

Summary and conclusion

Hepatocellular carcinoma is the most frequent primary tumor of the liver, the incidence of which is increasing worldwide. Cirrhosis of the liver, regardless of etiology, is considered to be the main risk factor for the onset of HCC. Hepatitis C and B virus are the main factor related to the presence of cirrhosis of the liver in patients with hepatocellular carcinoma. Trans arterial chemoembolisation (TACE) is the most widely used treatment for hepatocellular carcinoma in non surgical patients not suitable for radiofrequency ablation .

To best assess the prognosis of hepatocellular carcinoma patients it is recommended that the staging system takes into account tumor stage, liver function and physical status. Currently, the BCLC system is the only staging system that accomplishes this aim. Patients who have intermediate-stage hepatocellular carcinoma according to the BCLC staging system are the optimal candidates for transcatheter arterial chemoembolization as a palliative treatment. Palliative options should aim to improve survival without greatly impairing the quality of life.

In conventional TACE therapy, tumor selectivity is achieved when chemotherapeutic agents are mixed with lipiodol , to induce ischemia in tumors. In addition, there are side effects of Lipiodol as it penetrates the portal venules and hepatic sinusoids and affects the hepatic microcirculation, also doxorubicin is lost from lipiodol in a very short period of time.

DC Bead microspheres are a new embolic material for TACE, in which the embolization particles are made from a unique drug –eluting bead (DEB) technology based on polyvinyl alcohol (PVA) hydrogel that has been modified with sulphonate groups. They can be loaded with a chemotherapeutic agent widely accepted for treatment of HCC.

The advantage of using it is sustained release of chemotherapeutic agent over a long period of time, which contrasts with the more rapid release of the agents from the lipiodol solution in standard TACE therapy. With a controlled gradual and local release, contact time of the drugs with the tumor is greater and plasma levels of the drugs are lower than those

with standard TACE therapy, also less side effects and doubling the dose using 150 mg instead of 70 -100 mg using lipidol

Good results are generally observed when a reduced number of not very large tumors are embolized in a selective fashion (ideally through a distinct feeding vessel). From a mechanistic point of view, DEB are a much more reasonable and reproducible way to perform TACE. In fact, the two particles available are claimed to turn TACE into a feasible and well-tolerated procedure associated with a low complication rate and a promising tumor response rate.(**Bruno Sangro et ,2011**).

Secondary endpoints, including reduction in drug-related adverse events or increased intra tumoral necrosis (which makes the difference between RECIST and EASL criteria), have been proven successful and are consistent with the well-known characteristics of the beads as shown in preclinical work. The potential advantage of DEB-TACE over conventional TACE in the subgroup of patients with the worst prognosis (Child-Pugh B, ECOG 1, bi lobar or recurrent disease, Okuda stage I tumor and CLIP score ≥ 3) should be treated with caution because it comes from the analysis of a very small group of patients and it is generally recognized that TACE should be indicated very in this subgroup of patients who have a poor prognosis for which a survival advantage has not been shown after conventional TACE, The safety profiles of the two modalities of treatment appear similar.. .(**Bruno Sangro et ,2011**)

authors of a recent prospective randomized comparison (**Malagari K et al 2010**) of chemoembolization with doxorubicin-eluting beads and arterial embolization with Bead Block (Biocompatibles, UK) for HCC concluded that although ischemia plays

a role in the development of tumor necrosis, there is a clear additional benefit from the addition of doxorubicin. In that study, there was a complete response in 26.8% of patients in the drug-eluting bead group and 14% in the arterial embolization group at 6 months.

Altogether, the results of RCTs and retrospective series suggest that ¹³¹I-lip could achieve similar a disease control rate and overall survival a conventional TACE and that, in fact, it could be an alternative to TACE for patients with bi lobar disease or PVT as it is better tolerated and less likely to induce liver dysfunction. However, ¹³¹I-lip has not gained widespread use in the management of un resectable HCC, its major drawbacks being the need for radioprotection due to the gamma radiation emitted that keeps patients isolated for 7 - 10 days after therapy.

⁹⁰Y-RE circumvents these drawbacks and an incremental use has been observed in the last decade. How ⁹⁰Y-RE compares with TACE in the same patient population is a difficult question to answer due to the lack of RCTs comparing the two techniques. A rough estimate from the available survival data suggests that a non-inferiority trial would probably need to recruit more than 1000 patients, which makes such a trial quite unlikely. **(Bruno Sangro et ,2011).**

The decision to submit a patient for ⁹⁰Y-RE should then be taken individually. The rate of complete necrosis seems to favor the use of ⁹⁰Y-RE over TACE in those patients with early tumors that cannot be treated radically because of age, poor liver function, comorbidity, or lack of per cutaneous accessibility. Either procedure can be used as a bridge to liver transplantation or with the intention to downstage tumor at intermediate stage for radical therapies. TACE is certainly the standard of care for those patients with small to medium-sized tumors

that can be treated selectively, and it can be provided in most centers. (**Bruno Sangro et al ,2011**).

90Y-RE could be then be an alternative to repeated TACE for patients who fail to respond to initial TACE, and a first option in those who are poor candidates for TACE, mainly because of bulky disease and PVT, but who still have good liver function. Although, in this group of patients who are poor candidates for TACE, 90Y-RE may have a role as an alternative to sorafenib, more reasonably both therapies should be combined to extend disease control and suppress the development of new lesions.

Preliminary results from this combination are encouraging and a large clinical trial is underway to provide an answer to this relevant question. After years of indiscriminate use in unresectable HCC patients, the availability of alternative therapies with documented (sorafenib) or highly suspected (radioembolization) activity is progressively restricting the indications for TACE. In the coming years, much attention is likely to be paid to the combination of targeted agents with antiangiogenic activity and locoregional therapies. .(**Bruno Sangro et ,2011**).

The results of ongoing clinical trials will establish the best way of combining sorafenib and other targeted therapies with trans arterial procedures including TACE and 90Y-RE. Until they are reported, it is important to bear in mind that in those patients who are not good candidates for TACE (mainly because of a high tumor burden or the presence of vascular invasion) and in those who progress to the first sessions of TACE, a treatment switch to either 90Y-RE or sorafenib has to be seriously considered. Finally, there is the need to develop calibrated particles with an intermediate size (in the range of 50 -- 100 microns -- larger that those used in radio embolization but smaller than

those currently used in TACE) that could load anticancer agents (isotopes, chemicals, or biologicals). (**Bruno Sangro et al, 2011**)

(**Carr BI et al, 2010**) found therapeutic equivalence in survival when comparing radioembolization and chemoembolization in a two-cohort study of patients with unresectable HCC. In 2009, Lewandowski et al compared the downstaging effectiveness of chemoembolization versus radioembolization in 86 patients with unresectable HCC.

Disease in 58% of patients who underwent radioembolization was downstaged to stage T2, while that in 31% of those who underwent chemoembolization was downstaged ($P = .02$). Radioembolization was shown to be a better tool than chemoembolization for downstaging the disease from a size outside transplant criteria to a size within the Milan criteria for transplantation.

Recently, **Salem et al 2011** demonstrated similar survival times for patients with unresectable HCC treated with transarterial chemoembolization or radioembolization. In that comparative effectiveness analysis, radioembolization resulted in longer time to progression and less toxicity than did chemoembolization ($P , .05$).

CEUS is a feasible and safe method for rapid, onsite assessment of the effect of TAE/TACE. Similar to CEUS performed days or weeks after TACE intraprocedural CEUS easily differentiated necrotic (nonenhancing) from viable (enhancing) tumor components sonography can detect parenchymal and perfusional changes that occur hyperacutely within minutes after the injection of embolic material into liver tumor vessels. Although most of the relevant unenhanced sonographic findings correlate poorly with the efficacy of the treatment, CEUS may readily