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The ten commandments of chemoembolization: expert discussion and report from Mediterranean Interventional Oncology (MIOLive) congress 2017

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Abstract. – Transarterial therapies in the setting of primary and secondary liver malignancies are becoming an essential part of the oncology landscape. The mechanism of action of c-TACE is the induction of tumor necrosis due to the high concentration of the chemotherapeutic that is delivered only locally and to the embolic effect that causes ischemia and increased dwell time of the chemotherapeutic in the tumor. Recently, DEB-TACE has emerged as a variation of c-TACE with the potential for the selective delivery of large amounts of drugs to the tumor for a prolonged period, thereby decreasing plasma levels of the chemotherapeutic agent and related systemic effects. There is an increasing consensus that compared with conventional lipiodol-based regimen, DEB-TACE offers standardized methodology, is more reproducible and is associated with improved response and significantly better safety profile. Using an easy to access point by point format, this manuscript summarizes the expert discussion from the Mediterranean Interventional Oncology Live Congress (MIOLive 2017) about the role of TACE in the treatment of liver tumors.

Key Words:
Liver, Chemoembolization, Lipiodol, Beads, HCC, Locoregional treatment.

Introduction

Drug Eluting Microspheres/Beads (DEB) were first introduced as an intravascular loco-regional treatment for HCC at the end of 2004 with the first clinical series published in 2007-2008[1-3]. Slightly earlier, in 2002, two milestone studies from Llovet et al[4] and Lo et al[5] documented the survival benefit of conventional/lipiodol based

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chemoembolization (conventional transarterial chemoembolization – c-TACE) over Best Supportive Care (BSC) for HCC patients who were not surgical candidates. The mechanism of action of c-TACE is the induction of necrosis due to the high concentration of the chemotherapeutic that is delivered only locally, thereby sparing the surrounding non-tumorous liver and the embolic effect that causes ischemia and increased dwell time of the chemotherapeutic in the tumor. However, there are many formulations that have been used for c-TACE rendering its use not standardized, whereas DEB-TACE offers a reproducible alternative as it is able to achieve neoplastic vessel blockade and a prolonged time of constant elution of the chemotherapeutic in the tumor in a predictable manner[1,6,7].

This manuscript summarizes the expert discussion and report from the Mediterranean Interventional Oncology Live Congress (MIOLive 2017) that was held in Rome, Italy. The aim of this exercise and communication is to integrate evidence-reported literature and experience-based perceptions, while attempting to make the information easy to access using a point format, to assist not only residents and fellows who are training in interventional radiology, but also practicing colleagues who are attempting to gain further expertise with this intra-arterial treatment. Accordingly, we have organized these principles into a "ten commandments" framework.

The Ten Commandments – for Achieving Optimal Results With DEB-TACE

I. Know Your Devices

Today there are four drug-eluting embolization systems that are commercially available including DC/LC Bead™ (Biocompatibles UK Ltd., a BTG group company), Hepasphere/Quadrasphere™ (Merit Medical Inc., South Jordan, UT, USA), Tandem™ (Celonova Biosciences Inc. Boston Scientific) and LifePearl™ (Terumo, Tokyo, Japan).

The DC/LC Bead™ consists of beads of polyvinyl alcohol – hydrogel modified by sulfonate groups[6-8] and provides fast loading and elution kinetics with anthracycline derivatives such as doxorubicin, epirubicin and idarubicin ranging in size from 70 to 900 μm[9,10]. More than 99% of the intended dose of doxorubicin is loaded within the beads, with loading and safety levels of 37.5 mg of doxorubicin per ml of hydrated microspheres[1]. These microspheres shrink by a factor of about 10% after loading to sizes below 300 μm and become more rigid. Measurements of the concentration of doxorubicin in the embolized liver have shown that cytotoxic levels of the chemotherapeutic are present up to 600 μm from the surface of the microspheres for at least 2-3 weeks post embolization[11]. The first two studies of human plasma pharmacokinetics with this embolic[1,2] showed that concentration maximum (Cmax) and the Area Under the Curve (AUC) are significantly lower than those obtained by c-TACE which is associated with high systemic circulation exposure to the chemotherapeutic[1,2]. This is in accordance with the results of a large prospective randomized comparison study of DEB-TACE *vs.* c-TACE in which the DEB-TACE arm demonstrated statistically significant less toxicity associated with doxorubicin[12]. DC Bead LUMI™ uses iodine chemistry and the DC Bead™ platform provides a long-term radiographically visible drug-eluting embolic and currently a number of studies are underway to report clinical results**.**

From a clinical perspective, the Precision V trial, comparing c-TACE and DEB-TACE, showed only a limited superiority of DEB-TACE. Indeed, DEB-TACE achieved a better objective response (OR) over c-TACE[12] only in a subgroup of patients (i.e., those with more advanced disease, with recurrence, ECOG 1, Child Pugh B, and bilobar disease)[12]. Similarly, other investigators did not find a significantly better local response to DEB-TACE over c-TACE[13-16]. Median expected time to recurrence is reported by Sacco et al [16] as 8.9 months after DC bead chemoembolization with a time to radiological progression of 15.6 months. Another study treating tumors of a mean total volume of 5.36 cm reported up to 5 year recurrence rates[17], ranging between 36.7% and 38.4% locally with new lesions developing in up to 76.9% in 5 years in the previously non tumorous liver. The median interval time between initial recurrence and baseline treatment was 18 months (range 8-52). The same study[17] reported a dramatic increase in untreatable progression after 45 months from first embolization and that, once untreatable disease is established, death may occur within a median of 10 months (range 0.4-17 months). Pitton et al[18] reported median Progression Free Survival (PFS) of 216 days and median time to progression (TTP) of 336 days for the segmental DEB-TACE arm, while for the segmental radioembolization arm these parameters

were 180 days and 371 days, respectively[18]. These investigators did not find statistically significant differences between the two groups, while the lower rate of tumor progression in the radioembolization arm was offset by the greater occurrence of liver failure in the radioembolization arm[18].

Studies with DEB-TACE in patients not amenable to curative treatments report prolonged short-term survival, as Varela et al[1] report 1- and 2-year survival of 92.5 and 88.9%, respectively. Two publications report on long term survival. The first demonstrated a mean overall survival of 43.8 months[19], and 1,2,3, and 5- year survival rates of 93.6%, 83.8%, 62%, and 22.5% respectively[19], while the Barcelona investigators report mean survival of 40.2 months for Barcelona Clinic Liver Cancer (BCLC) stage A and 31.9 for BCLC stage B disease[20]. In the Precision Italia study, treating tumors of a median diameter of 2.6 cm, 1- and 2-year short-term survival of 86.2% and 56.8% for DEB-TACE and of 83.5% and 55.4% for c-TACE were recorded[16]. Interestingly, in the randomized comparison of selective radioembolization *vs.* DEB-TACE, the median overall survival was 788 days in the DEB-TACE arm, while for selective radioembolization it was only 592 days. This was probably due to the higher rates of locally advanced disease in the radioembolization arm[18].

HepaSphere™ in Europe or QuadraSphere in the United States (Biosphere Medical, Roissy, France) are microspheres from a superabsorbent polymer (sodium acrylate and vinyl alcohol copolymer SAP-MS), which when loaded with the anticancer drug, can release it in a controlled and prolonged manner[21-23]. The loading is based on chemical and electrostatic interactions since they have a negative ionic charge (ideal for positively charged anthracyclines and mechanical absorption of fluid)[21-23]. This double mechanism allows loading with anthracyclines, and platin derivatives[24-27] and requires a two-step loading process for optimal performance[28,29]. HepaSphere™ microspheres upon exposure to solution isotonic to plasma increase in size up to 4x their volume in dry form while they retain plasticity and squeeze themselves in vessels that may have actually a smaller nominal diameter than the embolic[30,31]. The predicted embolic particle size after the two step loading is 145-213 μm (148 ± 45) for the HepaSphere™ when using 30-60 μm microspheres (dry form), 200 to 300-400 μm (for 50 to 100 μm dry microspheres), 600 to 800 μm (for 150 to 200 μm dry microspheres)[30-32]. Eluted doxorubicin locally reaches high levels above a 50% inhibition concentration for up to one month post embolization with maximum values at 7 days up to 400-1600 μm from the surface of the microsphere to the tumor tissue[32]. When treating for HCC, plasma levels of doxorubicin after chemoembolization with HepaSphere have been shown to peak at 5 min post embolization with a Cmax and AUC significantly lower than the levels of c-TACE at 5, 20, 40, 60 min and at 24 h, 48 h and 7 days [21].

Local response has been reported in many studies[21,22,25,33]; complete response (CR) ranges from 12.6% to 48%[21], while partial response (PR) ranges between 36% and 51.1%. The local response of HCC in a study with the smallest available HepaSphere 30-60 showed a CR rate of 22.2% for the target lesion as assessed with mRECIST. Overall PR was observed in 51.1%, stable disease in 20%, and progressive disease in 11.11% of the 45 patients cohort[21]. Survival at one year was 100%[21]. Good local response in this and other studies may be associated not only to the small size but also to the plasticity of this embolic enabling obtaining an objective local response reaching 68.9% with a satisfactory safety profile[30]. A comparison with c-TACE showed no significant advantage but statistically significant less complications in the HepaSphere treatment arm[34]. Loaded with 25-30 mg of epirubicin HepaSphere achieved 1- and 2- year survival rates of 73.7 and 59%, respectively, with post-embolization syndrome (PES) being the more common adverse event at an incidence of 31.8%[24]. By switching from epirubicin to cisplatin in refractory cases, it was possible to achieve objective response at 6 months in 40% of patients[25]. Treatment related 30-day mortality rates ranged between 0-1%, and adverse events ranged from 2% to 11.4%[21,22,26,33,35].

TANDEM™/Oncozene™ (CeloNova BioSciences Inc., San Antonio, TX, USA) is a drug eluting microsphere with a hydrogel core made of sodium polymethacrylate. It possesses a negative charge and can bond with positively charged anthracyclines including doxorubicin and idarubicin diluted in water for injection. This embolic has tightly calibrated diameters at 40 ± 10, 75 ± 15 and 100 ± 25 μm with shrinkage of less than 5% after loading[36]. The maximum dose of doxorubicin recommended by the manufacturer is 50 mg/ml of TANDEM™ and loading of 98 ± 2% of the chemotherapeutic is achieved in 1 h. Until recently, there were only a few published clinical studies with this preparation including

a safety phase for the treatment of HCC and no specific recommendations or guidelines. In a recent pilot study 19 patients were initially enrolled using a dose and size escalation schedule[37] since there was no previous experience of doxorubicin-loaded microspheres ≤ 100 μm for HCC and there was a high concern of off-target embolization through small arteriovenous collaterals. Such small microspheres had been previously used only for bland embolization aiming to achieve complete anoxia throughout the tumor[38]. After the positive completion of the safety pilot evaluation, the study was completed and 52 patients were enrolled prospectively and were followed up for 3 years. Tumors of > 6 cm were treated with TANDEM™ 75 μm or 100 μm while smaller tumors were treated with 40 μm and patients were randomized in two groups according to the loading level, one using the maximum dose (standard dose) and one with a lower loading. Randomization parameters included size, Child Pugh score, AFP and number of lesions. Pharmakokinetic measurements were also performed measuring the plasma concentration of doxorubicin at 5 - 60 min, and 2, 6, 24, 48 h and 7 days after embolization. The two groups were found to not have statistically significant differences and the mean diameter of the treated tumors was 7.3±2.1 cm (range 4-12). Two scheduled sessions were performed and thereafter the patients were treated only "on demand". There was a 1.92% 30-day mortality rate due to a subcapsular tumor rupture (one patient treated with 40 μm in the high dose group). Transient ascites was seen in 4.1 to 5.8% across sessions while biliary toxicity in the form of asymptomatic biliary dilatation was seen in 5.7%. Moderate alopecia was recorded in 3.8% without myelosuppression and PES presented with prevalence of 12.9-43.6% across sessions. Plasma doxorubicin levels peaked at 5 min and were higher in the high loading group and the smaller diameters particles compared to the low loading and larger diameters (mean Cmax ± SD was 203.5 ± 225.8 ng/mL, notably 284.9 ± 276.2 ng/mL for the high and 108.5 ± 77.6 ng/mL for the low loading group ($p < 0.001$). There were no statistically significant differences in local response evaluated with m-RECIST between the high and low loading groups and CR of the target lesion was achieved in 30.6% at the second session while PR was obtained in 42.3%. On the whole, overall survival (OS) at 6 months, 1, 2 and 3 years was 98.1%, 92.3%, 88.5%, 82.6%, respectively OS and PFS showed no difference between the high and low loading groups ($p = 0.329$; HR = 1.1; $p = 0.586$; HR = 1.5, respectively)[37]. In a recent clinical study with early or intermediate HCC patients[39], response rate of treated tumors was 72.6% and 26.7% according to mRECIST and RECIST, respectively. Histological examination in 11 patients submitted to liver transplantation revealed necrosis > 90% in 78.6%. The overall time to progression was 13 months (11-21).

LifePearl™ is a drug loading and release device with a core material of polyethylene glycol (PEG) modified for drug loading and release. It is negatively charged with sulfonate groups allowing ionic bonding with positively charged molecules such as doxorubicin for HCC. It is available in three narrowly calibrated diameters of 100±25 μm, 200±50 μm and 400±50 μm. A head to head comparison of the four-drug loadable microspheres available[40] showed that the diameter distribution histogram of doxorubicin loaded LifePearl has a narrower collimation compared to DC Bead[40]. In addition, doxorubicin loaded LifePearl showed a longer time in suspension compared to DC Bead and HepaSphere and shorter than TANDEM™. Doxorubicin elution kinetics were similar to the other loadable microspheres.

II. Be Aware of Indications and Patient Selection

According to the BCLC staging system, DEB-TACE has the same indications as c-TACE including both BCLC B patients not-suitable for curative treatments in Child-Pugh A or B class with performance status 0-1[41,42] and also BCLC A patients who are poor candidates for surgery or ablation. In addition, DEB-TACE can be applied in selected patients with BCLC C disease who are not candidates for radioembolization and have locally advanced disease[41-44]. A number of patient and tumor related parameters have been shown to affect survival in HCC patients undergoing TACE. In a recent single-center study mainly including Child-Pugh A patients treated with c-TACE, non-tumor segmental portal vein thrombosis, serum sodium, diameter of largest nodule, number of nodules, alphafetoprotein (AFP) and alkaline phosphatase serum level were independent prognostic factors for overall survival[45]. Most results of DEB-TACE have been obtained from patients with HCC in the intermediate stage[1,12-15]. However, a large prospective randomized comparison between c-TACE and DEB-TACE with median tumor diameter of 2.6 cm re-

vealed that for small tumors both techniques are effective[16]. Therefore, HCC < 3 cm not amenable to curative treatments can be adequately treated with c-TACE or DEB-TACE. On the other hand, the PRECISION V trial[12] revealed that for larger and more advanced tumors DEB-TACE achieves better local response compared to c-TACE in patients without vascular invasion.

III. Choose the Extent of Treatment: Selective vs. Lobar

Lobar embolizations are associated with increased liver toxicity in the cirrhotic liver. Thus, segmental or subsegmental embolization is required. In several DEB-TACE clinical series, the feasibility of selective segmental or subsegmental embolization has been recognized as an independent and significant factor associated with longer TTP, PFS and OS[1,12,46]. It has been shown that even small HCC tumors smaller than 3 cm are often associated with satellite micrometastasis located within 1-2 cm from the the tumor edge that cannot be seen in imaging studies[47,48]. For this reason whenever feasible, after the superselective administration of the loaded microsphere suspension, the microcatheter should be withdrawn slightly to a more proximal position to shower a focal region of the liver peripheral to the tumor. The treatment of this zone in c-TACE is achieved by continuing the injection until portal venules are seen on fluoroscopy [47,48].

The end point of DEB-TACE from a technical point of view is to achieve stasis that clears after 2-3 heart beats. It is imperative to avoid wedging of the microcatheter since the microspheres are conveyed by blood flow to enter in the small vessels of the tumor. This is a key difference with c-TACE that often requires wedging and pushing of the emulsion until portal venules are opacified. High dilution is also recommended with DEB-TACE to avoid congregation and early proximal occlusion. This is particularly important with the soft and compressible HepaSphere[21,30].

IV. Treating Small or Large Tumors: Pros and Cons

The treatment of large tumors can be associated with rupture, systemic toxicity, and abscess formation[37,49]. Thus treatment should be performed in multiple sessions, particularly in patients with large subcapsular tumors that have a tendency to rupture after embolization due to edema-related increased tumor volume occurring in the embolized tumor[37]. Furthermore, the intratumoral contrast lake formation during embolization should be treated with complete occlusion of the feeding vessel to avoid rupture[37].

V. Sequential Embolization Sessions: on Demand or Scheduled?

From the clinical studies, it has been noted that the achievement of CR or PR may increase significantly after the second scheduled embolization performed with a time interval of 3-6 weeks from the first procedure. Therefore, the tumor can be characterized as non- responding only after two technically successful embolizations. In addition, it has been shown that complete and partial response are independent and significant prognostic factors for OS, PFS and TTP[19,46].

VI. Define Your Loading Levels

As suggested by clinical studies, for drug eluting microspheres loading levels of 37.5 mg/ml of doxorubicin of hydrated beads is safe and effective for HCC in patients with well compensated cirrhosis[1,42]. Levels of 25 mg/ml are recommended for patients with bilirubin levels of 2-3 mg/ml. However, in several studies low loading doses have been associated with insufficient results[49,50]. In one study, low loading levels of 25 mg/mL of DC Bead provided CR and PR in no more than 2.5% and 8.7% of the cases[48]. In another report by Golfieri et al[16] loading at 50 mg per vial (loading of 25 mg/ml of beads) yielded lower survival rates than that achieved in clinical studies performed with drug eluting microspheres (86.2% and 56.8% at 1 and 2 years). In another study higher loading at 50 mg per vial showed a more significant degree of necrosis compared to lower loading as documented pathologically[53]. However, as noted above, for the small and tightly calibrated microspheres < 100 μm lower loading doses are better[37].

VII. Safety of Small Sizes

When DEB-TACE was introduced in clinical practice, there was a concern about peribiliary plexus necrosis and non-target embolization through arteriovenous communications when using particles smaller than 300-500 μm. In a prospective study[52] with 237 patients the toxicity profile of different sizes of microspheres was examined and diameters smaller than 100-300 μm were not found to be less safe than the larger ones. More recent works[55-57] seem to support a safe use of small microspheres 70-150 μm in size. Small diameter microspheres can deeply penetrate into the intratumoral vessels and some

researches have shown that both 40 μm and 70-150 μm microspheres can achieve more distal embolization safely[55-57].

Nevertheless, for the tightly calibrated sizes of 40-75-100 μm there is a serious concern related to the presence of arteriovenous communication with the central or portal venous system. In the former case they may lead to systemic embolization whereas in the latter case the embolic material may occlude non-tumorous liver vessels with subsequent liver tissue injury[58]. If and when no communication is detected in pre-embolization angiography small size microspheres can be used safely as demonstrated in several studies[37,55,59]. Furthermore, in clinical investigations performed in which these small diameters particles were used to treat tumors up to 6 cm in diameter no increased toxicity was recognized[37,59].

Another concern for small microspheres ≤ 100 μm is peribiliary plexus occlusion producing toxic effects at the level of the biliary vessel walls[60]. Although the peribiliary plexus is hypertrophied in patients with cirrhosis and the occurrence of biliary toxicity is low in these patients compared to patients with metastatic disease, it has been reported that the smaller tightly calibrated microspheres of 40 and 75 μm may be associated with biliary toxicity if loaded with 37.5 mg/ml of hydrated microspheres[37]. Therefore, small particle diameters are safe if no recognizable arteriovenous fistula is present especially in tumors less than 6 cm in diameter. However, for microspheres with diameters <100 μm loading should be lower than that used for the other DEBs in order to avoid biliary and systemic toxicity. Accordingly, it can be inferred that for the small microspheres the anoxic effect at the tumor level is higher and then less chemotherapeutic drug is required.

VIII. Bland or Drug Loaded Particles?

HCC cells are chemotherapy-resistant and, apart from sorafenib, which is a tirosin-kinase inhibitor with antiangiogenetic properties, systemic chemotherapy is not considered an effective treatment option. However, the intratumoral high levels of doxorubicin achieved with chemoembolization have been regarded as the main mechanism of HCC cellular apoptosis and death. Idarubicin is more cytotoxic than doxorubicin[36] and has been proposed as an alternative. At the beginning of the DEB-TACE it seemed that a prospective randomized clinical trial (RCT) comparing loaded and unloaded microspheres was a reasonable way to assess the role of the chemotherapeutic in addition to the anoxia caused by the microspheres and two such studies have been published. In the first study, which included patients without extrahepatic disease and with a mean sum of tumor diameters of 8.35 cm for the loaded group and 8.1 cm for the bland ($p < 0.69$) without vascular invasion, the group treated with doxorubicin loaded microspheres demonstrated a longer TTP and less local recurrences compared to the group undergoing bland embolization with non-loaded microspheres[46]. In this study, no difference in OS was observed, probably due to the short follow up period. A more recent RCT comparing loaded and non-loaded beads revealed no significant differences in OS, PFS, and local response[61]. However, the study population was markedly different as in this study were included many patients with portal vein thrombosis, extrahepatic disease and in BCLC stage C or with tumors below 3 cm. These differences in the patient and tumor characteristics can readily explain the conflicting results of these two studies. We can argue that bland and loaded embolization provide similar results in patients with advanced tumors or in patients with small tumors < 3 cm. However, for larger tumors within BCLC B stage and for BCLC A patients with single tumor larger than 3 cm not suitable for surgery or ablation the presence of the chemotherapeutic in the microsphere seems to provide better results[47].

IX. New lesions/Tumor Recurrence

Patients treated with DEB-TACE need a strict follow-up with both imaging techniques and serum AFP assay even if CR has been achieved since local recurrence may occur in up to 38.4% with new lesions developing in up to 76.9% in the previously non-tumorous liver[17]. These high recurrence levels suggest that DEB-TACE cannot be considered a curative treatment even when CR has been achieved. Local recurrence rates for c-TACE are similar ranging from 20% to 53.2% for segmental embolization and from 58% to 78% for non- segmental embolization[17,63,64].

X. Toxicity and Adverse Events

Adverse events of DEB-TACE do not differ from those of c-TACE with the exclusion of doxorubicin-related effects, tolerability and post embolization syndrome (PES) that are reported to be milder with DEB-TACE[12]. Grade 4-5 complications are reported to range between 1.26-5.48% of the cases[1,13,54,55]. The most common adverse event is PES that occurs in 16.6-63.6% of the cases in

clinical case studies[1,2,12,37]. This great variability in reporting the PES occurrence is probably due to the fact that some investigators report as side effects single components of PES such as pain, fever and nausea/vomiting[64]. Transient liver enzyme elevation after DEB-TACE is frequently reported but less frequent than in c-TACE[12].

Conclusions

TransArterial ChemoEmbolization (TACE) is a minimally invasive procedure with an established role for the management of primary and secondary hepatic tumors. Recently, DEB-TACE has emerged as an advancement of c-TACE having the potential for the selective delivery of large amounts of antineoplastic drugs to the tumor for a prolonged period of time, thereby decreasing plasma levels of the chemotherapeutic agent and related systemic effects. Among the parameters affecting the effectiveness of DEB-TACE the most important are an appropriate patient selection performed in a Multidisciplinary Tumor Board program, a careful evaluation of the hepatic as well as the extrahepatic arterial anatomy, and a deep knowledge of main technical features of the microspheres.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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