EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Chemoembolization for intermediate HCC: Is there proof of survival benefit?

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COMMENTARY ON:
Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma. Oliveri RS, Wetterslev J, Gluud C. Cochrane Database Syst Rev 2011 Mar 16;3:CD004787. Copyright (2011) Cochrane Collaboration, reproduced with Permission.

http://www.ncbi.nlm.nih.gov/pubmed/21412886

Abstract: Background*: Hepatocellular carcinoma (HCC) results in more than 600,000 deaths per year. Transarterial embolisation (TAE) and transarterial chemoembolisation (TACE) have become standard loco-regional treatments for unresectable HCC.*
Objectives*: To assess the beneficial and harmful effects of TACE or TAE.*
Search strategy*: We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Cancer Network register, The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, and The Latin American Caribbean Health Sciences Literature (LILACS) from dates of inceptions up to September 2010.*
Selection criteria*: We considered for inclusion all randomised trials that compared TACE or TAE versus placebo, sham, or no intervention. Co-interventions were allowed if comparable between intervention groups. Trials with inadequate randomisation were excluded.*
Data collection and analysis*: For all-cause mortality, we calculated the log hazard ratio (HR) with standard error as point estimate and pooled them for meta-analysis using the inverse variance method. Sub-group analyses were performed regarding intervention regimen, trial truncation, or co-interventions. We validated the results with trial sequential analyses. We used random-effects model in all meta-analyses in anticipation of statistical heterogeneity among the trials.*
Main results*: We included nine trials with 645 participants. Six trials assessed TACE versus control and three trials assessed TAE versus control. Seven trials had low risk of selection bias based on adequate generation of allocation sequence and concealment – but all these trials had other risks of bias. Three trials were stopped early due to interim inspections and one due to slow accrual. For all-cause mortality, statistical heterogeneity between trials was low to moderate (I2) = 30%). Meta-analysis of trials with low risk of selection bias showed that TACE or TAE versus control does not significantly increase survival (HR 0.88; 95% CI 0.71–1.10). Two trials with low risk of selection bias, no early stopping, and no co-intervention did not establish any significant effect of TACE or TAE on overall survival (hazard ratio 1.22, 95% confidence interval 0.82–1.83; P = 0.33). Trial sequential analysis confirmed the absence of evidence for a beneficial effect of TACE or TAE on survival indicating the need for future randomisation of up to 383 additional participants. Substantial differences in criteria for assessing tumor response did not allow quantitative analyses. One trial investigated quality of life but did not detect any significant differences between the intervention groups. A range of adverse events including post-embolisation syndrome and serious complications were reported.*
Authors' conclusions*: There is no firm evidence to support or refute TACE or TAE for patients with unresectable HCC. More adequately powered and bias-protected trials are needed.*

Hepatocellular carcinoma is an orphan disease in terms of scientific evidence. Only few randomized controlled trials (RCT) or meta-analysis of individual data have been conducted, none of them including more than 1000 patients. In addition, most of the widely accepted treatments with impact on survival such as surgical resection, liver transplantation, and local ablation are supported by cohort analysis, categorized as low-medium level of evidence according to the main categories of evidence-based medicine [1]. Only two treatments options in HCC have proven their impact on survival at a higher level of evidence by positive RCTs: transarterial chemoembolization (TACE) for intermediate HCC and sorafenib for advanced HCC [2]. The demonstration of efficacy of TACE was reinforced in 2002 at the time of the publication of two positive RCT after previous trials with discordant results [3,4]. Two meta-analysis of pooled data published afterwards established the value of TACE in this scenario [5,6] and this assessment became the background for accepting TACE as the

Received 18 August 2011; accepted 21 August 2011
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primary standard of care option for intermediate HCC as defined by the BCLC staging system [2]. Oliveri *et al.* questioned the robustness of the scientific evidence supporting the use of TACE and run a new systematic review and meta-analysis including novel RCTs conducted beyond 2002 using the methodology proposed by the Cochrane collaboration. According to the reported results, the authors concluded that there is no firm evidence to support or refute TACE or TAE for patients with unresectable HCC, calling for more adequately powered and bias-protected trials to confirm the utility of these treatments in this scenario [7].

The message delivered by this Cochrane review is relevant as it casts doubts about the usefulness of TACE for HCC. However, there are several aspects that need to be considered regarding the studies used and the methodology applied to define their quality and their incorporation into the assessment. Firstly, the authors justified the need of a new meta-analysis because of the publication of additional RCTs after 2002. In one of these studies, categorized as high risk of bias by Oliveri *et al.*, the authors evaluated the combination of transarterial embolization (TAE) + ablation versus ablation alone in patients with solitary tumors, most of them belonging to the early stage category. In this RCT, the hypothesis was that TAE + percutaneous ablation could be superior to the standard treatment (in this case ethanol injection or radiofrequency) for early non-resectable HCCs. Thus, they do not investigate TACE compared to best supportive care or suboptimal therapies, as expected for consistency in this meta-analysis. In addition, they failed to include the target population for this therapy, meaning patients with intermediate HCC [8]. The second paper was published by Doffoël *et al.* in 2008 [9]. In this study, 138 patients were recruited from 15 centers during an inclusion time of around 7 years. The study included a high proportion of alcoholic-induced HCC patients and with segmental vascular invasion. Stratification was based upon Child-Pugh and Okuda stage, which do not provide major insights about tumor stage as per today's knowledge. Median survival was 12 months for TACE patients and 11 months for those treated with tamoxifen. Outcome figures expected during the years that the study was conducted points to a median survival for the active arm of 20 months. Therefore, our hypothesis to understand these certainly low survival rates according to standards for effective TACE was that patients were sub-optimally staged, selected and/or treated. In fact, most of the patients were symptomatic and would fit into BCLC C -advanced stage- and hence they would no longer be considered ideal candidates for TACE as per current guidelines. In addition, the large number of centers and long time period needed to conduct this trial suggest that the participant centers were not referral institutions with a high volume/expertise. The same concerns about selection and treatment application affects the Pelletier *et al.* study in 1990 [10]. This study was discarded in two previous meta-analyses [5,6] because the authors only reported 1-year survival rates, which indeed was unacceptably low and prone to induce bias. It is worth mentioning that in this trial the obstructing agent used was gelfoam powder that has been abandoned because of known risk of biliary damage and severe treatment-related complications [11].

Therefore, by including trials not targeting the proper population and treatment strategy, and trials including patients that do not fit into the accepted profile for TACE, the meta-analysis turned negative. The stratification into different subgroups according to bias or other criteria prevented to reach the needed strength of the data as the sample size is clearly suboptimal, while the low-profile trials were still used. Finally, when willing to estimate the sample size that would be required for robust assessment, it appears that Oliveri *et al.* have used a very modest expectation in survival improvement: 10%. The background rationale for this assumption is not available and sure this is one of the controversial issues for which there is no solid data.

According to their findings, Oliveri *et al.* state that there is an urgent need of more adequately powered and bias-protected trials to confirm the utility of these treatments in this scenario. Additional trials with proper design and target population would be welcome, but attempts in this direction failed to recruit in United Kingdom. A trial comparing TACE *vs.* systemic doxorubicin was launched time ago (PI: OJ Garden, NCT00079027) but it was prematurely closed because of insufficient recruitment.

While years ago there were major discrepancies and heterogeneity in patients' selection and treatment application, the current situation is far more structured. The optimal population for TACE has been identified (namely BCLC B patients with compensated liver disease) and the technique application has been improved. Hence, information collected from studies in which current knowledge is not followed does not provide further knowledge but rather trigger more confusion. The current status about indication of TACE, its application and how retreatment policy should be implemented has been recently summarized by a panel of experts [12].

All these comments serve to frame the limitations of the Oliveri's meta-analysis and why it may provide a vulnerable message that would bring the controversy back to where it was a decade ago. Efforts should be directed at avoiding the misuse of an effective treatment and to further improve its effectiveness. Several areas of uncertainty exist: which is the best embolic agent, which the best chemotherapeutic, what is the best follow-up and retreatment policy (repeat treatment according to a fixed schedule or upon disease progression after initial response) and to which extent we could develop combined therapies. Trials are ongoing in this direction and hopefully will result in an extension of the survival benefits of an effective approach if applied as recommended.

Conflict of interest

J.L. is consultant for Biocompatibles.

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