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Chemoembolization of hepatocellular carcinoma with HepaSphere™

Hepatic Oncology

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Practice points

- HepaSphere™ is a thoroughly examined embolic material/loadable device available in four different sizes. *In vitro* experiments, animal studies and clinical trials, give insight on its mechanics and pharmacokinetics.
- The device can be used as a bland embolic but is mostly loaded with chemotherapeutics with a positive charge, mainly doxorubicin. The safety profile is satisfactory with no grade 5 or 4 complications.
- Higher rates of local response are achieved with the smaller diameters of HepaSphere in which achieve improved rates of midterm survival for both intermediate and advanced hepatocellular carcinoma.
- Prospective randomized studies with survival as an end point comparing with other drug-eluting embolics are necessary for the future.

SUMMARY This review discusses the current data on Hepasphere™ in the treatment of hepatocellular carcinoma. HepaSphere is a drug-loadable microsphere that can be bound with doxorubicin, epirubicin, cisplatin or oxaliplatin. *In vitro* and *in vivo* studies confirm lower systemic exposure to the drug and fewer systemic doxorubicin-related side effects. Studies suggest that this technique is better tolerated than conventional lipiodol-based chemoembolization (c-TACE). In intermediate and early stage hepatocellular carcinoma – nonresponsive to curative treatments – complete response and partial response rates range from 22.2 to 48% and 43.7 to 51%, respectively. Studies with survival as an end-point are needed and head-to-head comparisons with other drug-eluting beads are necessary.

KEYWORDS:

- conventional chemoembolization
- drug-eluting chemoembolization
- hepatocellular carcinoma

Hepatocellular carcinoma (HCC) represents the sixth most common neoplasm, while ranking third among deaths related to cancer [1]. At present, patients with HCC are clinically managed according to the Barcelona Clinic Liver Cancer (BCLC) classification [2]. According to this classification system, patients with intermediate stage HCC are treated with trans-arterial chemoembolization (TACE) [1–6]. Further advances in classification include locally advanced HCC traditionally treated with systemic medication [1,5]. There is level 1 evidence that TACE improves survival of patients with intermediate HCC [3,4]. Conventional TACE (c-TACE) is a technique utilizing the selective injection of a chemotherapeutic regime which is emulsified in lipiodol (viscous oily carrier which persists in tumor for prolonged period) followed by particle embolization of tumoral feeding arteries. Due to the fact that lipiodol cannot gradually release and contain the chemotherapeutic regime within the

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tumor, there are chemotherapy-related systemic side effects [6]. Trans-arterial chemoembolization with microspheres loaded with the chemotherapeutic (drug-eluting chemoembolization) seems to overcome this with similarly high efficacy concerning tumor control when compared with c-TACE [6]. Drug-eluting microspheres have been introduced in clinical practice since 2004, and provide a more standardized procedure compared with conventional chemoembolization (c-TACE) [6,7]. *In vitro* and *in vivo* animal studies have shown that chemotherapeutic-eluting microspheres have favorable loading and release curves that allow continuous release of the chemotherapeutic in the tumor, while systemic exposure to the chemotherapeutic is minimal [8,9,10]. Today, there are three microsphere devices that can be used in clinical practice including DC Bead™ (Biocompatibles, BTG; HepaSphere/QuadrSphere™, (Biosphere) and Tandem™ (Celonova). Of them, only HepaSphere™ and DC Bead are CE marked for the indication of drug delivery. Tandem is available in 40, 75, 100 μm without significant increase in diameter after loading. No embolic is US FDA approved for this indication. In this review, research results of HepaSphere/QuadrSphere are presented. Unlike the other microspheres HepaSphere is the only loadable microsphere that is more elastic and has a better contact with the vessel wall of the tumor causing necrosis [9,10,11,12]. HepaSphere loading and elution occurs in the same time window for the two smaller available sizes ranging from 15 min to 2 h and 1 h to 14 days, respectively [13]. Animal studies with HepaSphere have shown that bland HepaSphere presents lower cancer cell killing effect compared with HepaSphere loaded with doxorubicin [14]. Clinical series have shown minimal side effects without grade 4 or 5 complications while local response is high and mid-term survival rates are comparable to c-TACE [15,16]. Currently, there is no level 1 evidence that HepaSphere prolongs overall survival compared with c-TACE. The Hi Quality study has been designed to answer this very important question and its results will be released in about 2 years [17].

The use of such microspheres reduces the related risk of systemic effects by having low plasma levels of the chemotherapeutic agent, due to their ability to prolong contact time between cancer cells and chemotherapeutic agents, avoiding hepatic microcirculation damage [6,7,20,21].

Liposomal doxorubicin combined with local ablation and molecular therapies are attractive alternative tumor-targeted treatments but there is ongoing research and their clinical applications yet remain to be evaluated [22,23].

In this review, we will describe HepaSphere™ which is a loadable embolic device-microsphere, its action – mechanism, guidelines for use in HCC and details including local response, survival and safety issues.

Mechanism of action, pharmacokinetics

HepaSphere in Europe or QuadraSphere™ in the USA (Biosphere Medical, Roissy, France) are superabsorbent polymer microspheres (SAP-MS) which are loaded with the anticancer drug and release it in a controlled and prolonged manner inside the tumor with low systemic toxic exposure [20–22]. SAP comprises sodium acrylate and vinyl alcohol copolymer that has the ability to absorb fluids and swells within minutes in a predictable manner [20,22,23]. HepaSphere is intended to conform to the shape of tortuous and narrow vessels and has been used for bland embolization with positive results due to the products' gel-like constitution [20,21].

HepaSphere microspheres are provided in a 'dry state' and upon exposure to aqueous-based medium, they swell by a predictable percentage of size when absorbing fluid [8,9,12,23]. This swelling from the dry form is governed by the porous nature of the superabsorbent polymer which results in the formation of highly compliant and flexible microsphere [8–10,12,24]. HepaSphere microspheres expand up to 4x their volume upon exposure to a solution isotonic to serum plasma; they possess a negative ionic charge and provide a spherical particle for drug binding to positively charged molecules such as anthracyclines via electrostatic interactions [8–10,12,24]. In contrast with DC Bead™, in which the chemotherapeutic binds in the surface, in HepaSphere the binding of doxorubicin is throughout the volume of the sphere. The size prediction during fluid absorption and loading, ranges from 145 to 213 (148 ± 45) μm for the HepaSphere 30–60 μm (dry form), 200 to 300–400 μm (for 50 to 100 μm dry microspheres) to 600–800 μm (for 150 to 200 μm dry microspheres) [8,9,20]. Delivery of the swollen/loaded microspheres can be performed through the majority of currently available microcatheters [12]; the pliable swollen microspheres are able to adapt to the morphology of

the vascular lumen warranting its persistent occlusion [8–10,12,24].

Reports in the literature strongly suggest a two-step loading process both for smaller (30 to 60 μm) and larger HepaSphere [8,10,12]. The two-step loading method seems to avoid microsphere aggregation and fragmentation (as observed by Jordan *et al.*) [15] and can also result in more favorable elution [8,10,12,20,24]. In addition, the sizes of the particle and elution kinetics are influenced by the type of solvent in which the lyophilized doxorubicin is dissolved [25–27]. The use of normal saline (instead of water for injection that is needed for DC Bead) in combination to the two-step loading method are required to allow maximum binding of doxorubicin in both smaller (30 to 60 μm) and larger diameter of HepaSphere (as shown by Liu *et al.*) [24]. Liu *et al.* also report an unstable condition if HepaSphere is reconstituted with doxorubicin dissolved in hypertonic saline [24]. This study also shows that HepaSphere demonstrates a better doxorubicin loading and release profile if they are first reconstituted in doxorubicin dissolved with saline solution in two steps instead of saline alone [16–18]. Loading and release mechanics are optimal when the quantity of doxorubicin ranges between 50 and 75 mg per HepaSphere vial and not higher [24].

In their *in vitro* study, Kos *et al.* loaded HepaSphere 30–60 μm and 50–100 μm with doxorubicin from a dry lyophilized state [8] using two different procedures. One with pre-hydration of the microspheres with normal saline for 10 min (one-step technique) and a second procedure in two steps, in other words, one vial of dry HepaSphere hydrated with 10 ml of a normal saline solution of doxorubicin for 10 min (first step) before adding the rest 10 ml of doxorubicin solution to the vial to allow further loading (second step). They showed that loading and elution occurred in the same time window for both sizes: 15 min to 2 h and 1 h to 14 days respectively. However, HepaSphere 30–60 μm loaded faster in the first 15 min with the two-step technique and presented higher cumulative elution at 14 days (19.3 vs 17.83 mg, one step vs two-step; $p = 0.02$). In clinical practice, after loading further dilution with contrast and saline before administration is of paramount importance to avoid proximal embolization and early stasis, (notably the final volume should reach 30 cc per vial of loaded HepaSphere) [20].

***In vitro* pharmacodynamics & mechanics; animal studies**

In vitro experiments [9,24,25] allow kinetic studies but only partially provide an understanding of what happens in the more complex physiological environment. Animal studies are more representative of *in vivo* kinetics and allow target tissue examination [10,11].

The mechanical properties of HepaSphere before loading with doxorubicin (as a bland embolic) have been assessed by Bilbao *et al.* [11] by embolizing 124 kidneys in pigs. The authors compared the unloaded HepaSphere with currently available nonloadable embolics and found that the mean deformation for HepaSphere was $26\% \pm 19.7$ (the highest deformation index compared with the nonloadable microspheres with the exception of Contour). In addition, in their study using microscopy they observed that HepaSphere microspheres were found to cause distal embolization (into the interlobar and arciform arteries), producing complete occlusion of the arterial lumen with a minimal inflammatory reaction, mainly composed by giant cells and neutrophils up to 4 weeks [11]. Although the other embolics in this study, had lower deformation indices (however at a nonsignificant level) their study demonstrated that the compressibility of HepaSphere 50–100 μm (dry diameter) was $26\% \pm 19.7$. Similar findings were recorded by de Luis *et al.* for HepaSphere dry-state diameters of 50–100 and 150–200 μm ; [10] Notably, they report a mean *in vivo* deformation of $17.1 \pm 12.3\%$, while the final size of the microspheres expressed as the largest diameter (mean $\pm$ SD) measured 4 weeks postembolization was $230.2 \pm 62.5 \mu\text{m}$ for the 50–100 μm dry-state diameter and $314.4 \pm 71 \mu\text{m}$ for the 150–200 μm dry-state microspheres. The distal embolization was also documented in the animal study of Dinca *J. Vasc. Interv. Radiol.* [28] in which HepaSphere 30–60 μm provided a more distal occlusion and more dense distribution of microspheres (more embolized vessels per volume of tissue) in the embolized territory than HepaSphere 50–100 μm – a fact that suggests that there may be no significant conglomeration of the smaller microspheres and therefore embolization level depends on the diameter of the embolic.

Lee *et al.* in a Vx-2 tumor model in rabbits showed 82–94% loading of doxorubicin within 2 h and 6% release within the first 6 h [14]. In their study, the peak intratumoral concentration

of doxorubicin was seen at 3 days and remained at measurable levels up to 7 days (the study's end point). During the first 3 days intratumoral concentrations were 40.632–50.052 nM/g, decreasing to 23.1372 nM/g at day 7. Peak plasma doxorubicin concentration was 0.1041 μ M that was seen at 20 min after treatment [14]. In the same study they compared necrosis achieved with doxorubicin-loaded HepaSphere to unloaded HepaSphere and they found that drug-loaded HepaSphere caused more necrosis than the bland HepaSphere (notably, 20 and 30% more at 3 and 7 days postembolization, respectively).

Doxorubicin loading reaches 100% and requires a mean of 2.2 h to reach 75% of the plateau value for the eluted drug [9]. Doxorubicin release profile of HepaSphere in the study of Jordan *et al.* [9] was similar to DC Bead HepaSphere with similar $t_{75\%}$ values. Measurements obtained after 1 week extracted 27% $\pm$ 2 for DC Bead and 18% $\pm$ 7 for HepaSphere from the microspheres. This partial drug elution may explain the low systemic exposure to doxorubicin but may also be accountable for suboptimal anticancer function. The final levels of eluted drug were lower for HepaSphere with a statistically significant difference compared with DC Bead [9]. HepaSphere 30–60 μ m reaches a diameter of 148 $\pm$ 45 μ m after loading [27], while deformation factor decreases after loading (7.9 $\pm$ 7.3 before and 5.6 $\pm$ 5.4 after). HepaSphere 50–100 μ m enlarges in solution reaching a diameter of 222.8 $\pm$ 66.9 [10]. The microspheres acquire their final size when they reach osmolarity equilibrium within the vessel and surrounding tissue. This reason accounts for the differences between size measurements *in vitro* and *in vivo*. Jordan *et al.* found that loaded HepaSphere are more elastic compared with DC Bead (Biocompatibles, BTG), with a mean value of 11.5 $\pm$ 0.9 for HepaSphere and 15.3 $\pm$ 3.4 for DC Bead [9]. Both microspheres harden after doxorubicin loading increasing the elastic modulus by a factor (x fold-increase) of 2.8 for DC Bead and 7.1 for HepaSphere. This elastic property allows better contact with the endothelium leaving no empty spaces and enables diffusion of doxorubicin into the tumor [18]. It is not clear if this elasticity can also cause clogging in vessel bifurcations. In the *in vitro* comparison by Jordan *et al.* [9], doxorubicin-loaded HepaSphere formed aggregates while DC Beads tended to remain separate. However, it is not clear if in this particular study HepaSphere

was loaded with doxorubicin solution in saline, or water for injection and did not follow the two-step loading technique. While the first (normal saline) is appropriate for HepaSphere the second affects drug binding and microsphere mechanics. By contrast, de Luis *et al.* (in their *in vivo* study in animal kidneys with HepaSphere 50–100 μ m) report that it maintains its spherical shape *in vivo* for 4 weeks after embolization [12]. Gupta *et al.* embolizing with HepaSphere loaded with doxorubicin in a rabbit liver tumor model compared with two control arms of hepatic arterial infusion (HAI) and c-TACE [13]. They revealed that the C_{max} in plasma was lower with the loaded HepaSphere (309.9 vs 673.4 ng/ml), while measurable levels of doxorubicin were still in the tumor up to 14 days [13]. The highest level of doxorubicin in the tumor (196.5 $\pm$ 312.8 ng/mg) was measured in the HepaSphere group at 1 day postembolization and was higher than the other techniques at a statistically significant level even at 3 and 7 days (p = 0.0065 and p = 0.023, respectively). Intratumoral doxorubicin fluorescence was detected at all time points (2, 3, 7 days) in the HepaSphere group but only at 1 day in the c-TACE group. As measured by doxorubicin fluorescence in the same study doxorubicin extended up to 400–1600 μ m into the surrounding tumor tissue [13]. Direct comparisons of DC Bead and HepaSphere regarding spatial doxorubicin concentration have not been published yet. The findings of Gupta *et al.* [13] show that HepaSphere chemoembolization results in sustained release of doxorubicin in the target tumor with significantly lower levels of doxorubicin in plasma compared with c-TACE. However, they did not quantify the fluorescence intensity and therefore they do not allow measurements of drug concentration gradient in the target tumor. Overall, for all drug-eluting microspheres, doxorubicin binding is favorable but release is to a certain point limited after the first 6 h.

Effective drug delivery for cisplatin is also feasible; Maeda *et al.* studied *in vitro* cisplatin-loaded HepaSphere in ioxaglic and iohexol contrast and found that the elution profile was similar with cisplatin fractions of 15, 40, 70 and 95% at 1, 3, 6 and 24 h, respectively [25]. In the same study, it was shown that when mixed with iohexol HepaSphere can be loaded with ten-times larger dose of cisplatin while the microsphere expands twice as large with ioxaglic acid.

Comparison studies to Tandem™, a tightly calibrated loadable microsphere of 40, 75 and 100 μm in diameter are not available yet.

Clinical evidence of pharmacokinetics

A randomized Phase II trial enrolled 30 HCC patients with different BCLC stages and randomly assigned them to control group (c-TACE) or drug-eluting chemoembolization with HepaSphere [15]. This study reported statistically significant lower C_{max} of doxorubicin and smaller AUC in the HepaSphere arm compared with controls (mean C_{max} 495 ± 293.9 ng/ml, mean AUC 69.7 ± 26.9 ng/ml min vs mean C_{max} 1928 ± 560.8 ng/ml, mean AUC 165 ± 32.3 ng/ml/min; $p < 0.001$) and they reported no grade 3, 4 or 5 side effects in the HepaSphere group [15]. Of importance is that the HepaSphere group presented less systemic toxicity (notably bone marrow toxicity and hair loss) and less liver toxicity in terms of liver transaminases compared with the c-TACE group. It is worth mentioning that in this study the dose of doxorubicin that was administered to the c-TACE group was similar to the HepaSphere group but much higher (75–150 mg) than the usual dose of 50 mg that is common with c-TACE and this fact bias the results.

Today pharmacokinetic results of doxorubicin-loaded HepaSphere 30–60 μm in human clinical trials are available; in a recent study 45 patients with HCC measurements of doxorubicin levels in plasma were obtained at 5, 20, 40, 60, 120 min at 6, 24 and 48 h and at 7 days [20]. The plasma values of doxorubicin presented a peak (C_{max}) in plasma at 5-min postembolization that was considerably lower compared with the C_{max} that was measured for c-TACE with the same amount of doxorubicin (control group); (C_{max} 83.9 ± 32.1 vs 761.3 ± 58.8 ng/ml). The AUC was 35.195 ± 27.873 and $103,960 \pm 16.652$ (ng $\times$ min)/ml for HepaSphere and c-TACE, respectively. Levels of doxorubicin in the plasma were consistently lower in the HepaSphere 30–60 μm group at all time points. A similar pharmacokinetic study was performed by Varela *et al.* with similar distribution using DC Bead [7]. A criticism applicable to both these studies is that they compared drug-eluting plasma kinetic of doxorubicin with c-TACE that was performed with 150 mg of doxorubicin – a dose that is very high for c-TACE that universally does not exceed 50–60 mg. This was clearly done to facilitate comparison; however

it created a bias for c-TACE and future studies are necessary.

A head-to-head study comparing pharmacokinetic profile of HepaSphere versus DC Bead loaded with epirubicin was recently published by Sottani *et al.* [29]; in their study, they found low peak serum epirubicin concentrations in serum with greater drug exposure for the DC Bead group ($p < 0.05$). The peak concentration was measured at 5 min postinjection in both groups – a finding that was also observed in the pharmacokinetic study in plasma in the study with HepaSphere 30–60 μm of Malagari *et al.* [20]. Notably, in Sottani *et al.* study, the median C_{max} of epirubicin in serum was 73.5 ± 24.5 ng/ml for DC Bead and 33.9 ± 11.0 ng/ml for HepaSphere. The dose-normalized C_{max} values were 1.37 ± 0.45 versus 0.44 ± 0.41 in the DC Bead and HepaSphere, respectively. The median dose-normalized AUCs were similar (248.7 ± 65.1 ng h/ml vs 179.0 ± 141.8 ng h/ml in the DC Bead and HepaSphere groups, respectively). The median half-life of epirubicin was 8.7 ± 5.6 h and 8.4 ± 5.3 h in DC Bead and HepaSphere Microsphere™ TACE, respectively. The results of Sottani *et al.* are in accordance with the results of pharmacokinetic study with DC Bead in humans [7], and show the low systemic exposure to the chemotherapeutic with both embolics but there are no data beyond 24 h.

The safety profile of chemoembolization with drug-eluting microspheres includes less systemic toxicity from doxorubicin (constitutional symptoms such as fatigue, hair loss, myelosuppression, myocardial toxicity) and is explained by the low levels of plasma doxorubicin that is due to the slow release of the drug from the microspheres into the tumor and has also been consistently found in all kinetic studies with DC Bead [6,7,19].

Poggi *et al.* [30] examined the pharmacodynamics of oxaliplatin (that is occasionally used in HCC). Metastatic liver disease was included in their study, they used HepaSphere loaded with oxaliplatin and performed an *in vitro* and *in vivo* evaluation and found that the loading time was 10–15 min (with 50 mg oxaliplatin) diluted with 5 ml nonionic contrast [30]. They measured tissue levels of oxaliplatin in the lesion and surrounding parenchyma (by liver biopsy) as well as plasma concentrations (P_{max} , AUC and time taken to obtain these levels- T_{max}). They also compared with the levels of controls that received systemic chemotherapy. This study revealed that C_{max} in plasma was 3 $\times$ higher in the systemic

chemotherapy group, T_{max} was reached earlier in the chemoembolization group and AUC was lower in the chemoembolization group (2.693 ng/ml min $\pm$ 127 vs 1.483 ng/ml min $\pm$ 838; $p = 0.028$). In the liver, median concentration ratio was 18.53 (1.27–71.2) in the chemoembolization group and 1.10 (1.08–1.38) in patients treated by systemic chemotherapy ($p = 0.014$) [30]. This study highlights the issues of assessing the pharmacokinetics of chemoembolization in humans, requiring a highly invasive procedure that cannot be reproduced routinely.

Indications, guidelines & technical recommendations

According to the BCLC staging system, chemoembolization is indicated for intermediate HCC (BCLC B disease) that is not suitable for curative treatments in Child-Pugh A or B cirrhotics with performance status 0–1 [1,2,5]. Guidelines for chemoembolization with DC Bead have been published by a panel of experts [31] but not yet released for HepaSphere. Drug-eluting microspheres can also be used in BCLC stage A patients that are poor surgical candidates [31], and those who have lesions treatable with local ablation with respect to size but are in difficult areas to access. Such areas include the liver dome – in contact to the diaphragm or pericardium –, areas in contact with the intrahepatic portion of the inferior vena cava, and areas located deep into the liver hilum within 1 cm from the biliary tree and portal vein. Finally, similar to c-TACE chemoembolization with drug eluting microspheres can be used as a bridge to transplantation. A recent study comparing explanted livers in patients that had undergone transplantation showed that bridge for transplantation was equally effective in the drug eluting bead arm and the c-TACE arm [16]. Notably, complete necrosis in their series was achieved in 50.9 and 57.1% of c-TACE and drug-eluting bead arm, respectively while at least 50% necrosis was evident in approximately three-fourths of patients in both groups. Dropout from the transplant list was equal in both groups.

The safety and efficacy of drug eluting beads in advanced HCC has been studied by Kalva *et al.* [32], who observed that patients with ECOG PS ≤ 1 demonstrated a median survival of 17.7 months compared with 5.6 months for patients with ECOG PS > 1 ($p = 0.025$). Bland embolization with microspheres below 120 μ m

has been used alternatively for the same indications in some centers with comparable success rates [18]. Level 1 evidence supports the use of chemoembolization for early and intermediate HCC while level 2 evidence supports the use of radioembolization for the treatment of intermediate to advanced HCC [33,34]. A comparison study of radioembolization with drug eluting beads has shown no significant difference in progression-free survival, overall survival and time to progression [35]. Radioembolization is US FDA approved for the treatment of HCC and is preferably used in patients with portal thrombosis, or biliary obstruction [33,34]. Cost-effectiveness studies of radioembolization versus c-TACE indicate that the former may be justified for BCLC-C disease but not for BCLC-A disease [36]. For BCLC-B disease more randomized studies comparing drug eluting beads and radioembolization are needed. The liver function parameters which govern a safe and effective drug eluting chemoembolization are the same as those for c-TACE (bilirubin <3 mg/dl; aspartate amino transferase (AST) and alanine amino transferase (ALT) levels <270 IU/ml) [18,29]. Contraindications include nontreatable arteriovenous shunts, extrahepatic disease and portal thrombosis (main trunk) [18].

Preprocedural set-up includes pretreatment imaging with contrast-enhanced computed tomography scan (triple phase: arterial, portal, delayed) or magnetic resonance imaging with sequences post gadolinium injection and diffusion [18]. Antibiotic prophylaxis is optional; prolonged antibiotic prophylaxis prior and postchemoembolization is indicated in patients with violated sphincter of Oddi [18,19].

The two-step loading with a solution of lyophilized doxorubicin in normal saline is the optimal to maintain the best loading and release profile [8,24,20]. The long loading time required for all existing drug eluting microspheres comprises a disadvantage comparing with c-TACE that requires only a few minutes for the preparation of the lipiodol emulsion.

Seki and Hori used cisplatin solution at high concentrations (1.4 mg/ml) that was reported to contain 6.6 mg/ml in iohexol 300 mgI/ml [27]. Notably at these concentrations loading time was 20 min for the microspheres to expand and absorb the cisplatin sufficiently (HepaSphere 25 mg/vial loaded with 25 mg cisplatin powder dissolved in 5 ml of nonionic contrast medium 350 mgI/ml) [27].

The end point of embolization for drug-eluting microsphere studies is complete disappearance or considerable decrease of the tumor-staining at selective or superselective angiography after the embolization [20,37,38]. Microcatheter use is imperative for segmental and subsegmental embolization but the microcatheter should not be wedged to allow blood flow to drive the microspheres into the tumor microcirculation. Local pooling forming intratumoral contrast staining resembling contrast lakes or extravasation is sometimes observed [20]. This phenomenon has been attributed to intratumoral hemorrhage by some experts and needs additional bland embolization to complete stasis.

Local response, survival & safety profile

Local response is evaluated 1 month post the embolization session with dynamic MRI or multidetector CT (arterial, portal and delayed phase post intravenous injection of contrast medium) [18,30,31]. Local response results concerning HepaSphere are summarized in **Table 1**.

Seki *J. Vasc. Interv. Radiol.* [26] using larger HepaSphere loaded with epirubicin achieved complete response in 12.6% and partial response in 43.7%. An Italian multicenter study enrolled 50 patients who underwent chemoembolization with HepaSphere 50–100 µm loaded with doxorubicin or epirubicin in an ‘on demand’ schedule of chemoembolization [38]; They embolized HCC of a mean diameter of 42.5 mm and tumor response was evaluated according to the WHO criteria as modified by the European Association of the study of the Liver (EASL). The technique

was well tolerated with a complete response of 48%, partial response in 36% and stable disease in 16% after the first session [38]. After repeat embolization at 6 months complete response was seen in 51.6%, partial response in 25.8% and progressive disease in 22.6%. In their study, they report a temporary increase of liver enzymes postembolization, 18% postembolization syndrome and 3% minor periprocedural complications [38]. Pancreatitis was reported in 2% in this study. The limitation of this study is that survival was not evaluated.

Dekervel *et al.* enrolled 64 patients who underwent 144 chemoembolization sessions with HepaSphere loaded with doxorubicin [21]. Objective response of 67.5% was reported after the first session and 44.5 and 25% after the second and third sessions as defined by MRI with mRECIST criteria. During the 14 months of follow up 45% of patients died with a median overall and transplant-free survival of 20.5 and 18 months, respectively [21]. Mild postembolization syndrome was observed in 85.9% with no grade 4 serious adverse events. In this study, hepatic artery occlusion was reported in 1.5%, and reversible liver failure including increase of bilirubin levels was observed in 3.1% [21]. Overall, in this study the follow-up time was too short and the death rate at the first year is too high.

Van Malenstein *et al.* [15] in their randomized comparison of Hepasphere of 50–100 µm versus c-TACE found that the two groups had no statistical significance difference in terms of local response. Therefore, in their study the

Table 1. Local response and survival after treatment of hepatocellular carcinoma patients with HepaSphere™.

Study (year)	Patient number	Local response (%)	Survival (%)	Comments	Ref.
Grosso <i>et al.</i> (2008)	50	CR: 51.6% PR: 25.8% PD: 22.6%	NA	Used both doxorubicin- and epirubicin-loaded HepaSphere	[18]
Seki <i>et al.</i> (2011)	135	Objective tumor response rate was 52.6%	At 12 months 73.7% At 24 months 59.0%	Used epirubicin-loaded HepaSphere	[25]
Von Malenstein <i>et al.</i> (2011)	30	SD: 77% PD: 23%	NA	Randomized Phase II trial	[15]
Dekervel <i>et al.</i> (2014)	64	Objective response rates 67.5% (after first), 44.5% (after second) and 25% (after third) DEB TACE, with disease control rates of 80, 74.5 and 46%.	Overall survival 20.5 months Transplant-free survival 18 months	Prospective study using doxorubicin-loaded HepaSphere	[21]
Malagari <i>et al.</i> (2014)	45	Overall objective response (CR + PR) 68.9%	At 12 months 100%	Prospective study using doxorubicin-loaded HepaSphere 30 to 60 µm	[20]

CR: Complete response; DEB TACE: Drug eluting bead TACE; NA: Not applicable; PD: Progressive disease; PR: Partial response; SD: Stable disease.

only statistical significance was the lower rate of complication in the HepaSphere group.

Malagari *et al.* used 30 to 60 μm HepaSphere in 45 HCC patients who were escalated by lesion, dose and frequency of re-embolization [20]. This prospective study reports that chemoembolization with doxorubicin-loaded HepaSphere is well tolerated with an acceptable safety profile and no 30-day mortality or grade 5 complications [20]. Response rates were assessed with mRECIST; including all dosage levels complete response was seen in 17.8% reaching 22.2% for the target lesion. Overall partial response was observed in 51.1%, stable disease in 20% and progressive disease in 11.11% of the 45 patients that were enrolled. Survival at 1 year was 100% [20]. The authors infer that the higher flexibility of 30 to 60 μm HepaSphere allowed deeper penetration into the tumor vasculature with the objective local response reaching 68.9% (with an intended 50–100 mg doxorubicin dosage) with no damage to adjacent healthy tissue as demonstrated by aspartate transaminase (AST) and alanine transaminase (ALT) levels [20].

Seki *et al.* used 50 to 100 μm dry microspheres of the same composition and nature as HepaSphere which were prepared in a laboratory for limited use and were loaded with 25–30 mg of epirubicin [26]. This study was performed in 135 patients with advanced HCC, refractory to c-TACE, who had intrahepatic metastases or remarkably increased tumor markers [26]. At 6 months 3.5% achieved complete response, 36.5% partial response, 17.6% stable disease and 42.4% progressive disease. The overall 1- and 2-year survival rates in this study were 73.7 and 59.0%, respectively. Adverse events included 31.8% incidence of postembolization syndrome of grade 1 or 2, temporary elevation of liver enzymes of grade 1 or 2, temporary effects on white blood cells, platelets and red cell series and minimal damage to the hepatic artery [26]. Hepatic artery damage was reported in 9.1% in this series. Their study shows that disease control can be achieved even in advanced stages but their results are not easily reproducible.

Osuga *et al.* assessed the embolic effect of HepaSphere in patients with HCC that underwent surgery and at histology found the HepaSphere inside and at the margin of the tumors without accumulation in the hepatic sinusoids, peribiliary plexus, portal vein and hepatic vein [39]. Their results show that

HepaSphere does not penetrate as deep as the lipiodol emulsion.

Cisplatin powder-loaded HepaSphere of diameters 50–10 μm was used for the embolization of patients with HCC refractory to epirubicin-loaded microspheres in a recent study by Seki and Hori combined with 5-FU using 2.4 F microcatheters [27]. Switching from epirubicin to cisplatin in their study resulted in 3.5% complete response, 36.5% partial response, 17.6% stable disease and 42.4% progressive disease at 6 months, with median overall survival and time to treatment failure 13.3 and 7.2 months, respectively [27].

Overall, the safety profile of doxorubicin-eluting microspheres including HepaSphere and DC Bead, show less liver and systemic toxicity compared with c-TACE [6,15,20,21,31,38,39]. There are no safety data published for Tandem yet. Treatment related 30-day mortality is 0–1%, and inclusively adverse events range from 2 to 11.4% [15,20,21,29,37–39]. The most common adverse event in HepaSphere chemoembolization in HCC is postembolization syndrome (PES) occurring in <17.8% in Seki *et al.* series of grade 1 or 2 [20], and in 18% in Grosso *et al.* series [38]. PES was observed in 18.54% in a recent study with HepaSphere 30–60 μm [20]. Similar rates of PES have been reported in studies with DC Bead ranging from 25 to 42% [40] and in 24.7% in the Precision V study with DC Bead [6,19], this is considerably less than in c-TACE. Cholecystitis is reported in 0–3.1% in studies with HepaSphere [20,21]. High levels of cholecystitis had been reported in a DC Bead study ranging between 3.6 and 5.06% across sessions [41] but all of them were an ultrasound diagnosis and none of them were treated invasively. Other biliary complications have not been reported with HepaSphere yet. Abscess has not been reported in HepaSphere yet but it has developed with DC Bead in 1.4 to 3.7% [6,7,37,40]. Irreversible liver failure has been reported with DC Bead in 1.68 to 2.85% [6,19,37,40], while transient increase in liver enzymes has been reported in 4.2% in DC Bead [6,19,37,40].

Recurrence rates of chemoembolization with doxorubicin-loaded HepaSphere have not been reported yet. Long-term recurrence rates have been published with DC Bead; Nicolini *et al.* in their comparison study of drug eluting bead chemoembolization to c-TACE report 3-year recurrence-free survival higher in the drug-eluting

bead arm compared with c-TACE (87.4 vs 61.5%, $p = 0.0493$) [42]. A long-term recurrence analysis was published by Malagari *et al.* where they report recurrence-free survival at 5 years of 8.9%, median time of initial recurrence from baseline treatment of 18 months [40]. In the same study, it was found that lesion morphology displayed significance for recurrence-free survival ($p = 0.014\%$). Reported local recurrence rates for c-TACE at 1 and 3 years post baseline embolization include: 20 to 53.2% [43,44], 50.2 to 71.7% [43] for segmental embolizations that rise to 58 to 78% for nonsegmental embolization [43].

Conclusion

Today, there are abundant data about the mechanics and pharmacokinetics of HepaSphere loaded with doxorubicin *in vitro*, in animals and in clinical series. Chemoembolization using SAP microspheres (HepaSphere) loaded with doxorubicin, epirubicin, cisplatin or oxaliplatin seems to be a safe and efficient technique for intermediate or advanced HCC treatment. Data report lower systemic exposure of the drug and fewer systemic doxorubicin-related side effects (particularly myelosuppression, hair loss and myocardial toxicity) rendering the technique better tolerated than c-TACE. This low toxicity profile of HepaSphere has also been reported extensively with DC Bead and allows consecutive treatments, particularly in patients with cirrhosis and reduced liver function. Studies using HepaSphere report high complete response rates

ranging from 22.2 to 48% [20,30] and partial response ranging from 43.7 to 51% [20,26,30]. The major limitation of all published studies is that they do not have survival as the primary end point, and randomized comparisons with other drug eluting microspheres are still lacking. More studies (preferably prospective, randomized, comparative ones) are necessary to prove efficacy of HepaSphere (mainly in terms of survival) over conventional chemoembolization or other drug eluting microspheres. Finally, cost-effectiveness studies are necessary since drug eluting chemoembolization is more expensive than lipiodol-based c-TACE.

Disclaimer

In addition to the peer-review process, with the author(s) consent, the manufacturer of the product(s) discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made at the discretion of the author(s) and based on scientific or editorial merit only.

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