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**TRANSARTERIAL EMBOLIZATION  
FOR HEPATOCELLULAR CARCINOMA :  
CURRENT TRENDS**

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# Transarterial embolization for hepatocellular carcinoma : current trends

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## SUMMARY

Transarterial chemoembolization (TACE) is the most widely used loco-regional treatment for hepatocellular carcinoma (HCC), not only in the intermediate-stage, but often also in early or advanced disease.

Amongst the HCC therapies, TACE is the least standardized, both in terms of indications and techniques.

The conventional TACE (with intra-arterial administration of chemotherapeutic drug emulsified with Lipiodol, followed by embolisation of the tumour-feeding blood vessels with gelfoam particles) is progressively challenged by drug-eluting beads (DEB)-TACE that maximise the concentration of cytotoxic drug at tumour level, with a minimal systemic exposure, and guarantees a calibrated arteries obstruction.

The microspheres, along with their embolic properties, sequester the chemo-therapeutic agent and release it over a one-week period.

At present, the data in the literature do not confirm the superiority of DEB-TACE and the choice is therefore left to the operator. Several cytotoxic drugs are administered, either in conventional or DEB-TACE. The most widely used is doxorubicin, with however no evidence of its superiority over other chemotherapeutics and also epirubicin proved to be effective and safe.

Recently, idarubicin, an anthracycline approved for haematological malignancies, was investigated in the context of HCC chemoembolization. In vitro studies identified idarubicin as the most active drug on HCC cell lines but, at present, there are scanty data on its tolerability and efficacy in vivo. The most important adverse event of anthracyclines is the irreversible cardiotoxicity that develops after a total cumulative dose of 450 mg/m<sup>2</sup> for doxorubicin and 93 mg/m<sup>2</sup> for idarubicin.

In conclusion, the most widely used loco-regional treatment for hepatocellular carcinoma is the least standardised. There are currently no sufficient data to establish the superiority of DEB- over conventional-TACE and uncertainty also concerns the cytotoxic drug to use. There is no evidence that doxorubicin, the most frequently administered drug, is the best chemotherapeutic agent for TACE while recently idarubicin proved to be effective and safe, but the limited data available needs confirmation in large prospective randomized trials.

## EVIDENCE REGARDING TACE FOR HCC TREATMENT

Transarterial chemoembolization (TACE) is the most widely used treatment for unresectable hepatocellular carcinoma (HCC) and is the recommended first-line therapy for patients with intermediate-stage disease (BCLC B).<sup>[1]</sup> HCC, as a result of its intense neo-angiogenetic activity during progression, is almost entirely fed by arterial blood flow, unlike the surrounding parenchyma that receives the majority of the inflow through the portal system. The rationale for TACE is that the intra-arterial infusion of a cytotoxic agent followed by embolization of the tumour-feeding blood vessels will cause the necrosis of the neoplasia, based on the effect of the local chemotherapy and of embolization-induced tumour ischaemia.

The survival benefits of TACE, compared to best supportive care, was basically demonstrated by two randomized controlled trials<sup>[2,3]</sup> and subsequent meta-analysis<sup>[4,5]</sup>.

Consequently, TACE is widely used in intermediate HCCs but also outside this specific scenario; actually, in clinical routine practice, approximately 40% of TACE procedures are performed in either BCLC A or, more rarely, BCLC C patients.<sup>[6]</sup> This approach has been used in patients with early-stage HCC as a bridge to liver transplantation or when curative treatments are not possible, mostly due to HCC position in the liver.

Amongst all the possible therapies in HCC, TACE is the least standardized, widely varying as for chemotherapeutic agents injected, treatment devices used and therapeutic schedule<sup>[7]</sup>. This poor standardization is outlined in some guidelines, such as the Chinese ones, for instance, that recommend to perform individualized chemoembolization protocols<sup>[8]</sup>. The heterogeneous practices among interventional radiologists were outlined in two surveys, in terms of indications, techniques and also in the assessment of tumour response<sup>[6,9]</sup>.

Conventional TACE (the so called Lipiodol-TACE) is based on the delivery of aqueous solution of cytotoxic agents, emulsified with Lipiodol, followed by embolization with particles (the most widely used being gelatine sponge, or Gelfoam). In the past 2 decades however, strategies to improve anti-tumour activity and safety of chemo-embolization have been developed. The ideal TACE technique should guarantee high intra-tumour chemotherapeutic drug levels with minimal systemic exposure, along with calibrated tumour arteries obstruction. Therefore, embolic microspheres were developed with ability to sequester the chemotherapeutic agent and release it over time (a one-week period). These microspheres (or drug-eluting beads - DEBs) are composed of a hydrophilic, ionic polymer that can bind anthracyclines via an ion exchange mechanism.

TACE with drug-eluting beads (DEB-TACE), using calibrated microspheres pre-loaded with doxorubicin, has shown more sustained and tumour selective drug delivery, with low circulating drug levels and with permanent embolization. With this technique the side effects are reduced, due to the minimum passage of doxorubicin in the systemic circulation<sup>[10]</sup>.

Several trials compared c-TACE and DEB-TACE both in terms of efficacy and safety.

The most relevant, the PRECISION V study<sup>[11]</sup> elucidated some advantages of DEB-TACE: the drug-eluting bead group showed higher rates of objective response and disease control rate compared with conventional TACE, despite not meeting the hypothesis of superiority in terms of tumour response at 6 months. However, more fragile patients (Child-Pugh B, ECOG-PS 1, with bilobar or recurrent disease) showed a significant increase in objective response. Moreover DEB-TACE was associated with improved tolerability, with a significant reduction in serious liver toxicity and a lower rate of doxorubicin related adverse events.

A second randomized controlled trial<sup>[12]</sup> compared the two TACE techniques, confirming the absence of any difference in terms of overall survival and adverse events (with the exception of post-procedural pain, that was more frequent in the c-TACE group).

Finally, a meta-analysis confirmed the equivalence of the two procedures<sup>[13]</sup>. The current European guidelines do not endorse one technique over the other, due the lack of sufficient evidence, and leave the choice to the operator<sup>[1]</sup>. At least in Italy, DEB-TACE seems to be performed nowadays more frequently than conventional TACE (52% vs. 32%)<sup>[6]</sup>.

An additional debatable point is the choice of the chemotherapeutic drug to use. There is indeed no univocal agreement on the optimal chemotherapy to use in TACE and no cytotoxic agent definitely proved superiority over the others<sup>[14]</sup>. The agent most frequently used, either in conventional or DEB-TACE, is doxorubicin, administered at a dose varying from 30 to 75 mg/m<sup>2</sup> (to a maximum of 150 mg per session)<sup>[15]</sup>. When loaded in microspheres, doxorubicin is progressively released and the maximal blood concentration (C<sub>max</sub>) and the area under the curve (AUC) of doxorubicin are considerably inferior in DEB-TACE patients in comparison with what found evaluating patients treated in the conventional way. This is due to the passage of the drug in the systemic circulation being lower even when very high doses are used<sup>[10]</sup>.

RCTs and meta-analysis demonstrated that doxorubicin administered in the setting of DEB-TACE is as effective as administered when emulsified with Lipiodol<sup>[11-13]</sup>. Also regarding safety no substantial differences were observed.

Despite being the most frequently used, there is no evidence that doxorubicin is the most appropriate chemotherapeutic agent for TACE in HCC. The rationale for its use is quite limited and no rigorous pre-clinical data have ever supported its preferential use respect to other cytotoxic agents<sup>[16]</sup>. There are no randomized studies demonstrating the superiority of doxorubicin over other drugs. The two RCTs that compared this drug to epirubicin in TACE for HCC did not show any difference in terms of efficacy<sup>[17,18]</sup>. A recent meta-analysis on epirubicin in TACE concluded that it is as effective and safe as the other drugs<sup>[19]</sup>.

With respect to specific techniques, in vitro studies demonstrated that the microspheres can be loaded with several different drugs<sup>[20,21]</sup>; epirubicin is one of them and data available show that DEB-TACE with epirubicin is effective and safe<sup>[22]</sup>. The pharmacokinetics of the drug in patients treated with epirubicin-loaded microspheres is similar to that of doxorubicin<sup>[23]</sup>.

Another frequently used cytotoxic agent administered in TACE is cisplatin<sup>[14]</sup>. Switching from epirubicin-loaded to cisplatin-loaded microspheres in the treatment of non-responders HCC patients proved to be an effective, safe and well tolerated salvage therapy<sup>[24]</sup>. Miriplatin was also investigated as chemotherapeutic agent in TACE, but it failed to demonstrate an improvement in efficacy<sup>[25]</sup>.

A study performed in vitro on three human hepatocellular carcinoma cell lines identified idarubicin as the most active among 11 drugs (anthracyclines, platinum derivatives, anti-metabolites, mitomycin-C, paclitaxel)<sup>[26]</sup>. Idarubicin is a key drug used in haematology to treat acute leukaemia<sup>[27]</sup>, and it has mainly an haematological and cardiac toxicity profile.

In Italy, idarubicin can be administered for myeloid and lymphoblastic leukaemia in adult and young patients, and for advanced breast cancer. Beyond being active on HCC cell lines, idarubicin proved to overcome the multidrug resistance (MDR) mechanism, so active in HCC cells, remaining longer within the cells as compared to other anthracyclines. Additionally, being a lipophilic molecule, it has a high penetration rate through the lipid double layer of tumour cell membrane<sup>[26]</sup>. There are two small studies investigating the use of idarubicin both in conventional and in drug-eluting beads TACE, demonstrating the tolerability and a promising efficacy<sup>[16,28]</sup>, but larger clinical trials are needed.

Amongst anthracyclines, in Italy there are no relevant differences in cost. There is no evidence for an anthracycline to be more active than the others and preferring doxorubicin with respect to epirubicin, or vice versa, probably is a centre-specific choice or a choice of the interventional radiologist. The larger Italian survey aimed to investigate how interventional radiologists perform the TACE procedure does not provide any information about the cytotoxic drug preferentially used<sup>[6]</sup>.

The development of cardiotoxicity is the most worrying adverse event in the administration of anthracyclines. The possible explanation for the toxicity in cardiomyocytes is related to the free radical formation caused by anthracyclines metabolism<sup>[29]</sup>. Acute cardiotoxicity is relatively rare and manifests as myopericarditis. Chronic cardiotoxicity is the most important form of cardiotoxicity: it can progress from early asymptomatic left ventricular systolic dysfunction to overt congestive heart failure (CHF)<sup>[30]</sup>. Chronic cardiotoxicity is further classified in early onset (within one year of therapy completion), which is more common, and late-onset (after the first year of completion of therapy). Exposure to anthracyclines results in myocyte necrosis and is irreversible<sup>[30]</sup>.

The most important determinant of the development of heart failure is the total cumulative lifetime anthracyclines dose, but others risk factors that can augment the possibility to develop cardiotoxicity are extreme age (> 65 or < 5), female gender, prior mediastinal radiation therapy, hypertension and pre existing cardiovascular disease<sup>[29,30]</sup>. It is generally accepted that a cumulative dose of doxorubicin higher than 450 mg/m<sup>2</sup> is associated with cardiotoxicity<sup>[30]</sup>. However, the risk of developing heart failure is directly proportional to the cumulative dose of doxorubicin administered (from 0.2% of patients with a CHF at a cumulative dose of doxorubicin of 150 mg/m<sup>2</sup> to 8.7% of patients with CHF at a cumulative dose of 600 mg/m<sup>2</sup>)<sup>[31]</sup>.

The comparison of various anthracycline agents for their cardiotoxicity is complex and no consensus exists regarding the equivalence ratios across them for cardiotoxicity<sup>[30]</sup>. Some phase II trials in the setting of breast cancer and haematological malignancies showed that idarubicin is associated with a lower cardiac function depression than doxorubicin<sup>[32,33]</sup> and also an experimental model (isolated perfused rat heart) confirm that the cardiac toxicity of idarubicin is significantly lower than that of doxorubicin<sup>[34]</sup>. To the best of our knowledge, there are no studies specifically addressing and estimating the risk of cardiotoxicity in patients treated by repeated TACE sessions.

An evaluation of cardiac toxicity in this setting can be extrapolated from data of the PRECISION V randomized trial, in which patients were randomized to be treated with conventional or DEB TACE, in both cases with doxorubicin<sup>[35]</sup>. Cardiac function was maintained in the DEB group, whereas there was a small but statistically significant deterioration in left ventricular ejection fraction in the conventional TACE group. In addition, in the conventional TACE group an increased incidence of cardiac events was observed (4.3% of DEB and 7.4% of conventional TACE patients). However, the interpretation of these results must be very cautious given the large number of not evaluable patients (most of whom withdrawn).

Considering a median dose of 50-75 mg/m<sup>2</sup> of doxorubicin for a single TACE procedure and a maximum cumulative dose of 450 mg/m<sup>2</sup> to avoid cardiotoxicity, 6-9 TACE are allowed in a single patient, but it has to be considered that in TACE doxorubicin is administered locally with a small amount of the drug reaching the systemic circulation.

However, according to European guidelines<sup>[1]</sup>, TACE should not be repeated when substantial necrosis is not achieved after two rounds of treatment or when follow-up treatments fails to induce marked necrosis at sites that have progressed after initial tumour response. Also the guidelines set at 450 mg/m<sup>2</sup> the limit of cumulative doxorubicin that should be administered. There are only few data in the literature regarding the cardiotoxicity of idarubicin in the context of TACE<sup>[16,28]</sup>. The cumulative dose of idarubicin associated with cardiotoxicity was 93-150\* mg/m<sup>2</sup> (and 450-720\* mg/m<sup>2</sup> for epirubicin) with a 5.9:1 ratio between doxorubicin and idarubicin for cumulative toxicities<sup>[16]</sup>. Additional studies on this issue are needed and currently a phase 2 trial on DEB-TACE with idarubicin-loaded microspheres is ongoing (IDASPHERE II).

The use of DEB-TACE in HCC patients led to a significantly lower rate of re-hospitalization for the management of TACE-related toxicities, with a better economic profile<sup>[36]</sup>. An Italian group presented a cost-effective analysis comparing c-TACE and DEB-TACE that showed that the direct incremental costs of DEB-TACE are not particularly high and can be amortized by the shorter hospital stay, the better quality of life and the mild survival improvement obtained (point not confirmed in the general literature)<sup>[37]</sup>. The authors concluded that DEB-TACE is cost-effective compared to the conventional procedure.

\*According to different EU SMPCs.

## CONCLUSION

In conclusion, TACE is widely used in the treatment of patients with HCC, not only in those with intermediate-stage disease but also in the early and, less frequently, advanced stages. Currently, there are not enough data to establish a superiority between conventional and drug-eluting beads TACE, but the latter seems to be more tolerable and cost-effective and is now gaining progressive sympathy.

A large number of cytotoxic drugs have been tested, either emulsified in Lipiodol or loaded into microspheres, and anthracyclines (doxorubicin and epirubicin) are the most widely used.

Cardiotoxicity related to the total cumulative dose of anthracyclines administered is the most relevant adverse event.

Despite the limited amount of data available, idarubicin seems to be an active and tolerable drug to be used in chemoembolization. The in vitro superiority of idarubicin remains to be confirmed in prospective randomized trials; however, this will be a challenging trial to perform, since TACE is not a standardized procedure.

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