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Cost-effectiveness of doxorubicin-eluting beads versus conventional trans-arterial chemo-embolization for hepatocellular carcinoma

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ABSTRACT

Background: Doxorubicin-loaded drug-eluting beads TACE (DEB-TACE) has been developed to maximize the therapeutic efficacy of conventional trans-catheter arterial chemo-embolization (cTACE) in patients with hepatocellular carcinoma (HCC); however, its cost-effectiveness (CE) still needs to be assessed.
Aims: To investigate the CE of DEB-TACE versus cTACE.
Methods: Results from a meta-analysis of the pertinent literature were used to construct a CE Markov simulation model which followed a hypothetical cohort of HCC patients who underwent DEB-TACE or cTACE, covering the entire post-TACE lifespan until death. Costs were assessed from the health-care provider perspective.
Results: Five randomized controlled trials (RCTs) and 11 observational studies, including 1860 patients (883 DEB-TACE and 977 cTACE), were used for the construction of the model. Considering only survival rates from RCTs (heterogeneity: 0%), DEB-TACE returned 4.0 quality-adjusted life-years (QALYs) and TACE returned 3.3 QALYs (effect size = 1.288). Total costs of cTACE were €10,389 and those of DEB-TACE were €11,418 (effect size = 0.791). DEB-TACE was found more cost-effective than cTACE when a minimum willingness-to-pay of about €2000–3500/QALY was accepted, mainly depending on shorter in-hospital stay and better quality of life.
Conclusions: Direct incremental costs of DEB-TACE can be acceptable in respect to cTACE, relying on financial resources available from the payer perspective.

1. Introduction

Hepatocellular carcinoma (HCC) represents one of the most common causes of cancer-related death worldwide, with a 5-year survival rate of only 10–15% [1–3]. This dismal prognosis mainly depends on the fact that potentially curative therapies, such as transplantation, resection, and thermal ablation can be applied in a relative small proportion of HCC patients [3]. Trans-arterial chemo-embolization (TACE) is usually adopted in patients who are not suitable for such treatments [4,5]. However, survival after TACE remains relatively poor and post-TACE adverse events are frequent and can be severe [6] so that there is need for a treatment refinement able to improve both safety and effectiveness of this technique. In this regard, drug-eluting beads TACE (DEB-TACE) have been proposed as a novel drug delivery embolization system, able to deliver higher dose of the chemotherapeutic agent to the tumour, to prolong the contact time of the drug with neoplastic cells and to reduce its systemic release [7–9]. Results of preclinical studies have shown that in HCC patients, TACE with drug-eluting beads produces a higher intra-tumoural concentration and lower systemic concentrations of doxorubicin, compared with conventional TACE (cTACE) [7,9]. Phase II studies also suggest that DEB-TACE have low toxicity than cTACE, reducing the risk of severe adverse events [8,9]. On this basis, DEB-TACE is particularly suggested in 'fragile' subjects, such as Child–Pugh B and/or performance status (PS) >0 patients, patients at risk of potential systemic toxic complications, as well as in those with bi-lobar or recurrent tumours.

However, it is still unclear whether DEB-TACE can provide a survival advantage over cTACE. In fact, both randomized controlled trials (RCT) and retrospective studies reported conflicting results [9]. Overall, literature suggests a superiority of DEB-TACE in controlling tumour progression but the long-term effect on overall

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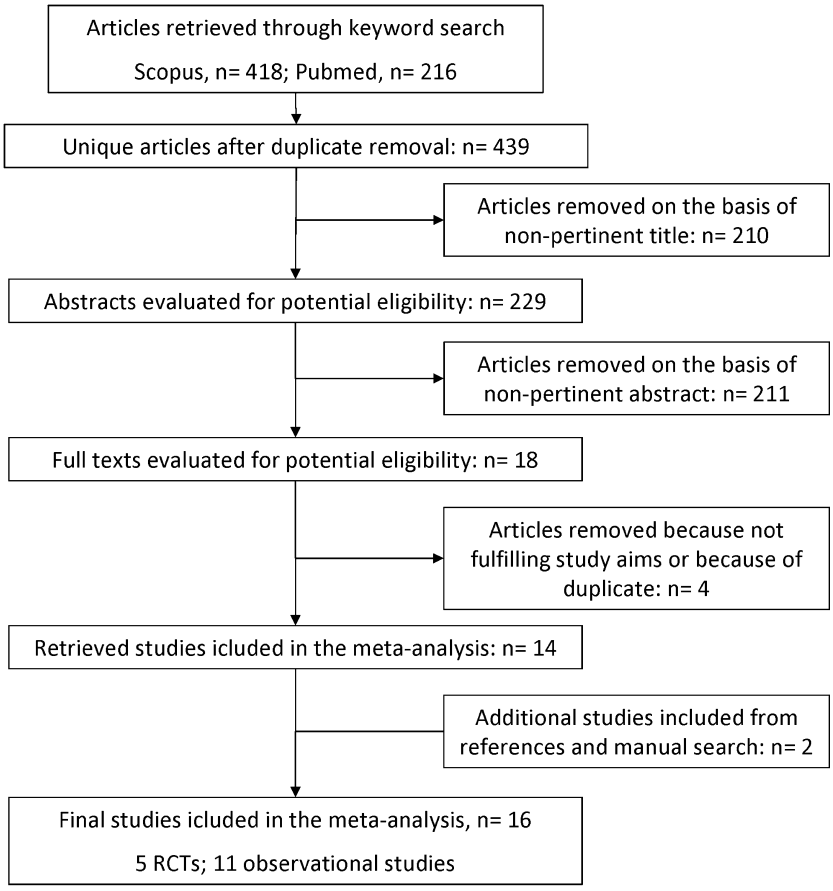

Fig. 1. Flow diagram showing the selection of articles reporting comparative data between drug-eluting TACE (DEB-TACE) and conventional TACE (cTACE) for unresectable hepatocellular carcinoma.

patient survival remains unclear [10]. When evaluating the effectiveness of a new treatment, the clinical benefits obtainable over the standard of care, if any, must be weighed according to its cost. Indeed, this information is crucial to assist physicians, scientific societies and healthcare managers in the decision-making processes needed to adopt a therapeutic innovation in the daily clinical practice. To the best of our knowledge, a formal analysis of cost-effectiveness (CE) of these two competing strategies for HCC has not yet been performed.

The aim of the present study was therefore to construct a model to estimate the CE of DEB-TACE and cTACE for unresectable HCC. A two-step approach was adopted to obtain the most robust estimates as possible: first, an updated meta-analysis of the pertinent literature was performed, distinguishing between RCT data and non-RCT data; then, results from meta-analysis were utilized to construct the CE model. Lastly, a probabilistic analysis was performed to investigate the uncertainties regarding the superiority of one treatment over the other.

2. Materials and methods

A meta-analysis of the pertinent literature was carried out to obtain absolute pooled values for variables included in the CE analysis: in fact, common statistical measures (such as odds ratios and/or relative risks) reported in ordinary meta-analyses are not suitable for such modelling study that conversely requires pooled estimates of each single variable used in each of the two treatment arms. Second, results from the present meta-analysis were utilized to construct a Markov simulation model using TreeAge-Pro-2008 (TreeAge Software Inc., Williamstown, MA, USA) which followed a hypothetical cohort of adult patients, suffering from unresectable HCC, who underwent DEB-TACE or cTACE (without cross-over between the two groups), covering the entire post-TACE lifespan as they moved across different health states until death. Due to the modelling nature of the present study, the Institutional Review Board approval was not required.

2.1. Literature search and meta-analysis

The literature search and meta-analysis were conducted following the PRISMA and MOOSE guidelines [11,12], covering the time span between 1 January 2000 and 27 January 2016 (Fig. 1). Pubmed and Scopus databases were searched to identify relevant studies which assessed the efficacy and safety of DEB-TACE versus cTACE in the treatment of HCC. The Medical Subject Headings (MeSH) '*carcinoma, hepatocellular*' and '*chemoembolization, therapeutic/methods*' were used for literature search, with the following keywords used to refine the research: '*hepatocellular carcinoma*', '*drug-eluting*', '*chemoembolization*' OR '*trans-catheter arterial embolization*'. Results were limited to human subjects. No language selection criterion was applied. Studies were evaluated for eligibility by two independent reviewers (M.R. and C.M) and any discrepancies in inclusion were resolved by discussion between the reviewers and a third investigator (A.C.[2]). In particular, this event occurred for a RCT comparing DEB-TACE with TAE [30]; however, since to date no evidence exists about a superiority (or inferiority) of TAE in respect to cTACE in terms of both safety and efficacy, we decided to retain this (high level of evidence) study in the base-case analysis and to perform additional analyses after its removal. If a study was followed by a more complete study or included the