Editorial

ART and science in using transarterial chemoembolization for retreating patients with hepatocellular carcinoma

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Abstract: Intermediate stage hepatocellular carcinoma (HCC) comprises of a highly heterogeneous patient population, both in terms of liver function and tumour burden. Transarterial chemoembolization (TACE) is the treatment of choice for this subgroup of patients, provided that liver function is relatively preserved. Not all patients respond to an initial session of TACE, and further session might impair liver function. The ART score consists of an increase of AST >25%, increase of Child-Pugh of one or two points and absence of radiological tumour response and helps identify patients that would not benefit from further TACE sessions. We critically appraise the use of this score, particularly in terms of patient selection and timing of calculation of its variables. Once sufficiently validated, it can become a safe, objective and accurate clinical tool in everyday practice.

Keywords: Prognosis; hepatocellular carcinoma (HCC); cirrhosis; transarterial chemoembolization (TACE); transarterial embolization (TAE)

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Hepatocellular carcinoma (HCC) is the fifth most frequently diagnosed cancer and the third cause of cancer-related mortality worldwide (1,2). Current management depends on the HCC stage at diagnosis and consists of hepatic resection, liver transplantation (LT), radiofrequency ablation, transarterial embolization/transarterial chemoembolization (TAE/TACE) or, systemic therapy (3).

The most widely adopted staging system for HCC is the Barcelona Clinic Liver Cancer (BCLC) staging system, which was endorsed by most liver associations. The BCLC classification divides patients with HCC in five stages (0, A, B, C and D) according to pre-established prognostic variables, and allocates therapies according to treatment-related status. Therefore, it provides information on both prognostic prediction and treatment allocation (1). Prognosis prediction is defined by variables related to tumour status (size, number, vascular invasion, metastasis), liver function (Child-Pugh's) and health status (Eastern Cooperative Oncology Group, ECOG). Treatment allocation incorporates treatment dependant variables, which have been shown to influence therapeutic outcome, such as bilirubin, portal hypertension or presence of symptoms-ECOG.

TACE is the most widely used primary treatment for unresectable HCC, and is the recommended first-line treatment for patients at intermediate stage of the disease (BCLC B) (4). HCC exhibits intense neo-angiogenic activity during its progression (5). The rationale for TACE is that the intra-arterial infusion of a cytotoxic agent followed by embolization of the tumour-feeding blood vessels will result in a strong cytotoxic and ischemic effect (6,7). Chemoembolization does not appear to have a survival advantage over bland embolization (8). Untreated patients at an intermediate stage (BCLC B) class (multi-nodular) have a median survival of 16 months, or 49% at 2 years (9). Chemoembolization extends the survival of these patients to a median of 20 months according to randomized controlled trials (RCTs) and meta-analyses of pooled data (9). Nonetheless, outcome prediction is heterogeneous for BCLC B subclass patients, and has been reported to

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range from 36-45 months (10) for the best responders to chemoembolization in recent series, to 11 months for the worst scenario of untreated candidates (placebo arm of the SHARP trial-BCLC B patients) (11). This is largely due to the fact that intermediate HCC comprises of a highly heterogeneous patient population, both in terms of liver function and tumour burden (12). A recent meta-analysis of RCTs assessing outcomes of patients in the control arm suggested that ascites—which is a contraindication for TACE treatment—is the worst prognostic factor for this subclass (13).

The benefits of chemoembolization should not be offset by treatment-induced liver failure. Treatment-related deaths are expected in less than 2% of cases if proper selection of candidates is in place. The best candidates are patients with preserved liver function and asymptomatic multi-nodular tumours without vascular invasion or extra-hepatic spread (14).

Liver functional reserve is a critical component for a careful selection of patients to undergo TACE. Patients should present relatively well preserved liver function (mostly Child-Pugh A or B7 without ascites), while those with liver decompensation or more advanced liver failure should be excluded since the ischemic insult can lead to severe adverse events. More intense regimes, i.e., TACE every 2 months, may induce liver failure in a subset of patients. Macroscopic vascular invasion and extra-hepatic spread are other contraindications for chemoembolization.

As far as response to treatment is concerned, several studies have assessed tumour-related dynamics after TACE including radiological, biochemical and clinical parameters in order to predict post-treatment outcomes. A few published studies have established scoring systems to predict survival in patients undergoing TACE. Among those, a study by Kadalayil *et al*. (15) described a simple scoring system, that predicts survival in TAE/TACE-treated patients better than other scoring systems, including Child-Pugh, Okuda, CLIP, BCLC and MELD. This scoring system was based on four readily available indices, namely albumin, bilirubin, AFP and tumour size, and was validated in an independent cohort.

A recently published study by Sieghart *et al*. (16) aimed to establish a clinically usable point score to guide the decision for retreatment with TACE in patients with HCC. This decision is key in patients without an initial response to treatment, whose survival might be further impaired by subsequent TACE. The authors developed a novel point score to predict patient outcome with respect to patient characteristics prior to the second TACE as well as the dynamic of tumour and liver function-related parameters after the first TACE session. Patients with HCC at BCLC stage A or B who received at least two TACE sessions within 3 months (90 days) were included in the study. The presence of Child-Pugh C cirrhosis, portal vein thrombosis, or ECOG >1 was considered a contraindication for retreatment with TACE.

The training cohort consisted of 107 patients; the majority of these were at BCLC stage B (88%), while 27% of patients had received an antitumor therapy prior to the first TACE including liver resection, PEI, and RFA. Most patients (72%) were treated with chemoembolization (conventional TACE or DEB-TACE), while the remaining 28% received bland embolization (TAE). Between the first and second TACE session, 32 patients had a Child-Pugh score increase by at least 1 point, while 59 patients showed no change and 16 patients showed a decrease of the Child-Pugh score by at least 1 point. Prior to the second TACE, the majority of patients (67%) had Child-Pugh A cirrhosis. Overall, the median number of TACE interventions was 3 (range, 2-12) and the median time interval between the first and second TACE was 45 days (range, 13-90 days). In the validation cohort (n=115), the majority of patients were at BCLC stage B (n =79, 69%) and nine patients (8%) had received other anti-tumour treatment prior to the first TACE.

The authors used a stepwise Cox regression model based on the statistically significant parameters to develop a point score (ART: Assessment for Retreatment with TACE). The ART score consists of an increase of AST by >25%, an increase of Child-Pugh of 1 or ≥2 points and the absence of radiologic tumour response and differentiates patients into two groups (0-1.5 points; ≥2.5 points) with distinct prognosis [median overall survival (OS): 23.7 *vs*. 6.6 months]. These results were confirmed in an external validation cohort. The authors concluded that an ART score ≥2.5 prior to second TACE could be used to identify patients with a dismal prognosis who may not benefit from further TACE sessions.

The same group subsequently investigated the prognostic significance of the ART score prior to the third (TACE-3) and fourth TACE (TACE-4), and the feasibility of an ART score guided re-treatment strategy by sequential assessment of the ART score in HCC patients treated with multiple TACE sessions (17).

In this study, 109 patients diagnosed with intermediate stage HCC and treated with ≥3 TACE sessions over a 1-year period were included. The ART score prior to each TACE session was assessed in comparison to the TACE

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naïve liver. This study showed that pre-TACE-3 ART score discriminated two groups with different prognosis and remained a valid predictor of OS independent of Child-Pugh score, CRP-levels and tumour characteristics. Similar results were observed when the ART score was applied before TACE-4 confirming that sequential assessment of the ART score can be a useful tool to identify patients with unfavourable prognosis prior to each TACE session.

These two studies (16,17) have a significant clinical value for multiple reasons. Firstly, ART score is a simple and easily applicable scoring system in a real-life clinical setting even in countries with limited healthcare resources. Secondly, the application of the ART score may protect patients with subtle, otherwise unrecognized laboratory changes from detrimental retreatment with TACE. Thirdly, the use of the ART score may also prevent under-treatment with TACE as these studies also included patients with Child-Pugh stage B >7 points and patients with ascites of any grade which is otherwise considered to be a relative contra-indication.

Despite the above, there are a few issues that need to be critically addressed. To start with, there was significant heterogeneity among the patients as far as the treatment modality was concerned. Patients were treated with different embolization techniques, namely TAE, cTACE, and DEB-TACE, and the authors claimed that the ART score remained a significant prognostic factor regardless of the TACE techniques. However, their results seem to contradict their conclusion as patients treated with DEB-TACE showed a better treatment response compared with conventional TACE, while TAE showed no significant survival benefit. We have consistently shown that TAE and TACE are equivalent regarding patients outcome (18,19), and also that TAE might be preferable in specific settings (20). The reported results could be explained by the allocation of TAE to sicker patients in order to spare them the effects of chemotherapy or to an era effect and the improvement in patient selection over a 10-year period. Furthermore, a significant proportion of patients included in the study (27%) had previous treatment with RFA, PEI or resection, which could have an effect on the liver reserve and therefore on outcome and prognosis.

As far as patient selection is concerned, patients with intermediate stage exhibit significantly different characteristics in terms of liver tumour volume and number of lesions and therefore prognosis (12). This study provided limited data with regards to tumour volume and number of lesions, which may have a significant effect on TACE outcomes. Tumour size was analysed as a qualitative value with a high cut-off of 7.5 cm, while tumour number only focused on unifocal and multifocal disease. The era effect, although pertinent as the treatment guidelines changed during the recruitment period (1999 to 2009), was not analysed. Indeed, there were patients with ascites and Child-Pugh score of 8 and above that would not be treated with TACE in the current era.

The authors concluded that an increase in the Child-Pugh score by one or two points was an independent prognostic factor of survival following TACE. They haven't stated though, whether that difference was attributed to development of ascites, or encephalopathy, increase in bilirubin levels or decrease in albumin levels. For example, can development of ascites or encephalopathy be weighted equally as a drop in albumin levels, especially if the latter does not necessarily represent liver synthetic dysfunction but also sepsis, malnutrition or inflammatory response? A more detailed analysis maybe therefore needed in order to clarify this issue.

Additionally, this study showed that an AST increase >25% was associated with a worse median OS and was included in the prognostic model building of ART score. AST was not analysed as a time-dependent variable and given that TACE time intervals differed significantly this finding may be overstated. AST rise may be present for days/week(s) following TACE and therefore a more careful study design may be needed in order to support this statement. The authors have also shown that CRP >1 mg/dL was an independent predictor of prognosis. Again further clarity and homogeneity in the time of CRP assessment is needed in order to draw accurate and valuable conclusions. Furthermore, it is unclear how many patients developed complications including sepsis post TACE, which would affect both CRP and AST values and this needed further clarification.

It is apparent that re-treating patients with TACE remains a difficult decision with often detrimental impact on patient's survival, especially in the context of treating patients with borderline liver reserve and function. The development of a validated clinical score in order to have a more objective judgement for further TACE treatment is therefore warranted. Intermediate stage HCC is a heterogeneous disease stage and one size does not necessarily fit all. The ART score is a useful and easily applicable bedside-scoring system for patients that are potential candidates for further TACE, but needs to be validated in larger cohorts of patients with more

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homogeneous characteristics including tumour burden, Child-Pugh score, previous treatments, TAE techniques and time assessment of the laboratory values, in order to be established as a safe, objective and accurate clinical tool in everyday practice.

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