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The Use of Transarterial Chemoembolization in the Treatment of Unresectable Hepatocellular Carcinoma: A Response to the Cochrane Collaboration Review of 2011

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Abstract

This commentary is written in response to a recent Cochrane Collaboration review published in March 2011 (1). The authors of this commentary would like to express their concerns over the conclusions of the Cochrane review, which state, “There is no firm evidence to support or refute transarterial chemoembolization (TACE) or transarterial embolization (TAE) for patients with unresectable hepatocellular carcinoma (HCC).”

BACKGROUND

The Cochrane Collaboration is a well-recognized international entity consisting of > 28,000 individual contributors who, using strict methodologic techniques, produce systematic review articles on topics throughout the gamut of medicine. There are currently > 50 Cochrane review groups ranging from the general (“Back”) to the specific (“Incontinence”), and > 6,500 topics have been reviewed. Because of the strict methodology and quality of the investigators, Cochrane reviews are perhaps the most well-recognized evidence-based reviews in the United States and worldwide. These types of reviews are becoming increasingly influential in the era of comparative effectiveness. In March 2011, the Cochrane Collaboration published a review entitled, “Transarterial (chemo)embolization for unresectable hepatocellular carcinoma” (1). The review, including the methods and results, is discussed subsequently.

As in all Cochrane reviews, the authors’ methods included a comprehensive search of the available medical literature. The search for this particular review comprised all major medical databases, including the Cochrane collections, MEDLINE, EMBASE, Science Citation Index Expanded, and The Latin American Caribbean Health Sciences Literature

databases from 1980–2010. The primary outcome measure assessed was all-cause mortality, with multiple secondary outcomes (tumor response, quality of life according to the measures used in the individual trials, adverse events, duration of hospital stay, and cost-effectiveness) recorded when possible. As with nearly all Cochrane reviews, the types of studies used in the review were limited to randomized clinical trials, and types of interventions were limited to studies that compared chemoembolization (transarterial chemoembolization) or bland embolization (transarterial embolization) with placebo or sham procedures or with no treatment. During the data analysis phase, the authors calculated hazard ratios comparing all-cause mortality of patients undergoing transarterial chemo-embolization or transarterial embolization with patients not undergoing the procedures. The authors also classified trials based on the risk of bias, determined largely by the randomization process and blinding of the investigators—in particular, studies in which the randomization and blinding were unclear were considered to be at high risk for bias. The I^2 statistic, a test frequently used in meta-analyses to determine the heterogeneity between trials that cannot be ascribed to randomness, was calculated.

The authors initially identified 1,701 references; however, after further review all but 13 trials were excluded. Subsequently, four additional studies were excluded for various reasons (largely owing to incomplete reporting), leaving nine trials included for analysis (2–9). One trial (6) appears to have been counted twice because it included both transarterial chemoembolization and transarterial embolization arms. Of the trials used in the analysis, six reported results for transarterial chemoembolization, and three reported results for transarterial embolization; three had cointerventions performed in addition to the embolization procedure (one with radiofrequency or alcohol ablation and two with concomitant systemic tamoxifen administration). The nine trials reported 645 subjects, which constituted the population in the meta-analysis phase. The risk for bias was considered low in seven trials and high in two investigations.

Results of the meta-analysis showed no significant effect of transarterial chemoembolization or transarterial embolization on survival (hazard ratio 0.81, 95% confidence interval 0.64 – 1.02, $P = .07$). Subgroup analysis, stratified to include only the seven trials determined to be at low risk of bias, showed less of a trend toward a significant effect of the interventions (hazard ratio 0.88, 95% confidence interval 0.71–1.10, $P = .27$). Secondary outcome analyses either could not be performed because of the lack of published data in the primary reports (tumor response, adverse events, hospital stay, and cost-effectiveness) or showed no significant improvement (quality of life after procedure [one study]) (9).

In the Discussion section, the authors state, “Contrary to current clinical practice, we conclude that there is absence of evidence of TACE or TAE having a beneficial effect on survival in participants with unresectable HCC” (1). They specifically address other meta-analyses that have shown positive effects of embolization procedures for the treatment of HCC (10–13) and claim that, owing to stricter methodology, the current Cochrane review is more robust than the previous reviews. They complete their review by offering suggestions for further research, including the call for more “adequately powered and bias-protected trials.”

ANALYSIS OF COCHRANE REVIEW

We have several criticisms of the Cochrane review, nearly all of which have to do with the methodology used during the data accumulation. *First*, the authors excluded all studies in which transarterial chemoembolization or transarterial embolization was used but in which the procedure was not compared with a sham procedure, placebo, or no management. In clinical investigations, placebo or sham procedures are used to control for the “placebo” effect (14), and although this effect is significant in some disease states, there is no basis for imputing this phenomenon in individuals with cirrhosis with HCC who have a life expectancy of a few months. Although the methodologies used in the Cochrane review provide for the strictest inclusion criteria, we believe that these are overly restrictive and unnecessarily exclude other well-designed studies that show a definite advantage of transarterial chemoembolization over historical controls (2–7,15–35). In addition, once any therapy becomes accepted and standard care (which transarterial chemoembolization is in Europe, Asia, and North America), placebo-controlled or sham trials, not to mention withholding treatment altogether, are widely considered to be unethical (36). The Declaration of Helsinki, most recently updated in 2008, specifically states that, “The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. *Extreme care must be taken to avoid abuse of this option*” (37). It is our opinion that in 2011, with the widespread acceptance of transarterial chemoembolization as a first-line treatment for unresectable HCC, a placebo-controlled or sham-controlled trial would be unethical and unnecessary.

Second, because of the methodology used in the review, the authors excluded all current literature regarding the efficacy of transarterial chemoembolization. Of the nine articles included in their analysis, none was published after 2002; four of the articles were published before 2000. Distinct technical advances in the performance of transarterial chemoembolization and improved patient selection and management have occurred over the past decade, and ignoring these reports excludes many well-designed (but non–placebo-controlled) studies that show a clear survival benefit of transarterial chemoembolization (26–35). In addition, all of the primary data sources that the authors used for their analysis were published before routine use of the Barcelona Clinic Liver Cancer staging classification system. The Barcelona Clinic Liver Cancer classification system is widely used to determine which subset of patients may most benefit from interventions for HCC, including transarterial chemoembolization. Finally, all of the primary sources used by the authors were reported before the appearance of published guidelines regarding the appropriate use of transarterial chemoembolization for HCC from such respected bodies as the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the National Comprehensive Cancer Network.

Third, the authors combined data from patients undergoing transarterial embolization and patients undergoing transarterial chemoembolization, failing to recognize that these are not equivalent procedures. There are very few centers worldwide that continue to perform

transarterial embolization in the setting of HCC, although multiple analyses (primary and secondary) have shown mixed results with regard to a clinical benefit of using transarterial chemoembolization over transarterial embolization (10,11,16,30). Because transarterial embolization generally may have worse outcomes in the setting of HCC, combining these two procedures may skew the data.

Fourth, the authors specifically excluded studies in which allocation sequence (the method by which subjects were randomly assigned) or allocation concealment (blinding) were considered inadequate. Although this methodology is sound and important for some investigations requiring potentially subjective outcomes (eg, RECIST [Response Evaluation Criteria In Solid Tumors] interpretations), the use of such strict criteria assessing an outcome as obvious as all-cause mortality is inappropriate.

Fifth, we have concerns about the methodology employed by Cochrane analyses specifically related to procedural- based topics. In fields with rapid technologic advances such as interventional radiology, using publications that are many years or even decades apart may produce spurious results by combining data that are obsolete with data that are more contemporaneous. A therapy such as transarterial chemoembolization is a perfect example of such a topic; because of significant technical improvements, few physicians perform transarterial chemoembolization now as they did 10 years ago.

Sixth, the authors seem to be preoccupied with the risk of bias in the studies included in their analysis. The potential for bias in terms of blinding is most relevant in measures that may be subjective but less appropriate in assessing survival. The authors report that seven of nine articles included in their analysis were free of the risk of significant bias, even though none were blinded to all-cause mortality. It is also curious that the review regarded one of the seminal and most influential articles on the subject of transarterial chemoembolization and HCC (7) as having a high risk of selection bias, particularly because the only risks appear to be due to the lack of blinding. Particularly confusing is the fact that many of the studies determined by the authors to be at low risk for bias had more areas for potential concern (see Figure 2 in the initial Cochrane review).

The Cochrane Collaboration published a separate report entitled, “Radiofrequency thermal ablation versus other interventions for hepatocellular carcinoma” (38). This report was first published in 2002 and updated in 2004 and 2009. In this report, as well as many others published by Cochrane, the authors included in their methodology, “All randomized trials investigating radiofrequency thermal ablation versus placebo, no intervention, or *any other therapeutic approach* were considered for inclusion, *regardless of blinding*, language, and publication status” (38). It is disturbing and unclear why such criteria were considered appropriate for the radiofrequency review but inappropriate for the transarterial chemoembolization review.

CAUTIONARY STATEMENT ABOUT LEVELS OF EVIDENCE

Randomized, double-blinded, controlled clinical trials that result in Level 1 evidence provide the best protection against nearly all types of bias through the blinding process and against confounding through the randomization process (39). This type of investigation is

without a doubt the most scientifically sound clinical study design. However, it is not without its drawbacks (eg, cost, patient enrollment, lengthy data collection), and it is not always the only (or even the best) study design to answer a specific clinical question. Case-control studies are typically used in the evaluation of therapies involving very rare diseases; performing a randomized trial in such disease states, even if practical, may take decades to enroll enough patients to determine a treatment effect.

There are many examples of current and widely accepted medical practice that have occurred in the distinct absence of Level 1 data, including insulin for the treatment of diabetes, closed reduction and splinting of long bone fractures with displacement, suturing for the repair of large wounds, and the use of general anesthesia during surgical procedures (40). One of us (C.E.R.) likes to illustrate this point to his trainees by asking whether or not they believe that smoking causes cancer. After the inevitable “yes” answer, the next question is why do they hold that belief, since there is not one shred of Level 1 evidence to support their contention (what is an investigator to do—randomly assign subjects to smoke)? This point is driven home by the tongue-in-cheek article about conducting a randomized trial supporting the use of parachutes when jumping out of an airplane (41). Level 1 evidence is robust, it is scientifically sound, it is desired, but it is not the only evidence that exists or that is valid. The absence of Level 1 evidence is not equivalent to the absence of evidence altogether.

An informal PubMed search was performed at the time of this writing using the key words “hepatocellular carcinoma AND chemoembolization.” In the last 30 years, > 2,600 articles have been published on the topic, of which > 500 have been published in the last 2 years. Of the > 2600 articles, 309 are listed as clinical trials, 114 as randomized controlled trials, and 19 as metaanalyses. It is incomprehensible that all of these articles in peer-reviewed journals, individually and in aggregate, are without merit.

Between this explosion of information and the use of transarterial chemoembolization as frontline therapy in major medical centers throughout the world, it is impossible to believe that we have missed the mark entirely with this therapy and that, as the Cochrane authors contend, “There is not sufficient evidence to support or refute TACE or TAE for patients with unresectable HCC.” Finally, we contend that given the current level of evidence, for the Cochrane authors to actively suggest that locoregional treatment be withheld in patients with a devastating illness such as unresectable HCC while awaiting “further trials” is irresponsible.

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ABBREVIATION

HCC hepatocellular carcinoma

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