Digestive and Liver Disease xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: A meta-analysis

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ARTICLE INFO

Article history:
Received 22 November 2015
Accepted 12 February 2016
Available online xxx

Keywords:
cTACE
DEB-TACE
HCC
Survival

ABSTRACT

Background: Despite the promising results of earlier studies, a clear superiority of drug-eluting beads transarterial chemoembolization over conventional chemoembolization in unresectable hepatocellular carcinoma patients has not been established yet.
Aims: To evaluate the efficacy and safety of the two treatments in unresectable hepatocellular carcinoma patients.
Methods: Computerized bibliographic search on the main databases was performed. One-year, two-year, three-year survival rates were analyzed. Hazard ratios from Kaplan–Meier curves were extracted in order to perform an unbiased comparison of survival estimates. Objective response and severe adverse event rate were analyzed too.
Results: Four randomized-controlled trials and 8 observational studies with 1449 patients were included in the meta-analysis. Non-significant trends in favor of drug-eluting beads chemoembolization were observed as for 1-year (odds ratio: 0.76, 0.48–1.21, $p = 0.25$), 2-year (odds ratio: 0.68, 0.42–1.12, $p = 0.13$) and 3-year survival (odds ratio: 0.57, 0.32–1.01, $p = 0.06$). Meta-analysis of plotted hazard ratios confirmed this trend (hazard ratio: 0.86, 0.71–1.03, $p = 0.10$). Pooled data of objective response showed no significant difference between the two treatments (odds ratio: 1.21, 0.69–2.12, $p = 0.51$). No statistically significant difference in adverse events was registered (odds ratio: 0.85, 0.60–1.20, $p = 0.36$).
Conclusions: Our results stand for a non-superiority of drug-eluting beads chemoembolization with respect to conventional chemoembolization in hepatocarcinoma patients.

1. Introduction

Hepatocellular carcinoma (HCC) represents the sixth most common cancer worldwide and the leading cause of mortality among patients with liver cirrhosis [1,2].

Transcatheter arterial chemoembolization (TACE) is commonly adopted as the first line treatment for patients with large or multinodular HCC and relatively preserved liver function, absence of cancer-related symptoms and no evidence of vascular invasion or extrahepatic spread, i.e. those classified as intermediate stage according to the Barcelona Clinic Liver Cancer (BCLC) staging system [2,3]. However, it should be noted that intermediate-stage HCC includes a heterogeneous population of patients varying widely in terms of tumor burden, liver function and disease etiology, hence an univocal therapeutic recommendation for BCLC B patients is not possible [4].

Furthermore, in clinical practice, many patients in the early stage (i.e. single nodule or up to 3 nodules under 3 cm) carrying contraindications to curative approaches – liver resection, liver transplantation (LT) or radiofrequency ablation – are treated with TACE [5].

Conventional TACE (cTACE) combines transcatheter delivery of chemotherapeutic drugs, associated with lipiodol emulsion, with the obstruction of arterial blood supply by a variety of embolic agents, achieving a strong cytotoxic and ischaemic effect. However, cTACE is an heterogeneous and not standardized technique, due to the difficulty in obtaining reproducible and stable lipiodol/drug emulsions with standard droplet size and the lack of consensus on which embolic agent to use [5,6]. Furthermore, the time elapsed between chemotherapy injection and embolic agent placement allows the clearance of a large proportion of drug into the systemic circulation [6,7]. Therefore, drug-eluting beads (DEBs) were developed in order to overcome the drawbacks of cTACE and provide higher levels of consistency and repeatability offering the

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http://dx.doi.org/10.1016/j.dld.2016.02.005
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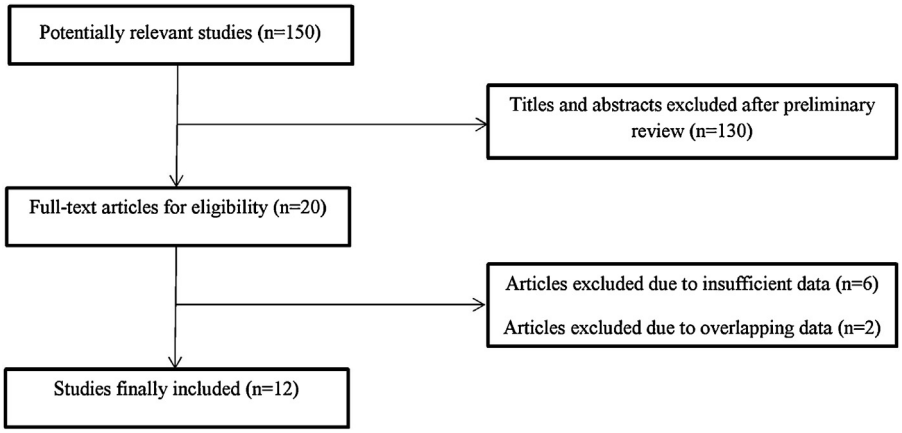

Fig. 1. Flow chart summarizing study selection.

opportunity to implement a more standardized approach to HCC treatment. DEBs slowly release the loaded chemotherapeutic agent upon injection and increase the intensity and duration of ischemia while enhancing the drug delivery to the tumor [6,8].

Despite the promising results of earlier studies, a clear superiority of DEB-TACE over cTACE has not been established yet. Aim of this meta-analysis is to retrieve and systematically analyze the published data on the comparison between the two techniques in terms of survival rate (SR), objective response rate (ORR) and safety profile.

2. Methods

This meta-analysis is performed following indications described in the Cochrane Handbook [9] and is conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines [10].

2.1. Search strategy and selection criteria

Fig. 1 reports the search strategy followed in the meta-analysis.

Computerized bibliographic search was performed on PubMed/Medline, Embase, Google Scholar, Cochrane library databases independently by two authors (AF, MDM) using the following Keywords: "transarterial chemoembolization"; "drug-eluting beads"; "hepatocellular carcinoma"; "HCC" and "liver cancer". Complementary manual search was performed by checking the references of all the main review articles on this topic; in order to identify possible additional studies.

Eligible studies were randomized controlled trials (RCTs), prospective or retrospective cohort and case-control studies published until September 2015 meeting the following inclusion criteria: (1) compared directly cTACE and DEB-TACE in HCC patients; (2) reported at least one of the following data: response rate, survival and adverse events; (3) reported relative odds ratio (OR) and hazard ratio (HR) or provided data for their calculation; (4) articles written in English. Case reports and abstracts or studies with insufficient data were excluded. In case of repetitive publications from the same population, only most recent and complete articles were included. When incomplete information was available, attempts were made to contact the corresponding authors for additional data. Disagreements were solved by discussion and following a third opinion (NM).

The quality of the included studies was assessed by two authors independently (AF, MDM) according to the Cochrane Collaboration's tool for assessing the risk of bias [11] for RCTs and the Newcastle-Ottawa scale for observational studies [12]. Any disagreements were addressed by re-evaluation and following a third opinion (NM).

2.2. Statistical analysis

Primary endpoint of the current meta-analysis was the comparison of patients survival, expressed in terms of 1-year, 2-years and 3-years SR, between the two treatments. Data of SR, objective response (i.e. complete + partial response) rate and toxicity (expressed as severe adverse events rate) were pooled and analyzed in terms of OR and 95% confidence intervals (CI). In order to partially obviate to bias due to the different follow up length among the studies and, within each study, between the two treatment arms and to take into account not only the number of events but also their timing and the follow up of censored patients, HRs from Kaplan Meier curves were extracted in accordance with the methods described by Tierney et al. [13]. Comparisons between the two treatment groups across all the included studies were performed by using Mantel-Haenszel test for fixed-effects models [14] (in the case of low heterogeneity) or DerSimonian and Laird test for random-effects models [15] (in the case of high heterogeneity).

Heterogeneity between estimates was assessed in two ways. First of all, the Cochrane's chi-square was measured, which is computed by summing the weighted squared deviations of each study estimate from the fixed-effects summary estimate. Because tests for heterogeneity lack power, a p-value of <0.10 was considered significant. Secondly, to estimate what proportion of total variation across studies was due to heterogeneity rather than chance, I^2 statistic was calculated. In this, a value of >50% was suggestive of significant heterogeneity [16].

Once heterogeneity was noted, between-study sources of heterogeneity were investigated using subgroup analyses, by stratifying original estimates according to study characteristics (RCTs versus non RCTs), and meta-regression, performed with "backward" stepwise exclusion of the variable contributing the most heterogeneity. Again, in these analyses a p-value <0.10 was considered significant, due to the low power of the tests and the small number of studies included.

Publication biases were assessed using funnel plots visually and performing Begg and Mazumdar's test based on the rank correlation between the observed effect sizes and observed standard errors.

In order to assess the effect of low quality articles on the final results of the meta-analysis, studies with lower quality or outlier results were eliminated to perform sensitivity analysis.

All calculations were performed using Review Manager (version 5.0 for Windows; the Cochrane Collaboration, Oxford, UK) and

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Table 1
Characteristics of the included studies.

Study	Arm	Drug	Sample size	Study period	Design	Region	Previous TACE[a]	CP (A/B/C)	BCLC (A/B/C)	Quality
PRECISION V 2010 [23]	DEB-TACE	Doxorubicin	93	2005–2007	RCT	Europe	–	77/16/0	24/69/0	M
	cTACE	Doxorubicin	108				–	89/19/0	29/79/0	
Song et al., 2012 [25]	DEB-TACE	Doxorubicin	60	2008–2011	R	Korea	–	56/4/0	27/33/0	H
	cTACE	Doxorubicin or Epirubicin/ Cisplatin	69				–	62/6/0	28/41/0	
Sacco et al., 2011 [27]	DEB-TACE	Doxorubicin	33	2006–2009	RCT	Italy	–	29/4/0	22/11/0	M
	cTACE	Doxorubicin	34				–	25/9/0	22/12/0	
Van Malenstein et al., 2011 [28]	DEB-TACE	Doxorubicin	16	2006–2009	RCT	Belgium	–	14/2/0	2/9/5	M
	cTACE	Doxorubicin	14				–	14/0/0	1/10/3	
Golfieri et al., 2014 [29]	DEB-TACE	Doxorubicin	89	2008–2010	RCT	Italy	9(10%)	75/14/0	41/26/22	H
	cTACE	Epirubicin	88				15(17%)	77/11/0	41/23/24	
Ferrer et al., 2011 [30]	DEB-TACE	Doxorubicin	47	1999–2009	P	Spain	–	NA	NA	M
	cTACE	Doxorubicin	25				–	NA	NA	
Dhanasekaran et al., 2010 [31]	DEB-TACE	Doxorubicin	45	1998–2008	R	USA	–	22/11/12	NA	H
	cTACE	Doxorubicin/ Cisplatin/ Mytomicin-C	26				–	11/11/4	NA	
Wiggermann et al., 2011 [32]	DEB-TACE	Epirubicin	22	2003–2008	R	Germany	–	22/0/0	1/17/3	H
	cTACE	Cisplatin	22				–	22/0/0	4/15/2	
Recchia et al., 2012 [33]	DEB-TACE	Doxorubicin	35	2008–2010	P	Italy	–	NA	NA	L
	cTACE	Doxorubicin	70				–	NA	NA	
Facciorusso et al., 2015 [34]	DEB-TACE	Doxorubicin	145	2007–2011	R	Italy	–	129/16/0	58/81/6	H
	cTACE	Doxorubicin	104				–	93/11/0	41/63/0	
Arabi et al., 2015 [35]	DEB-TACE	Doxorubicin	35	2006–2014	R	Saudi Arabia	4(11%)	24/11/0	NA	M
	cTACE	Cisplatin	19				–	17/2/0	NA	
Kloeckner et al., 2015 [36]	DEB-TACE	Mytomicin-C	76	2002–2013	R	Germany	–	51/22/3	8/34/34	M
	cTACE	Mytomicin-C	174				–	103/64/7	30/59/85	

DEB, drug-eluting beads; TACE, transarterial chemoembolization; R, retrospective; RCT, randomized-controlled trial; P, prospective; CP, Child–Pugh; BCLC, Barcelona clinic liver cancer; H, high; M, moderate; L, low; NA, not assessed.
[a] Number (percentage) of patients who had already undergone TACE before enrollment in the study.

R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria), *metafor package* [17].

3. Results

3.1. Literature search

As shown in Fig. 1, 150 studies were initially identified. After preliminary exclusion of abstracts or papers not fulfilling searching criteria, 20 potentially relevant articles were examined. Among these studies, 6 were excluded due to incomplete data [7,18–22]. As two studies reported overlapping information [23,24] on the same population and other two studies were published by the same group with overlapping recruitment periods [25,26], the articles with the smaller number of patients and incomplete outcome report were excluded [24,26]. Finally, 12 studies, of which 4 RCTs [23,27–29] and 8 observational [25,30–36], with 1449 patients (689 treated with DEB-TACE and 760 with cTACE) were included in the meta-analysis.

3.2. Characteristics of included studies

Main characteristics of included studies are reported in Table 1.

The recruitment period ranged from 1998 to 2014. Four studies were RCTs [23,27–29], two prospective observational [30,33] and six retrospective cohort reports [25,31,32,34–36]. Among 12 included studies, 2 were multicentric [23,29] and 10 monocentric [25,27,28,30–36]; 9 were conducted in Western Europe [23,27–30,32–34,36], 1 in USA [31], 1 in Korea [25] and 1 in Saudi Arabia [35]. DEBs were loaded with doxorubicin in all the studies except for two German series [32,36]; on the other hand cTACE procedures were more heterogeneous in terms of drug used across the studies. In all the studies but those by Dhanasekaran [31] and Kloeckner [36], patients enrolled were within Child–Pugh B score and the great majority of participants were in BCLC A and B stage, except for the study by Golfieri et al. [29] that reported a relevant proportion of BCLC C patients (26%, mainly due to impaired performance status). Nearly all the articles considered previous treatment with TACE as an exclusion criterion, except for the study by Golfieri [29] and Arabi [35] which included a small percentage of patients who had already undergone cTACE with no difference between the two treatment groups ($p = 0.19$ and $p = 0.28$ in the two studies, respectively). None of the studies reported statistically significant differences in baseline demographic, clinical and tumoral parameters between the two treatment groups. One RCT [29] and four observational studies [25,31,32,34] were considered high quality; among the other studies, one was classified as low quality [33] and six as moderate [23,27,28,30,35,36]. More details on the methodological characteristics and quality of included articles are shown in Supplementary Table 1.

3.3. Survival rate

Nine studies with 1164 patients estimated overall survival (OS) by means of Kaplan Meier curves and compared the two groups using log-rank test [25,27,29–34,36]. As described in Table 2, 1-year SR was similar in the two groups with only a non significant trend in favor of DEB-TACE (OR 0.76, CI 0.48–1.21, $p = 0.25$). As long as time elapsed since the treatment, ORs tended to decrease, although not reaching the statistical significance, thus meaning better long-term outcomes in patients who underwent DEB-TACE (2-years SR: OR 0.68, 0.42–1.12, $p = 0.13$; 3-years SR: OR 0.57, 0.32–1.01, $p = 0.06$). Forest plots of 1-year, 2-years and 3-years SR are reported in Supplementary Figs. 1–3. The difference in follow up length among the studies and, within each study, between the treatment arms was most likely to be responsible of this trend, as well of the high heterogeneity found (see Table 2 for the details). Meta-analysis of plotted HRs gave as result a non-significant overall estimate in favor

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Table 2
Odds ratios and heterogeneity of 1-year, 2-year and 3-year survival rate.

Survival estimate	No. of studies	No. of patients	OR (95% CI)	*p*-value	Heterogeneity I^2	p
1-yr SR	9	1164	0.76 (0.48–1.21)	0.25	52%	0.03
2-yr SR	10	1218	0.68 (0.42–1.12)	0.13	69%	<0.001
3-yr SR	6	872	0.57 (0.32–1.01)	0.06	65%	0.01

SR, survival rate; OR, odds ratio; CI, confidence interval.

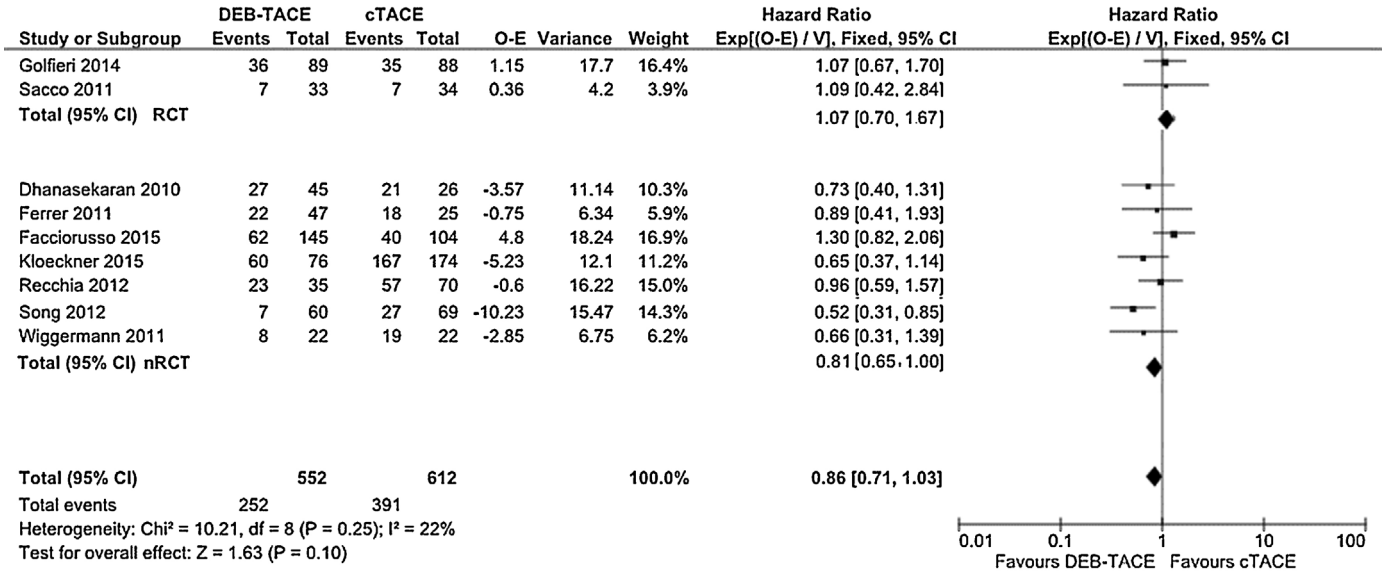

Fig. 2. Forest plot of hazard ratios for patient survival after DEB-TACE and cTACE. Fixed effect Mantel-Haenszel model found a summary odds ratio not significantly in favor of DEB-TACE with low heterogeneity. DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemoembolization; RCT, randomized-controlled trial; nRCT, non-randomized-controlled trial.

of DEB-TACE (HR = 0.86, 0.71–1.03, $p = 0.10$; Fig. 2). A low level of heterogeneity was found ($\chi^2 = 10.21$, d.f. = 8 [$p = 0.25$], $I^2 = 22\%$) and no evidence of publication bias was detected by visual examination of funnel plot (Supplementary Fig. 4) and with Begg and Mazumdar's test ($p = 0.34$). Subgroup analysis retrieved separately results of RCTs and of observational studies. In particular, meta-analysis of RCTs showed a similar efficacy of the two techniques with an HR close to 1.0 (HR = 1.07, 0.70–1.67, $p = 0.75$) and no evidence of heterogeneity ($\chi^2 = 1.25$, d.f. = 1 [$p = 0.54$], $I^2 = 0\%$). On the other hand, meta-analysis of non randomized studies reported a nearly significant superiority of DEB-TACE over cTACE (HR = 0.81, 0.65–1.00, $p = 0.06$), a finding not highly reliable due to the great level of heterogeneity ($\chi^2 = 8.49$, d.f. = 5 [$p = 0.13$], $I^2 = 41\%$). Sensitivity analysis conducted both by restricting analysis to high-quality studies and by excluding each article once per time did not change the main summary estimate (data not shown). Unfortunately, a meta-analysis performed by stratifying OS according to tumoral and clinical baseline characteristics was not possible due to missing data and heterogeneity in reporting survival outcomes. Moreover, univocal conclusions in this regard could not be drawn since the only two studies reporting significant differences showed discordant results, specifically the article by Dhanasekaran [31] found a superiority of DEB-TACE in less advanced patients while that by Song [25] higher survival rates after DEB-TACE in intermediate patients (Supplementary Table 2).

3.4. Objective response rate

ORR was reported in 8 studies [23,25,27,29,30,32,34,35]. Due to the high heterogeneity found among the included studies ($\chi^2 = 19.52$, d.f. = 7, $I^2 = 64\%$; $p = 0.007$), the DerSimonian and Laird test for random-effects models was used. Pooled data from these articles showed no significant difference between the two treatments with an OR of 1.21 (0.69–2.12, $p = 0.51$; Fig. 3). No evidences of publication bias were found (Supplementary Fig. 5).

Sources of heterogeneity were explored by means of subgroup analysis and meta-regression. Subgroup analysis conducted in RCTs and observational studies confirmed the non-significant OR in favor of DEB-TACE (OR = 1.31, 0.79–2.05, $p = 0.27$ and OR = 1.18, 0.49–2.94, $p = 0.72$, respectively) and detected, as expected, high heterogeneity among observational studies (see Fig. 3 for the details). Then, variables known to have an influence on response assessment (namely timing of response assessment, response criteria, study design and quality) were entered into a backward stepwise meta-regression model and individually assessed as potential contributors to heterogeneity (Supplementary Table 3). In the first step, analysis of pooled data from all the 8 studies showed that timing of response assessment (1 month versus delayed post-treatment response evaluation) contributed the most to study heterogeneity ($R^2 = 71.6\%$, $p = 0.01$). In the second step, analysis of 5 studies with response assessed at 1 month after-TACE found lower heterogeneity with respect to studies with delayed response evaluation ($p = 0.26$ and 0.03, respectively) and in both situations response criteria adopted resulted a significant contributor to heterogeneity (see Supplementary Table 3 for the details).

Sensitivity analysis performed by means of elimination of outlier studies [25,34] did not show significant deviations in overall summary estimate (data not shown).

3.5. Safety

Nine studies [23,25,27–29,31,32,34,35] with 1026 patients reported data on severe adverse event rate with no statistically significant difference between the two treatment groups (OR = 0.85,

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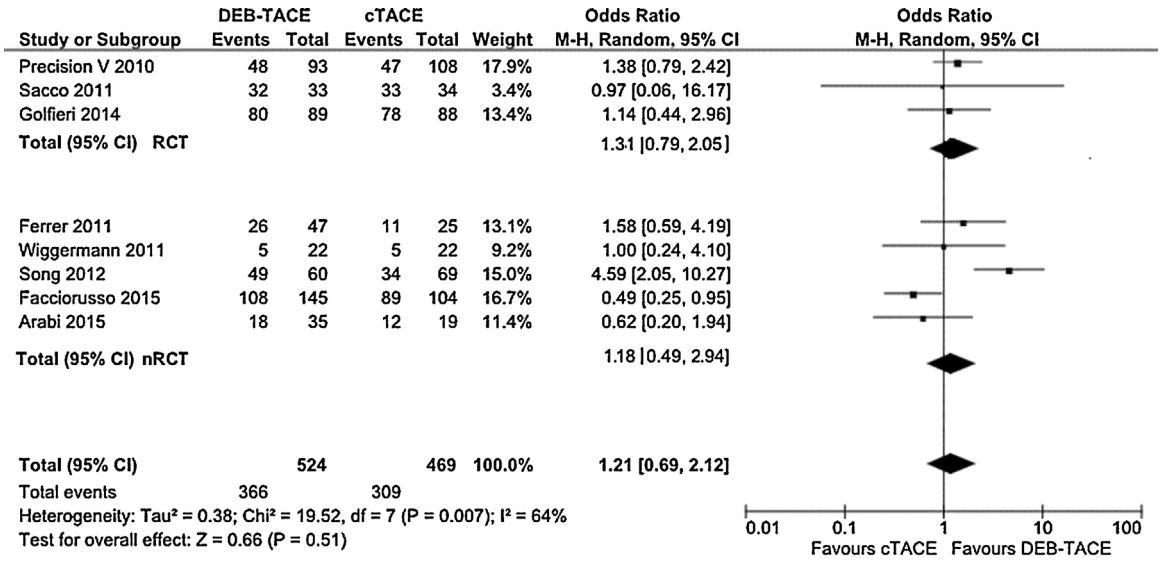

Fig. 3. Forest plot comparing objective response rate for DEB-TACE to that for cTACE. Random effect DerSimonian Laird model showed a summary odds ratio slightly higher after DEB-TACE without reaching the statistical significance. High heterogeneity was found. DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemoembolization; RCT, randomized-controlled trial; nRCT, non-randomized-controlled trial.

0.60–1.20, $p = 0.36$; Supplementary Fig. 6). There was no evidence of heterogeneity ($\chi^2 = 8.39$, d.f. = 8, $I^2 = 5\%$; $p = 0.40$) nor of publication bias (Supplementary Fig. 7). Subgroup analysis (RCTs versus nRCTs) and sensitivity analysis confirmed the non-significant OR in favor of DEB-TACE (data not shown). The detailed description of several adverse events registered in the included studies is reported in Supplementary Table 4. The most frequent adverse events reported for both DEB-TACE and cTACE in the included studies were the typical features of post-embolization syndromes, namely pain, fever, nausea and vomiting, whereas systemic doxorubicin-related complications were rarely observed (Supplementary Table 4). Unfortunately, a meta-analysis differentiating for each complication and for different subgroups of patients was not possible due to incomplete data (particularly on severe adverse events).

4. Discussion

Although TACE is usually considered as first-line treatment for intermediate unresectable HCC, it remains an heterogeneous procedure widely varying in terms of drugs injected, embolic agents and treatment schedules [5,37].

In order to overcome the lack of standardization of cTACE, the bead system has been recently developed to slowly and selectively release chemotherapy into the tumor with minimal discharge into the systemic circulation. Despite the promising results of earlier studies [7,8], data on comparison between conventional and drug-eluting beads TACE is still controversial.

In this comprehensive meta-analysis, bibliographic research of all the published reports comparing the efficacy and safety of the two procedures was performed. A total of 12 studies (4 RCTs and 8 observational) with 1449 patients were included. DEBs, with a size ranging from 100 to 700 μm, were loaded with doxorubicin in all the studies, except for two German series [32,36], while cTACE arms widely differed as regard to drugs used (Table 1). As described in Table 1, all the studies were well-balanced in terms of baseline liver function and tumoral stage and only two series [29,35] included a small percentage of patients previously treated with cTACE, equally distributed between the two study groups.

Pooled ORs of survival rate at 1.2 and 3 years didn't differ significantly but showed a decreasing trend in favor of DEB-TACE as time elapsed since treatment (0.76, 0.68 and 0.57, respectively). This finding, which is consistent with the conclusions of a systematic review recently published in this field [38], was largely due to the difference in follow-up time length between the two treatment arms in the majority of included studies. In fact, DEB-TACE represents a new technique recently introduced in the clinical practice and in many centers has replaced cTACE as standard therapy. Therefore, none of the observational studies reported contemporary cohorts thus resulting in higher rates of censored data and lower absolute number of deaths in the DEB-TACE cohorts. Furthermore, significant difference in terms of between-studies follow up time was also found, thus explaining the high level of heterogeneity ($I^2 = 52\%$, 69% and 65%, respectively). In order to partially obviate to the low quality of long-term data of nRCTs and to better represent time-to-event parameters, HRs were plotted from Kaplan–Meier curves and entered in a Mantel-Haenszel fixed-model giving as result a non-significant overall estimate in favor of DEB-TACE (HR = 0.86, 0.71–1.03, $p = 0.10$) with low heterogeneity ($I^2 = 22\%$, $p = 0.25$). In particular, when restricting the analysis to only RCTs [27,29], the aforementioned trend was not confirmed and the efficacy between the two techniques was absolutely comparable.

Previously published meta-analyses concluded that DEB-TACE outperforms cTACE in the management of unresectable HCC as achieves better objective response rate, however, these systematic reviews included a small number of studies and did not sufficiently explore the sources of the high heterogeneity found in their results [38–40]. Our findings, strengthened by the inclusion of three recently published large Western series [29,34,36], showed only a non-significant trend of superiority of DEB-TACE in terms of ORR (OR: 1.21, 0.69–2.12, $p = 0.51$). Such a trend was confirmed by subgroup and sensitivity analysis performed by removing the two outlier studies [25,34]. As expected, high heterogeneity was confirmed in our meta-analysis: in fact, tumor response rates reported in the literature depend on several variables as response criteria used and timing of assessment. Out of the 8 reports comparing response rate, in 4 the treatment efficacy was assessed according to EASL criteria [23,29,30,32] and in 4 by means of mRECIST criteria [25,27,34,35]. Response evaluation was performed at 1 month after TACE in 5 studies [27,29,30,34,36] and later (range 2–6 months) in 3 series [23,25,32]. Subgroup analysis and meta-regression identified timing of assessment and criteria adopted as main sources

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of heterogeneity, however, none of the aforementioned variables influenced the OR of response rate (Supplementary Table 3).

A potential criticism to these results is the well-known overestimation of tumor response after cTACE due to the "masking" effect of lipiodol staining at CT-scan images. However, even when response assessment was performed by means of Magnetic Nuclear Risonance (MNR), as in the case of PRECISION V trial, the aforementioned non-significant trend was confirmed [23].

Safety data meta-analysis was in keeping with previous systematic reviews and confirmed the similarity in toxicity profile between the two techniques with only a slightly lower incidence of severe adverse events after DEB-TACE [38–40]. In fact, despite the significant differences found in the PRECISION V trial as regard to systemic side effects [23], successive studies reported similar data in the two treatment arms and a negligible amount of systemic complications. However, it should be noted that in PRECISION V trial high doses (nearly doubled with respect to the other included studies) of doxorubicin (100–150 mg) were used in cTACE patients and this could be a variable contributing to the higher systemic side effect rate reported [23]. It is well known that cTACE requires lower doses of chemotherapeutic agent with respect to DEB-TACE due to the pro-necrotic effects of lipiodol in liver tumors [40,41] and the long-time retention of a considerable portion of the drug by the DC beads [19,42]. In fact, authors performing cTACE with 50–75 mg of doxorubicin reported competitive results in terms of objective response with a negligible incidence of systemic adverse events [27,34].

Therefore, we can conclude that similar efficacy and safety results between the two treatments, with only a non-significant trend in favor of DEB-TACE, are currently reported in the literature. Some pilot studies have recently reported promising results in terms of tumor response and safety with smaller beads, which may achieve a more distal embolization and better penetrate into the tumor nodules, but long-term results and survival data are still lacking [43,44].

There are some limitations to our study. First of all, both RCTs and observational studies were included, which may have introduced selection bias and heterogeneity in outcomes reported. In fact a considerable number of patients enrolled in the included RCTs were in BCLC A stage, for whom TACE is not recommended as first-line treatment by international scientific societies, while two observational studies included even Child–Pugh C patients who should be offered only best supportive care as per current guidelines. However, any possible sources of heterogeneity were searched and analyzed with appropriate statistical tools and subgroup analyses were performed in order to confirm summary estimates regardless of the methodological differences among the included studies. Unfortunately, a meta-analysis performed by stratifying outcomes according to baseline tumoral stage and liver function was not possible due to missing data. Second, follow up time length was different among the series and between the treatment arms within each observational study, thus leading to a significant increase in deaths in cTACE patients due to the longer period of observation. However, HRs were extracted from each study reporting survival data and analyzed in order to obtain unbiased estimates of overall survival. Third, tumor response assessment highly differed among the studies as regard to timing and criteria adopted. However, this further source of heterogeneity was explored by means of meta-regression analysis and no influence of these variables on the summary estimates was found.

In conclusion, despite these weaknesses, our meta-analysis represents the most comprehensive and updated reviews of the literature published in this field so far. The results of our paper stand for a non-superiority of DEB-TACE with the currently available DC beads with respect to cTACE although the moderate/low quality of data and the patient selection heterogeneity in several included studies make actually difficult to draw definitive conclusions. Therefore our results should be interpreted with cautions and need further confirmation in large RCTs.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2016.02.005.

References

[1] El-Serag HB. Hepatocellular carcinoma. New England Journal of Medicine 2011;365:1118–27.
[2] EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. Journal of Hepatology 2012;56:908–43.
[3] Bruix J, Sherman M. Practice guidelines committee American association for the study of liver disease. Management of hepatocellular carcinoma. An update. Hepatology 2011;53:1020–2.
[4] Bolondi L, Burroughs A, Dufour JF, et al. Heterogeneity of patients with intermediate (BCLC B) hepatocellular carcinoma: proposal for a subclassification to facilitate treatment decisions. Seminars in Liver Disease 2012;32:348–59.
[5] Facciorusso A, Licinio R, Muscatiello N, et al. Transarterial chemoembolization: evidences from the literature and applications in hepatocellular carcinoma patients. World Journal of Hepatology 2015;7:2009–19.
[6] Lencioni R, de Baere T, Burrel M, et al. Transcatheter treatment of hepatocellular carcinoma with doxorubicin-loaded DC Bead (DEBDOX): technical recommendations. Cardiovascular and Interventional Radiology 2012;35:980–5.
[7] Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. Journal of Hepatology 2007;46:474–81.
[8] Lewis AL, Taylor RR, Hall B, et al. Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. Journal of Vascular and Interventional Radiology 2006;17:1335–43.
[9] Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011. Available from: www.cochrane-handbook.org [accessed 06.07.15].
[10] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine 2009;151:264–9. W64.
[11] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. British Medical Journal 2011;343:d5928.
[12] Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses; 2015. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm [accessed 06.07.15].
[13] Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
[14] Robins J, Breslow N, Greenland S. Estimators of the Mantel-Haenszel variance consistent in both sparse data and large-strata limiting models. Biometrics 1986;42:311–23.
[15] DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7:177–88.
[16] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. British Medical Journal 2003;327:557–60.
[17] http://cran.r-project.org/web/packages/metafor/index.html [accessed July 2015].
[18] Kucukay F, Badem S, Karan A, et al. A single-center retrospective comparison of doxorubicin-loaded HepaSphere transarterial chemoembolization with conventional transarterial chemoembolization for patients with unresectable hepatocellular carcinoma. Journal of Vascular and Interventional Radiology 2015;26:1622–9.
[19] Namur J, Citron SJ, Sellers MT, et al. Embolization of hepatocellular carcinoma with drug-eluting beads: doxorubicin tissue concentration and distribution in patient liver explants. Journal of Hepatology 2011;55:1332–8.
[20] Malbranche C, Boulin M, Guiu B, et al. Economic impact of transarterial chemoembolization with drug eluting beads in the treatment of hepatocellular carcinoma. Bulletin du Cancer 2011;98:671–8.
[21] Nicolini D, Svegliati-Baroni G, Candelari R, et al. Doxorubicin-eluting bead vs conventional transcatheter arterial chemoembolization for hepatocellular carcinoma before liver transplantation. World Journal of Gastroenterology 2013;19:5622–32.
[22] Frenette CT, Osorio RC, Stark J, et al. Conventional TACE and drug-eluting bead TACE as locoregional therapy before orthotopic liver transplantation: comparison of explant pathologic response. Transplantation 2014;98:781–7.
[23] Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovascular and Interventional Radiology 2010;33:41–52.

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[24] Vogl TJ, Lammer J, Lencioni R, et al. Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with PRECISION TACE with drug-eluting beads: results from the PRECISION V randomized trial. American Journal of Roentgenology 2011;197:W562–70.
[25] Song MJ, Chun HJ, Song do S, et al. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. Journal of Hepatology 2012;57:1244–50.
[26] Song MJ, Park CH, Kim JD, et al. Drug-eluting bead loaded with doxorubicin versus conventional Lipiodol-based transarterial chemoembolization in the treatment of hepatocellular carcinoma: a case–control study of Asian patients. European Journal of Gastroenterology and Hepatology 2011;23:521–7.
[27] Sacco R, Bargellini I, Bertini M, et al. Conventional versus doxorubicin-eluting bead transarterial chemoembolization for hepatocellular carcinoma. Journal of Vascular and Interventional Radiology 2011;22:1545–52.
[28] van Malenstein H, Maleux G, Vandecaveye V, et al. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie 2011;34:368–76.
[29] Golfieri R, Giampalma E, Renzulli M, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. British Journal of Cancer 2014;111:255–64.
[30] Ferrer Puchol MD, la Parra C, Esteban E, et al. Comparison of doxorubicin-eluting bead transarterial chemoembolization (DEB-TACE) with conventional transarterial chemoembolization (TACE) for the treatment of hepatocellular carcinoma. Radiologia 2011;53:246–53.
[31] Dhanasekaran R, Kooby DA, Staley CA, et al. Comparison of conventional transarterial chemoembolization (TACE) and chemoembolization with doxorubicin drug eluting beads (DEB) for unresectable hepatocelluar carcinoma (HCC). Journal of Surgical Oncology 2010;101:476–80.
[32] Wiggermann P, Sieron D, Brosche C, et al. Transarterial chemoembolization of Child-A hepatocellular carcinoma: drug-eluting bead TACE (DEB TACE) vs. TACE with cisplatin/lipiodol (cTACE). Medical Science Monitor 2011;17:CR189–95.
[33] Recchia F, Passalacqua G, Filauri P, et al. Chemoembolization of unresectable hepatocellular carcinoma: decreased toxicity with slow-release doxorubicin-eluting beads compared with lipiodol. Oncology Reports 2012;27:1377–83.
[34] Facciorusso A, Mariani L, Sposito C, et al. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma. Journal of Gastroenterology and Hepatology 2016;31:645–53.
[35] Arabi M, BenMousa A, Bzeizi K, et al. Doxorubicin-loaded drug-eluting beads versus conventional transarterial chemoembolization for nonresectable hepatocellular carcinoma. Saudi Journal of Gastroenterology 2015;21:175–80.
[36] Kloeckner R, Weinmann A, Prinz F, et al. Conventional transarterial chemoembolization versus drug-eluting bead transarterial chemoembolization for the treatment of hepatocellular carcinoma. BMC Cancer 2015;15:465.
[37] Raoul JL, Sangro B, Forner A, et al. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treatment Reviews 2011;37:212–20.
[38] Xie ZB, Wang XB, Peng YC, et al. Systematic review comparing the safety and efficacy of conventional and drug-eluting bead transarterial chemoembolization for inoperable hepatocellular carcinoma. Hepatology Research 2015;45:190–200.
[39] Huang K, Zhou Q, Wang R, et al. Doxorubicin-eluting beads versus conventional transarterial chemoembolization for the treatment of hepatocellular carcinoma. Journal of Gastroenterology and Hepatology 2014;29:920–5.
[40] Han S, Zhang X, Zou L, et al. Does drug-eluting bead transcatheter arterial chemoembolization improve the management of patients with hepatocellular carcinoma? A meta-analysis. PLOS ONE 2014;9:e1026–86.
[41] Idée JM, Guiu B. Use of lipiodol as a drug-delivery system for transcatheter arterial chemoembolization of hepatocellular carcinoma: a review. Critical Reviews in Oncology/Hematology 2013;88:530–49.
[42] Hong K, Khwaja A, Liapi E, et al. New intra-arterial drug delivery system for the treatment of liver cancer: preclinical assessment in a rabbit model of liver cancer. Clinical Cancer Research 2006;12:2563–7.
[43] Malagari K, Pomoni M, Moschouris H, et al. Chemoembolization of hepatocellular carcinoma with HepaSphere 30–60 μm. Safety and efficacy study. Cardiovascular and Interventional Radiology 2014;37:165–75.
[44] Spreafico C, Cascella T, Facciorusso A, et al. Transarterial chemoembolization for hepatocellular carcinoma with a new generation of beads: clinical-radiological outcomes and safety profile. Cardiovascular and Interventional Radiology 2015;38:129–34.

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