Liver chemoembolization of hepatocellular carcinoma using TANDEM[®] microspheres

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Transarterial chemoembolization (TACE) combines intra-arterial delivery of a chemotherapeutic agent with selective embolization to obtain a synergistic effect. TACE is recognized as the standard treatment of hepatocellular carcinoma patients at an intermediate stage. If conventional TACE, defined as the injection of an emulsion of a drug with ethiodized oil, still has a role to play, the development of drug-eluting beads has allowed many improvements and optimization of the technique. TANDEM[®] microspheres are second-generation drug-loadable microspheres. This device raised a special interest due to its tightly calibrated spherical microspheres, with small sizes down to 40 μm available. In this review, we describe the technical characteristics of these microspheres, analyze the scientific literature and hypothesize on the future perspectives.

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Transarterial chemoembolization (TACE) is a technique combining intra-arterial delivery of a chemotherapeutic agent and selective embolization to obtain a synergistic effect of drug cytotoxic activity and ischemia. TACE can be performed for the treatment of a wide range of hypervascular tumors, and is the mainstay of treatment of hepatocellular carcinomas (HCCs), especially those at an intermediate stage, or when curative options cannot be performed [1–4]. Despite the large number of TACE procedures performed daily, practice among centers and interventional radiologists still vary widely [5]. There is no clear consensus on, or established standard for material choice and procedural technique, especially regarding the choice of the chemotherapeutic agent drug and vector used [6,7]. Currently, the most commonly used chemotherapeutic agent is doxorubicin, but proof of efficacy of this drug remains questionable. Recent *in vitro* and *in vivo* studies have demonstrated that idarubicin, another anthracycline, could challenge the drugs currently used [8,9].

The choice of the vector is also an important parameter for TACE procedures. Conventional TACE (cTACE) is defined as the injection of a water-in-oil emulsion of a chemotherapeutic drug and Lipiodol, into the artery feeding the tumoral nodules, followed by embolization of tumor vessels with embolic agents. Lipiodol is a very interesting vector, with pharmacokinetic properties still not fully understood and having the unique property of selective uptake and retention in hypervascular liver tumors. However, cTACE has limitations such as: the need for a complementary embolization of the targeted vessel, release in the systemic circulation of a non-negligible amount of drug and a nonstandardized extemporaneously prepared emulsion with pharmacokinetic profiles of drug release strongly depending on the type of emulsion [10,11].

To overcome these aforementioned limitations, nonabsorbable embolic microspheres with the ability to load cytotoxic agents, named drug-eluting beads (DEBs), were developed in the late 2000s. While DEB-TACE provided the potential to standardize and simplify the TACE procedure, many also had high expectations regarding improved efficacy compared with cTACE. Yet, two large multicenter randomized controlled trials, one from Europe (PRECISION V) and the other from Italy (PRECISION ITALIA) failed to demonstrate a superiority of DEB-TACE versus

cTACE regarding tumor response and clinical outcomes [12,13]. However, these studies confirmed that DEB-TACE strongly decreased the occurrence of side effects related to systemic release of the drug.

DEBs are a recent and very promising device that piqued the interest of many device manufacturing firms, resulting in the development of several types of DEBs within a few years. Among them, the second-generation drug-loadable TANDEM®, raised a special interest related to an improved pharmacokinetic profile, and the presence of tightly calibrated microspheres with small sizes down to 40 µm in diameter. In this review, we aimed to assess the way that the technique of TACE has been optimized these past years, describes the specificities of TANDEM microspheres, analyzes the scientific literature dedicated to this recent and promising device and hypothesizes on the future perspectives about DEB-TACE.

TACE optimization

Intra-arterial treatment of a liver tumor was first described in 1974 [14], and consisted of an embolization with gelatin sponge. Approximately 10 years later, intra-arterial chemotherapy was performed using Lipiodol as the vector [15], allowing both the transport of the drug and radio-opacity of the injected mixture. Since then, TACE has benefited from many technological advancements of devices dedicated to intra-vascular navigation but also great improvements of angiography suites and intravascular guidance tools. The development of DEBs obviously marked a watershed in the history of TACE. On the other hand, many issues, such as the choice of the best chemotherapeutic agent for HCC, are still unclear.

Tumor targeting & intravascular guidance tools

TACE procedures can be optimized by superselective catheterization of the tumor-feeding arteries. Performing TACE as selectively as possible increases the local exposure to chemotherapeutic and embolic agents and limits the injury to the surrounding non tumoral liver [16]. Recent imaging techniques include cone-beam CT allowing for 3D CT scan-like acquisitions (instead of initial 2D images), or even angio-CT hybrid suites, providing amazing tools for identification of the tumor(s) and its arterial feeders. Many studies demonstrated that the use of these modern tools was associated with improvements regarding the number of tumor and feeders detected [1,3,17], the rate of complete lesion targeting [18], the rate of complete response and lengthened progression time after treatment [19]. TACE should be performed in a manner ‘as selective as possible’ as recommended by experts consensus [7,20].

Chemotherapeutic agent

Doxorubicin and cisplatin are the most commonly used chemotherapeutic drugs worldwide for DEB-TACE and cTACE, however, proof of efficacy of these drugs on HCC tumors remains poor. Only one study, published in 1975 [21], showed HCC regression based on alpha-fetoprotein (AFP) levels in three patients after intravenous administration of adriamycin (doxorubicin). Since this study, no further proof of efficacy or superiority of doxorubicin has been brought to the table [5,22]. Recently, an *in vitro* study [8] exploring a wide range of chemotherapeutic agents tested on HCC cell lines, demonstrated that idarubicin was the most cytotoxic, far ahead of the other drugs including doxorubicin. The higher cytotoxic effect was related to a more lipophilic profile of idarubicin, which results in increased penetration of the drug through the lipophilic double-layer of cells. Additionally, idarubicin overcomes the multidrug resistance system (double-layer active transport protein) that pumps the drugs out of the cells. Therefore, idarubicin penetrates the cells better and avoids expulsion thereby explaining a higher intracellular concentration of idarubicin than other drugs [8]. A recent Phase II trial (IDASPHERE II, FFCD 1307, [23]) that assessed the response rate at 6 months in HCC patients treated using microspheres (DC Beads®, 300–500 µm) loaded with idarubicin, was stopped at interim analysis for efficacy. These promising preliminary results warrant further studies, especially Phase III trials to assess the superiority of idarubicin over doxorubicin and other drugs. This could be a great step toward a consensus of TACE procedures.

The vector: cTACE versus DEB-TACE

DEBs have been developed as a vector for TACE instead of Lipiodol in order to combine both effects of ischemia and local cytotoxicity, with expected higher precision of drug delivery and lower systemic effects. Initially, *in vitro* studies showed a good pharmacokinetic profile, leading to higher intratumoral concentrations than after cTACE [24]. Then, animal studies also demonstrated higher tumor and lower systemic drug concentrations following DEB-TACE [25,26]. Further *in vivo* investigations reported acceptable safety profiles [25–27] and significantly decreased systemic drug concentrations, with 2-year survival rates up to 88.9% in Barcelona Clinic Liver Cancer (BCLC)

B patients. While these results were very encouraging, in 2010 a large Phase II randomized study, PRECISION V [12], did not demonstrate any benefit regarding the primary end point (i.e., response rate at 6 months). The only significant positive element was the decreased systemic side effects related to doxorubicin ($p < 0.001$). Similarly, two meta-analyses published in 2014 [27,28] comparing DEBs versus cTACE did not show a survival benefit of DEB-TACE. Meanwhile, a few nonrandomized trials demonstrated results in favor of DEB-TACE but no randomized controlled trial has confirmed these results so far [29]. In 2012, a retrospective study showed that liver/biliary toxicity was increased with DEB-TACE as compared with Lipiodol-TACE, especially in liver metastasis from neuroendocrine tumors [30]. This higher local toxicity can be attributed to the vesicant effect of the drug when beads are located in nontumoral parenchyma, especially when nontumoral liver is not cirrhotic [30]. Recently, liver/biliary toxicity was shown even in cirrhotic livers but related to drug dose and prothrombin time [31], thereby suggesting that it is a critical point to inject DEBs in tumors while sparing nontumoral liver tissue.

Optimization of DEB-TACE

To favor antitumoral efficacy of DEBs and spare nontumoral liver tissue, we need to administer small-sized particles very selectively in arteries feeding the tumor(s) in order to reach the core of the tumor.

Particles size

Intratumoral vessels are smaller than extratumoral vessels with a cutoff estimated to be approximately 300 μm in a benign tumor model [32]. This has been confirmed in a VX2 tumor model in the rabbit as no beads were found inside the tumor at histopathology when more than 300- μm particles were injected into tumor-feeding arteries [33,34]. In another study of liver explants in humans, only 42% of occluded vessels were inside the tumor when using 100–300 μm DEBs [35].

Size of commercially available DEB varies considerably, ranging from 40 to 700 μm . Beads can be delivered either in a tight size calibration or including a range of various sizes (i.e., from 100 to 300 μm). When beads are not precisely calibrated, larger beads occlude larger vessels preventing deep tumor penetration [36]. Of note, the size indicated by the manufacturer corresponds to beads before drug loading. After drug loading, the actual size may decrease up to 24% [37]. A small size of DEB, especially when ≤ 100 μm , allows for a more distal embolization, and leads to a higher penetration and drug concentration in the tumoral arterial network [34,38,39]. Smaller beads penetrate further in the tissue, reaching more distal locations and result in an increased density of beads in the tissue, thereby also improving the drug coverage [40].

In clinical studies, it has been now acknowledged that the use of small-size beads decreases the rate of adverse events and complications compared with larger beads. In a review including five retrospective studies that compared small (100–300 μm), medium (300–500 μm) and large sizes (500–700 μm) of particles, adverse events were less frequent with the small sizes (16 vs 25/33%, respectively; $p = 0.02$) [41]. In another study, grade III adverse events and 30-day mortality were decreased using 100–300 μm DC beads[®] versus 300–500 or 500–700 μm (6.8 vs 20%; $p = 0.04$, and 0 vs 14.3%; $p = 0.001$) [42]. Accordingly, in a study by Aliberti *et al.*, no mortality occurred after 822 TACE sessions using 70–150 μm beads, and with 6.1% of grade III/IV adverse event only (mainly biological) [43]. A study by Padia *et al.* showed that postembolization syndrome and fatigue were higher after DEB-TACE using 300–500 μm particles than in 100–300 μm (40 vs 8%; $p = 0.01$ and 70 vs 36.1%; $p = 0.25$, respectively) [44]. This better tolerance and lower complications rate helps for repetition of TACE procedures [41], which can be usually performed for HCC treatment [1,45,46]. Caution is recommended when using very small beads, in other words, less than 60 μm , due to the risk of occult arteriovenous shunts in large HCCs, which can be responsible for lethal pulmonary embolism [47].

Interestingly, choosing small-sized particles increases safety but also improves efficacy of the TACE procedure. Prajapati *et al.* in 2014 [42] demonstrated significantly higher survival rate and lower complications using 100–300 μm beads versus 300–500 or 500–700 μm in a cohort of 94 HCC patients who underwent 269 DEB-TACE.

Drug loading & release

Loading and release properties vary from one bead type to other [9,37], and release can also vary for a same DEB type depending on the loaded drug [48,49], as well as the size of the beads (the smaller the beads, the faster the release) [24,50]. In a pig model, doxorubicin release from DC bead was very slow since only 43% was released 28 days after injection [51]. Even after 3 months, 11% of the drug still had not been released. These pharmacokinetic variations may have an impact on local and systemic concentrations of the drug and therefore on efficacy and side

Figure 1. Ion-exchange mechanism of TANDEM microspheres. Ionic interaction between the negatively charged polymer backbone and positively charged drugs enables drug loading and subsequent release after delivery to local tissue. DOX refers to doxorubicin, while IRI refers to irinotecan.

Table 1. TANDEM microspheres size offerings.		
Nominal size	Particle size range	Number of particles in 2 ml
40 μm	40 $\pm$ 10 μm	34 million
75 μm	75 $\pm$ 15 μm	5.8 million
100 μm	100 $\pm$ 25 μm	2.2 million

effects. Optimal loading should be as fast as possible in order to facilitate its preparation, whereas the release of the drug should be slow in order to sustain efficient intratumoral drug concentrations.

TANDEM design intent

TANDEM microspheres were designed to be a second-generation microsphere technology, offering more distal intratumoral embolization capability, higher drug-dosing ability and improved preparation and loadability for a controlled, predictable transarterial procedure. TANDEM was intended to provide mechanical occlusion of distal artery beds that feed the hypervascularized tumor. Consequently, TANDEM was developed with tight size distributions and small particle sizes in order to address the need for more distal intratumoral embolization.

TANDEM microspheres were also designed to be capable of rapidly loading an ancillary drug substance to provide a complementary mechanism of action to the mechanical occlusion of the microsphere. These microspheres are composed of a nonbiosorbable sodium methacrylate hydrogel matrix that mechanically occludes tumor-feeding hepatic arteries and provides a negatively charged ionic matrix by which the drug can interact with the microsphere through an ion-exchange-based mechanism. Due to the availability of the ion exchange sites on its hydrogel matrix, TANDEM has a high capacity for drug interaction as evidenced by its ability to load up to 50 mg of either doxorubicin or irinotecan, and is able to provide controlled elution of the drug upon delivery to the target tissue. It is through the ion exchange mechanism that TANDEM microspheres were designed to load and release positively charged drugs (Figure 1).

Finally, TANDEM microspheres were intentionally developed to provide flexibility to the physician end user. By providing an embolic microsphere manufactured without drug, but with design capabilities that enable drug loading, TANDEM allows the end-user physician to select and load TANDEM with the desired drug and dose to meet the individual treatment needs of the patient.

How the technology works

TANDEM microspheres are spherical, tightly calibrated, biocompatible, non-resorbable, hydrogel microspheres coated with a proprietary polymer (Polyzene™-F). The microspheres were designed for drug loading and elution of a local, controlled, sustained drug dose after embolization. They are available in three highly calibrated microsphere sizes (40, 75 and 100 μm) in volumes of 2 and 3 ml of product, and presented in prefilled syringes. Due to their tight and uniform size distributions (see Table 1) [36], more microspheres occupy the same volume as compared with a wider size range. For example, a sphere with a diameter of 300 μm occupies 27-times the volume of one 100- μm sphere, thus enabling more 100- μm spheres to occupy the same volume as one 300- μm sphere. The size distribution and microsphere count for TANDEM microspheres are shown below in Table 1.

As the primary mechanism of action of microspheres is to mechanically occlude tumor-feeding vasculature, TANDEM microsphere sizes were intentionally developed to embolize the diverse tumor vessel architecture.

Table 2. TANDEM microspheres drug-loading capabilities.

Attribute	Doxorubicin	Irinotecan
Loading amount	50 mg/ml TANDEM	50 mg/ml TANDEM
Loading	98 ± 2% in 60 min	98 ± 2% in 30 min

Table 3. Summary table of clinical abstracts and studies reporting experience of liver transarterial chemoembolization in patients with hepatocellular carcinoma using TANDEM/ONCOZONE microspheres as drug-eluting beads.

Study (year)	Study design	Number of patients	Tumor stage	Size of particles (μm)	Drug loaded	Objective response rate	Ref.
Schmitz (2014)	Retrospective cohort	26	Non resectable	75 and 100	Not precised	67%	[55]
Nani (2014)	Retrospective cohort	11	Nodular	40	Epirubicin	85%	[58]
Balli (2015)	Retrospective cohort	20	Not precised	40–75	Doxorubicin	61%	[59]
She <i>et al.</i> (2016)	Case report	1	Single HCC	40	Doxorubicin	Complete response	[56]
Greco <i>et al.</i> (2017)	Retrospective cohort	48	BCLC A/B	40	Doxorubicin	72.6%	[57]
Malagari <i>et al.</i> (2016)	Comparative study	52	BCLC B/C	40, 75 and 100	Doxorubicin	66%	[60]
Guiu <i>et al.</i> (2018)	Retrospective cohort	72	BCLB B	75 and 100	Idarubicin	66%	[61]

BCLC: Barcelona Clinic Liver Cancer; HCC: Hepatocellular carcinoma.

Regarding HCC, the tumor vasculature varies greatly, ranging from small shrubby vessel patterns (~60%) to more diverse cotton vessel patterns (~32%) and larger driftwood vessel patterns (~8%) [52]. Smaller microspheres are best able to achieve a goal of more distal embolization in all three vessel types of HCC tumor vasculature compared with larger sizes that can likely only provide distal embolization in larger driftwood vessel patterns. Smaller microspheres allow a better repartition of cytotoxic drug, increasing inside tumor concentration and decreasing peripheral diffusion [9].

As a secondary mechanism of action, microspheres release loaded drug to the embolized tumor vasculature. As TANDEM microspheres are not manufactured with drug, the specific drug and dosage are selected by the physician and loaded at the hospital pharmacy or by the physician. TANDEM microspheres are capable of loading 50 mg of either doxorubicin or irinotecan per milliliter microspheres in a short time period (Table 2) [36]. Loading of Idarubicin is also very efficient, with more than 99% of the drug loaded at 10 min [9]. Additionally, TANDEM microspheres undergo a minimal size change when loaded with drug (<10%) and are stable in suspension with contrast solution due to the stable nature of the polymethacrylate hydrogel core [36,37]. In contrast, other drug loadable microspheres have been reported to experience ≥20% decrease in diameter (50% volume reduction) upon doxorubicin loading [37].

Once loaded and delivered to the target tumor tissues, microspheres exert their primary mechanism of mechanical occlusion and then secondarily elute the loaded drug. *In vitro* bench data from validated dissolution methods have shown that TANDEM has a consistent, sustained release of doxorubicin and a more prolonged release of irinotecan (Figure 2) [36]. *In vivo* preclinical studies have shown that TANDEM microspheres have a more prolonged release of irinotecan in plasma and lower maximal concentration compared with other DEB [53]. The lower maximal plasma concentration over a prolonged release period observed with drug-eluting microspheres is important because it leads to lower systemic drug exposure overall than conventional chemoembolization [54].

Clinical studies

Compared with other available DEBs (Table 3), TANDEM microspheres have demonstrated interesting technical improvements in *in vitro* studies: a more precise size [37], faster loading capacities [9] and uniform peripheral drug distribution [53], a longer time in suspension [37] and decreased plasma concentration with a slower release profile [9]. Regarding clinical applications, several studies, mainly focused on HCC patients, have demonstrated a good safety profile and tolerance of these microspheres, as well as interesting and promising results. In a selected abstract at the

Figure 2. TANDEM release. *In vitro* release of doxorubicin-loaded TANDEM microspheres and competitors (A) and (B), irinotecan-loaded TANDEM microspheres and competitor.

Society of Interventional Radiology 2014 annual conference, Schmitz [55] described her first clinical experience of 26 HCC patients treated with TANDEM microspheres of 100 and 75 µm. She did not report any severe adverse events and showed 67% tumor control at 6 months.

Regarding clinical experiences with small-sized 40-µm TANDEM microspheres, a case report demonstrated a complete response after treatment of a single exophytic HCC of 2.5 cm [56]. More recently, Greco *et al.* [57] reported good tolerance of DEB-TACE using 40-µm TANDEM microspheres loaded with doxorubicin with no adverse event grade III/IV after 73 sessions, and an excellent tumor response with overall response rate (ORR) of 72.6%. Two other retrospective studies also reported excellent ORR: 85% for Nani [58] using 40-µm TANDEM microspheres loaded with epirubicin 100 mg in 11 nodular HCC and 61% for Balli [59] using 40 or 75 µm loaded with doxorubin in 20 patients.

In a very interesting study, Malagari *et al.* [60] compared TANDEM microspheres of different size (40, 75 and 100 µm) loaded with doxorubicin either at standard 100-mg concentration (standard loading group) or at high 150-mg concentration (high loading group), in 52 patients with an average tumor size of 7 cm. The results showed an absence of additional benefit for the high loading group regarding tumor response and outcomes, while this group exhibited more biliary toxicity. The safety profile in the standard loading group was good regardless of the size of the particles. Of note, systemic concentrations of doxorubicin were significantly increased in the high loading group, and for patients treated with 40-µm particles. ORR were 65 and 68% in the high and standard loading

Figure 3. Example of transarterial chemoembolization using TANDEM microspheres for a 67-year-old patient with an hepatocellular carcinoma of approximately 5 cm (and previous history of right hepatectomy). (A) Left-lobe hepatocellular carcinoma on arterio-CT in angio-CT hybrid suite. (B) Fluoroscopy image of hepatocellular carcinoma retention (black arrow heads) while delivering idarubicin-loaded TANDEM microspheres 100 μm . (C) Immediate post-treatment CT image showing spontaneous hyperattenuation of the targeted tumor due to high retention of beads. (D) Follow-up MRI (arterial phase) at 3 months: mRECIST response more than 90%, with necrosis (black arrows) and persistence of residual tumor tissue of 1 cm only (white arrow).

groups, respectively (p-value not significant). Overall survival at 6 months and 2 years were 98.08 and 88.46%, respectively.

Finally, our experience with TANDEM microspheres will be presented at the CIRSE 2018 annual conference. In the presented study, 72 consecutive patients with HCC at BCLC B stage were treated by DEB-TACE with 75- or 100- μm TANDEM microspheres loaded with idarubicin [61]. Best tumor response was complete and partial response in 21 and 45% of patients, respectively. With a median follow-up of 12 months, median overall survival was of 34.6 months (Figure 3).

Conclusion

Technical aspects of TACE procedures vary widely among centers, especially considering the drug and vector used. If DEB-TACE failed to prove superiority over cTACE regarding tumor response, it has the greatest advantages of improving the standardization of the procedure and decreasing drug-related side effects. TANDEM microspheres are a second generation of DEB with many technical improvements. These microspheres are spherical, tightly calibrated and with small size down to 40 μm available. The use of small-sized particles, such as 40 or 75 μm , is interesting when performing a selective TACE as it allows a better intratumoral repartition leading to a higher concentration of the drug and improved response rate, while providing lower rate of local complications. Moreover,

the hydrogel matrix of the TANDEM microspheres allows a fast and stable drug loading through an ion-exchange-based mechanism, which leads to decreased systemic concentrations of the drug and therefore, higher concentration of the chemotherapeutic agent within the tumor. These microspheres have the ability to be loaded with idarubicin, a chemotherapeutic agent that has been shown *in vitro* to be the most cytotoxic drug for HCC cells, with promising efficacy in clinical studies. To date, first clinical studies have shown an excellent tolerability of TACE performed using TANDEM microspheres, including using small-sized particles, and confirmed the expectations regarding tumor response and clinical outcomes. However, cohort studies in large patient population and randomized controlled trials are still lacking.

Future perspective

Interventional radiology techniques such as locoregional therapies for liver tumors are a rapidly evolving field. All the recent TACE improvements have largely contributed to increase the accuracy, efficacy and safety of TACE procedures. Regarding DEBs, we are just at the beginning of the journey, with many innovations and improvements still to come. First, DEB-TACE still has to prove its clinical efficacy in a Phase III trial including HCC patients. This step will be only achieved by an improvement in the selection of patients, the use of an optimized particle size and the use of an efficient chemotherapeutic drug such as idarubicin. More clinical evidence is also expected regarding other types of liver tumors such as cholangiocarcinomas or liver metastasis from colorectal cancers. Second, others technological innovations, such as radio-opaque particles [62] or bioresorbable particles [63], are already available or under investigation. Third, combined therapies will have a greater role to play in a near future. Regarding the amazing development of immunotherapies in the management of many cancers, embolic agents of the future should be able to be loaded by various and multiple drugs including immune therapies for increasing the efficiency of locoregional therapies. Finally, the daring combination of drug delivery, vessel occlusion and selective radiation therapy using the same embolic agent is certainly a path that needs exploring, and that makes us realize that this journey has just begun.

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Executive summary

Transarterial chemoembolization: cytotoxic effect of chemotherapy & ischemic effect of embolization.

- Transarterial chemoembolization (TACE) combines chemotherapeutic and embolic agents to obtain cytotoxic activity and ischemia. There is no current clear consensus about TACE procedures, especially about drugs and vector.
- Among all the recent improvements, drug-eluting beads (DEBs) are loadable microspheres, developed as an alternative vector to Lipiodol for drug delivery.

Vector: Lipiodol or DEBs

- DEBs or Lipiodol as chemotherapeutic vector is still under debate and two randomized controlled trials (PRECISION V and PRECISION ITALIA) failed to demonstrate clinical benefit for DEBs regarding tumor response and clinical outcomes.
- However, these studies confirmed that DEB-TACE strongly decreased the occurrence of side effects related to systemic release of the drug.

DEB-TACE optimization

- DEB-TACE optimization requires innovations and improvements of DEBs. This could only be achieved by collaboration between device-manufacturing firms and clinicians, concerning optimal size and stability of DEBs, gel core, loading and release pharmacokinetics, preparation conditions, visualization and others.
- In clinical studies, the use of small-sized beads decreases the rate of adverse events and complications compared with larger beads. A cohort study also demonstrated higher survival rate using 100–300 μm beads versus 300–500 or 500–700 μm .

TANDEM: second generation of DEBs

- TANDEM microspheres are spherical small particle sizes (40, 75 and 100 μm), with stable size after loading. TANDEM microspheres are not manufactured with drug and the gel core (Polyzene™-F) allows easy and fast loading of drugs (doxorubicin, idarubicin, irinotecan) at the hospital.
- *In vitro* and *in vivo* preclinical studies reported faster loading capacities, a uniform peripheral drug distribution, a longer time in suspension and decreased plasma concentration with a slower release profile of TANDEM microspheres compared with other DEBs.

TANDEM in clinical practices: currently available results are very encouraging

- The objective response rate reported in cohort studies for HCC treatment varies from 61 to 85%. Tolerance was good with limited adverse events, only reported on a study subgroup allocated for high drug concentration.
- Overall survival at 6 months and 2 years were 98.08 and 88.46%, respectively, in Malagary *et al.*'s study (doxorubicin), and median overall survival was of 34.6 months in Guiu *et al.*'s presentation.

Conclusion

- DEB as vector for TACE failed to prove superiority over cTACE regarding tumor response but has the greatest advantages of improving the standardization of the procedure and decreasing drug-related side effects.
- TANDEM microspheres are a second generation of DEB with many technical improvements that allow a better intratumoral repartition and improved pharmacokinetic profile.
- To date, first clinical studies have shown an excellent tolerability of TACE performed using TANDEM microspheres, and confirmed the expectations regarding tumor response and clinical outcomes. However, cohort studies in large patient population and randomized controlled trials are still lacking.

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