Chemoembolization of hepatocellular carcinoma with drug eluting beads

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Hepatocellular carcinoma is the most frequent primary tumor ofthe liver, the incidence of which is increasing worldwide. Cirrhosis of theliver, regardless of etiology, is considered to be the main risk factor forthe onset of HCC. Hepatitis C and B virus are the main factor related tothe presence of cirrhosis of the liver in patients with hepatocellularcarcinoma. Trans arterial chemoembolisation (TACE) is the most widelyused treatment for hepatocellular carcinoma in non surgical patients notsuitable for radiofrequency ablation .To best assess the prognosis of hepatocellular carcinoma patientsit is recommended that the staging system takes into account tumor stage,liver function and physical status. Currently, the BCLC system is the onlystaging system that accomplishes this aim. Patients who haveintermediate-stage hepatocellular carcinoma according to the BCLCstaging system are the optimal candidates for transcatheter arterialchemoembolization as a palliative treatment. Palliative options shouldaim to improve survival without greatly impairing the quality of life.In conventional TACE therapy, tumor selectivity is achievedwhen chemotherapeutic agents are mixed with lipidol , to induceischemia in tumors. In addition, there are side effects of Lipidol as itpenetrates the portal venules and hepatic sinusoids and affects the hepaticmicrocirculation, also doxorubicin is lost from lipidol in a very shortperiod of time.DC Bead microspheres are a new embolic material for TACE, inwhich the embolization particles are made from a unique drug –elutingbead (DEB) technology based on polyvinyl alcohol (PVA) hydrogel thathas been modified with sulphonate groups. They can be loaded with achemotherapeutic agent widely accepted for treatment of HCC.The advantage of using it is sustained release of chemotherapeuticagent over a long period of time, which contrasts with the more rapidrelease of the agents from the lipidol solution in standard TACE therapy.With a controlled gradual and local release, contact time of the drugs withthe tumor is greater and plasma levels of the drugs are lower than thoseSummary and conclusion- 135 -with standard TACE therapy, also less side effects and doubling the doseusing 150 mg instead of 70 -100 mg using lipidolGood results are generally observed when a reduced number ofnot very large tumors are embolized in a selective fashion (ideallythrough a distinct feeding vessel). from a mechanistic point of view,DEB are a much more reasonable and reproducible way to performTACE. In -fact, the two particles available are claimed to turn TACE intoa feasible and well tolerated procedure associated with a lowcomplication rate and a promising tumor

response rate.(Bruno Sangroet ,2011).Secondary endpoints, including reduction in drug-related adverseevents or increased intra tumoral necrosis (which makes the differencebetween RECIST and EASL criteria), have been proven successful andare consistent with the well-known characteristics of the beads as shownin preclinical work. The potential advantage of DEB-TACE overconventional TACE in the subgroup of patients with the worst prognosis(Child-Pugh B, ECOG 1, bi lobar or recurrent disease, Okuda stage Itumor and CLIP score _3) should be treated with caution because itcomes from the analysis of a very small group of patients and it isgenerally recognized that TACE should be indicated very in thissubgroup of patients who have a poor prognosis for which a survivaladvantage has not been shown after conventional TACE, The safetyprofiles of the two modalities of treatment appear similar.. .(BrunoSangro et ,2011)authors of a recent prospective randomized comparison(Malagari K et al 2010) of chemoembolization with doxorubicinelutingbeads and arterial embolization with Bead Block(Biocompatibles, UK) for HCC concluded that although ischemia playsSummary and conclusion- 136 -a role in the development of tumor necrosis, there is a clear additionalbenefit from the addition of doxorubicin. In that study, there was acomplete response in 26.8% of patients in the drug-eluting bead groupand 14% in the arterial embolization group at 6 months.Altogether, the results of RCTs and retrospective series suggestthat 131I-lip could achieve similar a disease control rate and overallsurvival a conventional TACE and that, in fact, it could be an alternativeto TACE for patients with bi lobar disease or PVT as it is better toleratedand less likely to induce liver dysfunction. However, 131I-lip has notgained widespread use in the management of un resectable HCC, itsmajor drawbacks being the need for radioprotection due to the gammaradiation emitted that keeps patients isolated for 7 - 10 days after therapy.90Y-RE circumvents these drawbacks and an incremental use hasbeen observed in the last decade. How 90Y-RE compares with TACE inthe same patient population is a difficult question to answer due to thelack of RCTs comparing the two techniques. A rough estimate from theavailable survival data suggests that a non-inferiority trial wouldprobably need to recruit more than 1000 patients, which makes such atrial quite unlikely. (Bruno Sangro et ,2011).The decision to submit a patient for 90Y-RE should then be takenindividually. The rate of complete necrosis seems to favor the use of90Y-RE over TACE in those patients with early tumors that cannot betreated radically because of age, poor liver function, comorbidity, orlack of per cutaneous accessibility. Either procedure can be used as abridge to liver transplantation or with the intention to downstage tumorat intermediate stage for radical therapies. TACE is certainly thestandard of care for those patients with small to medium-sized tumorsSummary and conclusion- 137 -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 forpatients who fail to respond to initial TACE, and a first option in thosewho are poor candidates for TACE, mainly because of bulky disease andPVT, but who still have good liver function. Although, in this group ofpatients who are poor candidates for TACE, 90Y-RE may have a role asan alternative to sorafenib, more reasonably both therapies should becombined to extend disease control and suppress the development of newlesions.Preliminary results from this combination are encouraging and alarge clinical trial is underway

to provide an answer to this relevantquestion. After years of indiscriminate use in unresectable HCCpatients, the availability of alternative therapies with documented(sorafenib) or highly suspected (radioembolization) activity isprogressively restricting the indications for TACE. In the coming years,much attention is likely to be paid to the combination of targeted agentswith antiangiogenic activity and locoregional therapies. .(BrunoSangro et ,2011).The results of ongoing clinical trials will establish the best way ofcombining sorafenib -and other targeted therapies with trans arterialprocedures including TACE and 90Y RE. Until they are reported, it isimportant to bear in mind that in those patients who are not goodcandidates for TACE (mainly because of a high tumor burden or thepresence of vascular invasion) and in those who progress to the firstsessions of TACE, a treatment switch to either 90Y-RE or sorafenib hasto be seriously considered. Finally, there is the need to developcalibrated particles with an intermediate size (in the range of 50 -- 100microns -- larger that those used in radio embolization but smaller thanSummary and conclusion- 138 -those currently used in TACE) that could load anticancer agents(isotopes, chemicals, or biologicals).(Bruno Sangro et ,2011)(Carr BI et al,2010) found therapeutic equivalence insurvival when comparing radioembolization and chemoembolization ina two-cohort study of patients with unresectable HCC. In 2009,Lewandowski et al compared the downstaging effectiveness ofchemoembolization versus radioembolization in 86 patients withunresectable HCC.Disease in 58% of patients who underwent radioembolizationwas downstaged to stage T2, while that in 31% of those who underwentchemoembolized was downstaged (P = .02). Radioembolization wasshown to be a better tool than chemoembolization for downstaging thedisease from a size outside transplant criteria to a size within the Milancriteria for transplantation.Recently, Salem et al 2011 demonstrated similar survivaltimes for patients with unresectable HCC treated with transarterialchemoembolization or radioembolization. In that comparativeeffectiveness analysis, radioembolization resulted in longer time toprogression and less toxicity than did chemoembolization (P , .05).CEUS is a feasible and safe method for rapid, onsiteassessment of the effect of TAE/TACE. Similar to CEUS performed daysor weeks after TACE intraprocedural CEUS easily differentiated necrotic(nonenhancing) from viable (enhancing) tumor components sonographycan detect parenchymal and perfusional changes that occur hyperacutelywithin minutes after the injection of embolic material into liver tumorvessels. Although most of the relevant unenhanced sonographic findingscorrelate poorly with the efficacy of the treatment, CEUS may readilySummary and conclusion- 139 -and reliably demonstrate decreased tumor enhancement caused byTAE/TACE.With increasing experience and refinements in thetechnique, intraprocedural CEUS could serve as a monitoring tool inselected cases of embolotherapy of liver tumors. (Malagari K et al2010)The future of transcatheter therapies is promising. Ongoingresearch in this field incorporates advances in the knowledge of livercancer biology, new concepts in targeting liver cancer, development ofnew drugs, improvement of intra arterial drug delivery techniques, andtechnological advances in imaging systems . (Liapi E et al, 2011).It is anticipated that delivered agents will become more potent,translating into higher efficacy and survival benefit. Furthermore, newtherapies will be developed that may

be more tumor specific or potent.These therapies may involve the delivery of genetic information. Recentresearch has investigated the targeted delivery of gene therapy to the liverby means of isolated hepatic perfusion or via the portal vein (Liapi E etal, 2011).The delivery of gene therapies and other future therapies willlikely use nanotechnology. Nanocomposites could also be tagged to betumor specific, tumor avid, visible at time of delivery, and carry aspecific therapy (Liapi E et al, 2011).Finally, new classes of drugs delivered intra arterially could leadto markedly more potent tumor kill than conventional chemotherapeuticagents. For example, a new class of anticancer drugs, such as 3-bromopyruvate, specifically targeting tumor metabolism could be infusedlocally by means of transcatheter delivery for increased potency, Bydisrupting the ability of the cancer cell to generate energy, but leavingnormal cells intact, this new approach is extremely promising.