p = 0.11$) patients with more advanced disease (Child–Pugh B, ECOG 1, bilobar involvement and recurrent disease) showed a statistically significant benefit with drug-eluting beads over

conventional chemoembolization regarding objective response ($p = 0.038$).

Comparison with bland embolization

The principle in bland embolization is the induction of complete anoxia causing necrosis by the occlusion of the intratumoral vessels. Nicolini *et al.* compared the results of DC Bead chemoembolization (100–300 μ m) with epirubicin versus bland embolization with unloaded DC Bead of 100–300 μ m and examined the results of the explanted livers after transplantation [25]. The mean target lesion size ($\pm$ SD) was 32 $\pm$ 15.4 mm. Chemoembolization with drug-eluting beads achieved complete necrosis in 77% of lesions whereas bland embolization achieved complete necrosis in 27.2% of lesions. There was a significant difference between bland embolization and chemoembolization with DC Bead with regard to histologic necrosis favoring DC Bead chemoembolization ($p < 0.043$). No significant treatment-related complications were observed for either group. At the time of publication 15 patients were alive with no tumor recurrence.

In a prospective randomized trial comparing bland embolization with chemoembolization with DC Bead loaded with doxorubicin at 75 mg of doxorubicin per vial it was found that at 6 months a complete response was seen in 26.8% in the DC Bead chemoembolization group and in 14% in the bland embolization group; a partial response was achieved in 46.3 and 41.9% in the DC Bead chemoembolization and bland embolization groups, respectively [26]. Recurrences at 9 and 12 months were higher for bland embolization (78.3 vs 45.7%) at 12 months. TTP ($\pm$ SD) was longer for the DC Bead chemoembolization group (42.4 $\pm$ 9.5 and 36.2 $\pm$ 9.0 weeks), at a statistically significant level ($p = 0.008$). Overall this study showed that for microspheres of 100–300 μ m, chemoembolization with loaded DC Bead presents a better local response, fewer recurrences, and a longer TTP than bland embolization. However, this study had only 1-year follow-up and survival benefit cannot be assessed. Today, now that smaller drug-eluting beads are available additional studies are required to generate data for these embolic sizes.

Survival

Survival results are summarized in Table 1. Varela *et al.* after a median follow-up of 27.6 months reported 1- and 2-year survival of 92.5 and 88.9%, respectively [4]. Kettenbach *et al.*

reported an overall survival rate at 6 months of 93% [17]. There are two studies with long-term survival; Malagari *et al.* embolizing tumors of a mean diameter of 7.6 ± 2.1 cm, single or multifocal (36.4%) with a number of scheduled chemoembolizations every 6–8 weeks and then on demand found overall survival at 1, 2, 3, 4 and 5 years was 93.6, 83.8, 62.0, 41.0 and 22.5%, respectively (Table 1) [27]. Higher rates were achieved in Child–Pugh class A compared with Child–Pugh class B patients (95, 88.2, 61.7, 45 and 29.4% vs 91.5, 75, 50.7, 35.2 and 12.8%). Mean overall survival was 43.8 months (range: 1.2–64.8). Cumulative survival was better for Child–Pugh class A compared with Child–Pugh class B patients ($p = 0.029$). For patients with dominant lesions <5 cm 1-, 2-, 3-, 4- and 5-year survival rates were 100, 95.2, 71.4, 66.6 and 47.6% for Child–Pugh class A and 94.1, 88.2, 58.8, 41.2 and 23.5% for Child–Pugh class B patients, respectively. Regarding DC Bead treatment, multivariate analysis identified number of lesions ($p = 0.033$), lesion vascularity ($p < 0.0001$), initially achieved complete response ($p < 0.0001$), and objective response ($p = 0.046$) as significant and independent determinants of 5-year survival. Similar 5-year survival rates have been reported by Burrell *et al.* in a single-arm clinical series with drug-eluting bead-doxorubicin (DC Bead chemoembolization) that used larger beads (in all cases >300 μm) [28].

Safety profile studies

In the study of Sacco *et al.* major complications were 2.9% [18]. Postembolization syndrome occurred in 55.9% of patients with conventional TACE and in 63.6% after DC Bead chemoembolization. The same group reports a significant ($p < 0.0001$) increase ($\pm\text{SD}$) in ALT level 24 h after treatment (67 ± 53 IU vs 161 ± 167 IU). This increase was significantly ($p < 0.007$) greater after conventional chemoembolization compared with DC Bead chemoembolization. ALT levels had decreased at the time of hospital discharge (mean of $91 \text{ IU} \pm 85$ in the whole population). The same trend was observed for bilirubin levels: a significant ($p < 0.003$) increase versus pre-procedural values (mean: 1.1 ± 0.6 mg/dl) was observed 24 h after chemoembolization (mean: 1.5 ± 0.9 mg/dl), with progressive reduction at discharge (mean: 1.4 ± 0.7 mg/dl); however, no statistical differences were observed between

conventional and DC Bead chemoembolization. Finally, significant decreases in serum albumin levels ($p < 0.04$) and prothrombin activity ($p < 0.04$) were observed at discharge (mean: 3.5 ± 0.5 mg/dl and $73.6 \pm 11\%$, respectively) compared with baseline values (mean: 3.8 ± 0.5 mg/dl and $78.2 \pm 13\%$, respectively), with no difference between treatment arms.

Padia *et al.* retrospectively compared the safety profile of DC Bead 100–300 μm to 300–500 μm in 61 patients; they found that there was a significantly lower incidence of postembolization-syndrome and fatigue after treatment in the 100–300- μm group (8 and 36%) versus the 300–500- μm group (40 and 70%; 100–300- μm group $p = 0.011$; 300–500- μm group $p = 0.025$) [29]. Mean change in tumor size was similar between the two groups based on WHO and EASL criteria and similar rates of objective response, but there was a trend toward a higher incidence of EASL complete response with 100–300- μm beads versus 300–500- μm beads (59 vs 36%; $p = 0.114$). This study was not randomized and low doses of doxorubicin were used to load the beads (50 mg). Their results are of consequence for the toxicities but not for response since the data used for the study referred only to the first embolization each treatment group had. With regard to toxicities it is interesting to see that the patients had Child–Pugh class A disease (77.1%) and BCLC status was A in 43.6%, B in 20.5% and C in 35.9%. The early stage in the majority of the patients and the fact that 35.9% had BCLC C disease clearly affected their results regarding liver toxicity. However, they had no grade 5 complications and no irreversible liver failure. However, they reported ascites in 10% in the 300–500- μm group and 5.6% for the 100–300- μm group ($p = 0.611$). Encephalopathy occurred in 10% in the 300–500- μm group.

Malagari *et al.* also examined the toxicity of DC Bead 100–300 μm compared with larger sizes in a prospective study in sequential DC Bead chemoembolizations in 237 consecutive patients [30]. The main difference with the study of Padia *et al.* is that the results of sequential chemoembolizations were included in the analysis simulating in this way clinical reality (Padia *et al.* had included only the first embolization of the patients). Another difference with the study of Padia *et al.* is that Malagari *et al.* had included 48.9% Child–Pugh A patients and 51%

Child–Pugh B. In their study Malagari *et al.* reported a 30-day mortality of 1.26%. The incidence of grade 5 complications was 1.26%. Grade 4 complications that included irreversible liver failure and cholecystitis occurred in 5.48%. Grade 2 liver function deterioration developed in ten patients (4.2%). Cholecystitis/grade 2 and 4 incidents were observed in 3.6–5.06% across sessions (overall 5.48%). Postembolization syndrome grade 1 or 2 was observed in up to 86.5%; however, grade 2 was observed in 25–42.19% across treatments. Grade 1 pleural effusion was reported in 3.37% ranging from 1.8 to 3.7% across treatments (grade 3 in 0.42%). Grade 1 procedure-related laboratory pancreatitis was seen in 0.45%, and grade 2 gastrointestinal bleeding was seen in 0.84%. Procedure-associated skin erythema/grade 1 was seen in 0.84%. There was no correlation of liver failure or transient liver function deterioration with the diameter of the beads ($p = 0.25–0.37$ and $p = 0.14–0.89$, respectively). Stratifying with the diameter of the beads correlation values were: for cholecystitis $p = 0.11–0.96$ across treatments, postembolization syndrome $p = 0.35–0.83$, temporary/grade 1 elevation of liver enzymes $p = 0.002–0.0001$, and bilirubin $p = 0.04–0.99$. These results showed the safety of beads sized 100–300 μm . Further studies examining the safety of beads below 100 μm in diameter have yet to be performed.

Poon *et al.* reported a treatment-related complication rate of 11.4%. There was no treatment-related death [5]. Reyes *et al.* reported toxicities ($n = 2$; grade 3) including enteritis and hypoalbuminemia [14]. Serious adverse events included pancreatitis (recovered) and gastric enteritis (recovered). Kettenbach *et al.* reported a 30-day mortality of all embolization procedures of 1% and major adverse events in 2% of the procedures (temporary liver failure and acute cholecystitis) [17]. Varela *et al.* observed postembolization syndrome in 41 and 18% of treated patients after the first and second treatment, respectively [4]. There were two cases of liver abscesses – one of them fatal. Spontaneous liver rupture after treatment with DC Bead has also been reported [31]. Recchia *et al.* in a retrospective analysis found DC Bead chemoembolization safer than lipiodol-based conventional chemoembolization [32].

In the Precision V randomized trial comparing DC Bead chemoembolization to conventional chemoembolization the former was associated with improved tolerability, with a significant reduction in serious liver toxicity ($p < 0.001$) and

a significantly lower rate of doxorubicin-related side effects ($p = 0.0001$) [24]. In the same study there was no statistically significant difference regarding serious adverse events within 30 days of the embolization. Observed postprocedural increases in the liver enzymes AST and ALT were significantly less in the DC Bead group than in the conventional chemoembolization group. The mean maximum ALT increase in the DC Bead group was 50% less than in the conventional chemoembolization group (95% CI: 39–65; $p < 0.001$) and 41% less with respect to AST (95% CI: 46–76; $p < 0.001$). Cardiac function was maintained in the DC Bead group, whereas there was deterioration in left ventricular ejection fraction in the conventional chemoembolization group. In addition, in this trial the incidence of alopecia seemed to be lower after chemoembolization with DC Bead (2.2%) compared with conventional chemoembolization (19.4%) [24].

Regarding portal vein embolization, segmental embolization with drug-eluting beads is safe in single-branch thrombosis, however, for main trunk thrombosis a future comparison with the results of radioembolization is necessary.

Conclusion

DC Bead entered into clinical practice in 2004. Since then it has been widely used in clinical practice with good results. The data on superiority over conventional chemoembolization to date are weak and more studies are necessary. However, long-term survival is clearly high in large single-arm series challenging the results of conventional chemoembolization. Toxicity is low and the procedure is better tolerated compared with conventional chemoembolization, particularly in terms of postembolization syndrome and doxorubicin-related toxicity. The use of the smaller calibers has proven to be safe and more effective than the larger sizes and the results of DC Bead 70–150 μm in HCC are currently being evaluated.

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