

Transcatheter Treatment of Hepatocellular Carcinoma with Doxorubicin-loaded DC Bead (DEBDOX): Technical Recommendations

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Received: 23 February 2011 / Accepted: 27 September 2011 / Published online: 19 October 2011
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Abstract Transarterial chemoembolization (TACE) has been established by a meta-analysis of randomized controlled trials as the standard of care for nonsurgical patients with large or multinodular noninvasive hepatocellular carcinoma (HCC) isolated to the liver and with preserved liver function. Although conventional TACE with administration of an anticancer-in-oil emulsion followed by embolic agents has been the most popular technique, the introduction of embolic drug-eluting beads has provided an alternative to lipiodol-based regimens. Experimental studies have shown that TACE with drug-eluting beads has a safe pharmacokinetic profile and results in effective tumor killing in animal models. Early clinical experiences have

confirmed that drug-eluting beads provide a combined ischemic and cytotoxic effect locally with low systemic toxic exposure. Recently, the clinical value of a TACE protocol performed by using the embolic microsphere DC Bead loaded with doxorubicin (DEBDOX; drug-eluting bead doxorubicin) has been shown by randomized controlled trials. An important limitation of conventional TACE has been the inconsistency in the technique and the treatment schedules. This limitation has hampered the acceptance of TACE as a standard oncology treatment. Doxorubicin-loaded DC Bead provides levels of consistency and repeatability not available with conventional TACE and offers the opportunity to implement a

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standardized approach to HCC treatment. With this in mind, a panel of physicians took part in a consensus meeting held during the European Conference on Interventional Oncology in Florence, Italy, to develop a set of technical recommendations for the use of DEBDOX in HCC treatment. The conclusions of the expert panel are summarized.

Keywords Chemoembolization · Doxorubicin · Drug-eluting bead · Hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related death [1]. Unlike most solid cancers, future incidence and mortality rates for HCC were projected to largely increase in several regions around the world over the next 20 years [2, 3]. A careful multidisciplinary assessment of tumor characteristics, liver function, and physical status is required for proper therapeutic management of HCC [4, 5].

Transarterial chemoembolization (TACE) has been established by a meta-analysis of randomized controlled trials as the standard of care for nonsurgical patients presenting with large or multinodular noninvasive tumor isolated to the liver and preserved liver function [6]. TACE is also used in patients with early-stage HCC when curative therapies—including liver transplantation, hepatic resection, and image-guided ablation—are precluded as well as in the setting of combination strategies including transcatheter and percutaneous treatments [7–12].

The ideal TACE scheme should allow maximum and sustained concentration of the chemotherapeutic drug within the tumor with minimal systemic exposure combined with calibrated tumor vessel obstruction [13]. Although conventional TACE with administration of an anticancer-in-oil emulsion followed by embolic agents has been the most popular technique, the introduction of embolic, drug-eluting beads has provided an attractive alternative to lipiodol-based regimens [11, 14, 15]. Experimental studies have shown that TACE with drug-eluting beads has a safe pharmacokinetic profile and results in effective tumor killing in animal models [16–18]. Early clinical experiences have confirmed that drug-eluting beads provide a combined ischemic and cytotoxic effect locally with low systemic toxic exposure [19–24].

Recently, the clinical value of a TACE protocol performed by using the embolic microsphere DC Bead (Biocompatibles, UK) loaded with doxorubicin (DEBDOX; drug-eluting bead doxorubicin) has been shown by randomized controlled trials. In particular, in a multicenter study including 201 European patients (PRECISION V), use

of DEBDOX resulted in a marked and statistically significant reduction in liver toxicity and drug-related adverse events compared with conventional TACE with lipiodol and doxorubicin [25, 26]. Contrary to the observation in the conventional TACE arm, high-dose doxorubicin treatment could be applied according to the planned schedule in the whole DEBDOX group, resulting in consistently high rates of objective response and disease control in all preplanned subgroup analyses [25]. Two other trials reported higher rates of tumor response and longer time to progression for the loaded DC Bead as compared to a bland embolic microsphere with similar characteristics [27, 28]. As a result of these investigations, DEBDOX has been increasingly used as the first-line transcatheter treatment for HCC [29–32].

An important limitation of conventional TACE has been the inconsistency in the technique and the treatment schedules. This limitation has greatly hampered the acceptance of TACE as a standard oncology treatment. DEBDOX provides levels of consistency and repeatability not available with conventional TACE, and offers the opportunity to implement a standardized approach to HCC treatment. With this in mind, a panel of physicians took part in a consensus meeting held during the European Conference on Interventional Oncology in Florence, Italy, to develop a set of technical recommendations for the use of DEBDOX in HCC treatment. The conclusions of the expert panel are summarized here.

Technical Recommendations for the Use of DEBDOX in HCC Treatment

The technical recommendations that are presented in this document represent the consensus of a panel of experts, all of whom have experience with the use of DEBDOX in HCC treatment. However, although these recommendations may be used as general guide to the use of DEBDOX in HCC treatment, the interventional radiologist treating the patient is the only physician who can decide how to approach the unique combination of patient and tumor characteristics that he or she is facing at the time of the procedure.

Pretreatment Imaging

Obtaining a triple-phase computed tomography (CT) or magnetic resonance imaging of the liver is required to integrate clinical and laboratory data to evaluate the indication to transcatheter treatment of HCC with DEBDOX in each individual patient by the local multidisciplinary liver tumor board. Additional imaging examinations to exclude extrahepatic disease should be performed as appropriate.

Periprocedure Medication

Pain medication should be provided according to standard hospital protocols. Antibiotic prophylaxis and gastric protection should be administered at the physician's discretion.

Loading Dose of Doxorubicin

Each vial of DC Bead (2 ml of beads) should be loaded with 50–75 mg doxorubicin (loading dose, 25–37.5 mg doxorubicin/ml of beads).

Planned Dose of Doxorubicin

The planned dose of doxorubicin should depend on the extent of the liver tumor burden. We acknowledge, however, that absolute recommendations cannot be issued in this regard, as individual patient- and tumor-related factors play an important role in the decision. As a general rule, different doses are recommended for patients with limited disease (defined as HCC within Milan criteria for liver transplantation: single tumor ≤ 5 cm or multiple tumors (up to 3) ≤ 3 cm each, or more advanced disease.

For disease within the Milan criteria, as a general rule, each single treatment should include a planned dose of up to 75 mg doxorubicin loaded into one vial of DC Bead. For disease beyond the Milan criteria, as a general rule, each single treatment should include a planned dose of up to 150 mg doxorubicin loaded into two vials of DC Bead.

In bilobar tumors, the two hepatic lobes can be treated in separate treatment sessions 2–4 weeks apart, in the absence of complications requiring a longer time interval between the two sessions. Obtaining confirmation that the liver enzymes have returned to baseline before performing the second treatment session is recommended. Treatment of both hepatic lobes in the same treatment session is possible in properly selected candidates if adequate interventional and clinical expertise is in place. In this case, the dose will be split according to the extent of the tumor burden in each lobe.

In very large tumors, even if unilobar, the same approach including two sessions should be followed, as a general rule. Indication to transcatheter treatment with DEBDOX in patients with tumor replacing more than 50% of the liver parenchyma, however, should be carefully evaluated. Adequate interventional and clinical expertise is required to manage patients with such advanced disease.

Choice of DC Bead Size

Use of 100–300 μm beads is recommended for a standard procedure. This choice is based on the demonstration that

such small particles are delivered inside the tumor or in close proximity to the tumor margin and thus are ideal for drug delivery or precise embolization [33]. However, individual patient and tumor characteristics, particularly the identification of arteriovenous shunting, should be taken into account when the safety of the treatment and the choice of DC Bead size are determined. In the case of significant arterioportal or hepatic venous shunting, embolization of the shunt with gelfoam pledgets is recommended before proceeding with DEBDOX administration. Angiographic confirmation that the shunt is no longer present must be obtained before DEBDOX injection can be performed, and a larger bead size may be preferred.

DC Bead Dilution

Loaded DC Bead should be mixed with a nonionic contrast medium. At least 5–10 ml of nonionic contrast should be used per 1 ml of DC Bead (i.e., 10–20 ml are required to dilute one vial of DC Bead) before injection. A good suspension of DC Bead in the contrast should be ensured before delivery.

Catheter Positioning

A superselective (i.e., segmental or subsegmental) approach should be used whenever possible by using a microcatheter. Use of 3D multiplanar reconstructions (MPR) obtained from C-arm rotational angiography with a flat-panel detector system (cone-beam CT) is recommended, if available, to improve the accuracy in identifying tumor-feeding arteries [34–36]. In addition, repeat cone beam CT is recommended after successful delivery of the DC Bead to confirm adequate targeting and saturation of the tumor(s).

For the segmental/subsegmental approach, the microcatheter is placed distally in the segmental/subsegmental tumor feeding vessel while ensuring that there is sufficient flow to the tumor. The clinician should avoid wedging the catheter to prevent reflux along the catheter shaft.

For the lobar approach, the catheter should be placed as selectively as possible in the right or left hepatic artery, with the clinician paying attention to identifying the origin of the cystic artery as well as other arteries supplying flow to extrahepatic organs. If identified, these vessels must be either embolized using coils or avoided by placing the catheter tip well beyond the origin of these vessels. In addition, forward flow into the desired vessel must be maintained because inadvertent administration or reflux of DC Bead into these extrahepatic vessels would be undesirable.

Injection Rate

The injection must be very slow. An injection rate of 1 ml of the contrast agent—DC Bead suspension per minute is recommended. Care should be taken to avoid sedimentation of the beads in the syringe by rotating the syringes or using a three-way stopcock to gently suspend the beads in the solution.

Embolization End Point

Injection should be continued until near stasis is observed in the artery directly feeding the tumor (i.e., the contrast column should clear within 2–5 heartbeats). At that point, injection must be stopped, regardless of the amount of beads that have been actually administered, to avoid reflux of embolic material. Once the embolization end point has been achieved, no additional embolic material should be injected.

If the near-stasis end point is not obtained after injection of the scheduled volume of loaded beads, two different options are possible. One option is to inject additional unloaded beads until the embolization end point has been reached. Another option is to not inject additional unloaded beads and to schedule the patient for a repeat course of treatment after imaging follow-up. This second option was supported by most panelists. However, there are insufficient data to mandate one strategy over the other.

Posttreatment Imaging

Obtaining a triple-phase CT or magnetic resonance imaging of the liver 2–4 weeks after treatment is recommended to assess tumor response and to plan further action. The panel recommends the use of the modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC guideline for response classification [37]. Tumor response measured by mRECIST after transcatheter or systemic therapy has been shown to be associated with survival [38, 39].

In patients with residual viable tumor—including partial response, stable disease, and progressive disease according to mRECIST—further treatment with DEBDOX can be scheduled after 4–8 weeks in the absence of contraindications. Obtaining confirmation that the liver enzymes have returned to baseline before repeating treatment is recommended.

In patients with no evidence of residual viable disease—i.e., with complete response according to mRECIST—imaging follow-up should be scheduled every 2–3 months.

Treatment Discontinuation

Treatment with DEBDOX should be discontinued—even if technically feasible—in patients presenting with

untreatable progression [40]. Untreatable progression is defined as failure to achieve objective response in the targeted tumor after at least two DEBDOX treatments. The emergence of new intrahepatic tumor foci remote from the treated territory, although clearly representing tumor progression according to mRECIST for HCC, does not contraindicate further treatment with DEBDOX. In cases of clinical or functional deterioration, treatment should be discontinued in patients who have clinical progression to ECOG performance status > 2 or who experience evolution to sustained hepatic decompensation (not merely after therapy).

Final Remarks

The technical recommendations that we summarize here represent the consensus of a panel of experts and are aimed at defining standards for an appropriate and consistent use of DEBDOX in the treatment of HCC. However, given the many patient- and tumor-related variables that play a role in the decision-making process, this is intended as no more than a general guideline. We fully acknowledge that, given the complexity of HCC, individual patient and tumor characteristics may require a different approach. Interventional radiologists should not follow these technical recommendations if, in their opinion, a different approach is required for the individual patient.

Finally, despite the improved tolerability profile of DEBDOX with respect to conventional TACE, it is imperative that interventional radiologists are fully aware of the spectrum of potential adverse events associated with the procedure to prevent complications or manage them properly [41].

Acknowledgment The authors thank the Research Analysis Library for assistance in the literature review and in the preparation and revision of the article, based on our detailed feedback. Editorial assistance was supported by Biocompatibles UK Limited.

Conflict of interest The authors declare that they have no conflict of interest.

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