Research Article

JOURNAL OF HEPATOLOGY

Retreatment with TACE: The ABCR SCORE, an aid to the decision-making process

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Background & Aims: Transarterial chemoembolization (TACE) is the standard of care for intermediate stage hepatocellular carcinoma (HCC) and it is the most commonly used treatment for HCC worldwide. However, no prognostic indices, designed to select appropriate candidates for repeat conventional TACE, have been incorporated in the guidelines.

Methods: From January 2007 to April 2012, 139 consecutive HCC patients, mainly with an alcohol- or viral-induced disease, were treated with TACE. Using a regression model on the prognostic variables of our population, we determined a score designed to help for repeat TACE and we validated it in two cohorts. We also compared it to the ART score.

Results: In the multivariate analysis, four prognostic factors were associated with overall survival: BCLC and AFP (>200 ng/ml) at baseline, increase in Child-Pugh score by $\geqslant$2 from baseline, and absence of radiological response. These factors were included in a score (ABCR, ranging from −3 to +6), which correlates with survival and identifies three groups. The ABCR score was validated in two different cohorts of 178 patients and proofed to perform better than the ART score in distinguishing between patients' prognosis.

Conclusions: The ABCR score is a simple and clinically relevant index, summing four prognostic variables endorsed in HCC. An ABCR score $\geqslant$4 prior to the second TACE identifies patients with dismal prognosis who may not benefit from further TACE sessions.

Keywords: HCC; Chemoembolization; BCLC; Radiological response; ABCR score; ART score; TACE.

Received 18 January 2014; received in revised form 23 October 2014; accepted 7 November 2014; available online 21 November 2014

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, the sixth most common cancer, and the third most common cause of cancer-related deaths in the world [1,2]. This cancer generally develops secondarily to an underlying chronic liver disease, due to different aetiologies (B or C viral hepatitis, alcohol abuse, non-alcoholic steatohepatitis, genetic iron overload) [3]. There is no "universally" recognized classification, which leads to wide variations in treatment practices, particularly when patients not eligible for curative treatment are concerned. Several Asian countries have their own staging system [4]. In Europe and the USA, the Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely used, endorsed by both AASLD and EASL, and used in most recent clinical trials. The BCLC classification is an algorithm linking clinical parameters, prognosis and therapeutic options [5,6]. HCC is a complex disease: underlying cirrhosis and portal hypertension (PHT) complicate the treatment of HCC and limit the available curative options. International Bridge study showed that transarterial chemoembolization (TACE) is the most widely used treatment for HCC worldwide, ahead of both surgical removal and systemic treatments [7]. In Europe and the USA, TACE is the standard of care for intermediate (BCLC B) stage HCC (PS 0, Child-Pugh A-B, multinodular or unresectable tumors, no portal vein invasion, N0, M0), but this group includes a heterogeneous population of patients with significant variations in tumor and liver characteristics [8]. In routine practice TACE has applications beyond intermediate stage HCC. TACE can also be applied to earlier HCC (BCLC A) not suitable for surgery or radiofrequency ablation [9]. HCC progression being mainly intrahepatic rather than metastatic [10], some authors postulate that advanced HCC is not necessarily contraindicated for TACE treatment in selected cases [11,12]. Previous Asian studies and a meta-analysis of eight trials (including five retrospective studies) showed that TACE could be safely performed for selected HCC involving segmental branches of portal vein, with survival benefit compared with conservative treatment [13–16], but the recurrence rate is relatively high in

Table 1. Baseline patient and disease characteristics in both series. In Nancy cohort, oesophageal varices were assessed as absent or present: 55% of patients had oesophageal varices.

Characteristic	Initial cohort n = 139	Internal validation cohort n = 78	External validation cohort n = 100
Age, median [95% CI]	67 [65-68]	69 [63-71]	68.5 [66-71]
Sex, M/F (%)	84/16	79/21	88/12
BMI, median [95% CI]	25 [24-25]	26 [24-27]	27.5 [26-29]
Cirrhosis or advanced fibrosis (F3) %	100	100	94
Aetiology: % virus/alcohol/virus + alcohol/NASH	47/35/6/10	36/36/10/13	27/46/6/8
Diabetes %	32	24	45
Child-Pugh score: A/B %	69/31	76/24	95/4
Oesophageal varices grade 0/1/≥2%	39/23/38	44/23/33	45/55*
BCLC A/B/C %	47/34/19	32/68/0	10/81/9
Infiltrative tumours %	17	6	2
Segmental portal vein thrombosis %	15	0	9
Unifocal tumour >50 mm %	9	10	15
AFP <200 ng/ml (%)	109 (78)	50 (64%)	77 (77)
AFP ≥200 ng/ml	30 (22)	28 (36%)	23 (23)
Diagnosis based on: imaging/biopsy %	85/15	73/27	80/20
Circumstance % incidental/screening/symptoms	17/70/13	37/55/8	19/66/15
Previous treatments (surgery, RFA) %	15	17	18

BMI, body mass index; NASH, non-alcoholic steatohepatitis; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; RFA, radiofrequency ablation.
* In Nancy cohort, oesophageal varices were assessed as absent or present and therefore 55% of patients had oesophageal varices.

patients with vascular invasion [17]. In the randomized study by Lo *et al.*, about 20% of the patients treated with TACE presented with segmental portal vein thrombosis, but no significant difference in survival was detected amongst these patients whether they were treated with TACE or not [18].

For some authors, the benefits of TACE are debatable: only two randomized controlled trials including 112 and 80 patients gave positive results, the survival benefit was limited (4 months) and meta-analysis results are conflicting [18–21]. This skepticism is maintained by the lack of homogeneity in treatment modalities (drugs to be used, the interval between courses). In the randomized study by Llovet *et al.*, doxorubicin-based TACE were performed 2 months and 6 months after the initial session, and then every 6 months until progression, depending on individual tolerance [19]. In the randomized study by Lo *et al.*, cisplatin-based TACE was performed every 2 to 3 months until disease progression, depending on individual tolerance [18]. On the other hand, antitumor efficacy of TACE can be counter-balanced by its toxicity, with immediate toxic effects due to the embolization process (haemorrhages, tumor rupture, renal insufficiency, ascites, liver failure) and with delayed toxicity related to worsening liver function [22,23]. New embolic devices (drug-eluting beads) seem to improve systemic toxicity and perhaps liver toxicity [24]. The indications and contraindications of TACE are better defined than previously; treatment algorithms for the repetition of TACE have been proposed, based on the radiological assessment, but the objectives are different according to the authors (response or stabilization) [25,26]. The contrast uptake criteria – both EASL and mRECIST – differ in terms of target lesions and calculation methods, but they are comparable and correlated with survival after TACE [27,28]. However, these criteria are not applicable for all types of HCC [29]. There are no guidelines concerning the number of TACE to be performed before switching to another treatment strategy. On the other hand, sorafenib has recently been shown to improve survival in advanced HCC (BCLC C), including BCLC B patients after TACE failure [30,31]. In view of the highly diverse nature of HCC and practices and the therapeutic options now available, a tool to help to decide whether or not to continue with TACE will be useful. There is no prognostic score designed to help for repeat TACE incorporated into the guidelines. The ART (Assessment for Retreatment with TACE) score, calculated before performing a second TACE, allowed to differentiate two groups (0–1.5 points *vs.* 2.5 points and over) with different prognosis (median overall survival of 23.7 and 6.6 months respectively) [32]. It is based on three parameters (increase of AST by >25%, increase in Child-Pugh score from baseline and tumor response). Increase (+25%) in AST was the parameter associated with the most powerful coefficient, the lowest was allocated to the radiological response. This system was developed using a regression model in a cohort of 107 patients enrolled over 10 years, most of whom presented with alcoholic cirrhosis and were BCLC B HCC. The authors suggested continuing TACE until the score changes from 0 to 1.5. This score is also applicable to subsequent courses [33]. We calculated from the prognostic variables of our population a new score and we validated it in two independent cohorts of patients mainly BCLC B treated by TACE similar to the two Austrian cohorts. We compared it to the ART score.

Patients and methods

Patients

From January 2007 to April 2012, 353 consecutive patients have been hospitalized for HCC in our Hepatology department. Diagnosis was done following EASL–AASLD criteria; if patients do not have liver cirrhosis, a biopsy was required. TACE was done in 185 of these patients (52.4%). In all cases, data (clinical, biological, radiological, follow-up, therapeutic options, response to treatment and side effects) were prospectively collected.