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Predictive factors of transarterial chemoembolisation toxicity in unresectable hepatocellular carcinoma

Mathieu Boulin[a,b,*], Héloïse Adam[a], Boris Guiu[c,b], Ludwig Serge Aho[d], Jean-Pierre Cercueil[c,b], Cyrille Di Martino[d], Philippe Fagnoni[a,b], Anne Minello[b,e], Jean Louis Jouve[b,e], Patrick Hillon[b,e], Laurent Bedenne[b,e], Côme Lepage[b,e,**]

[a] Department of Pharmacy, CHU (University Hospital), 21000 Dijon, France
[b] University of Burgundy, 21079 Dijon, France
[c] Department of Radiology, CHU (University Hospital), 21000 Dijon, France
[d] Department of Pharmacy, Georges Francois Leclerc Anticancer Center, 21079 Dijon Cedex, France
[e] Department of Hepatogastroenterology, CHU (University Hospital), F-21079 Dijon, France

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ABSTRACT

Background: Transarterial chemoembolisation (TACE) is an effective treatment for unresectable hepatocellular carcinoma (HCC), but can cause severe toxicity.
Aim: To identify predictive factors of severe TACE-related toxicity in patients with unresectable HCC.
Methods: All HCC patients who underwent TACE at the Dijon University Hospital between 2008 and 2011 were included in this retrospective study. Severe TACE-related toxicity was defined as the occurrence of any adverse event grade ≥4, or any adverse event that caused a prolongation of hospitalisation of >8 days, or any additional hospitalisation within 1 month after TACE. Factors predicting toxicity were identified using a logistic regression model. The robustness of the final model was confirmed using bootstrapping (500 replications).
Results: 124 patients were included, median age was 67 years and 90% were male; 22 patients (18%) experienced severe TACE-related toxicity. Factors that independently predicted severe TACE-related toxicity in multivariate analysis were total tumour size (OR, 1.15 cm^{-1}; 95%CI, 1.04–1.26; $p = 0.01$), and high serum AST levels (OR, 1.10 per 10 IU/l; 95%CI, 1.01–1.21; $p = 0.04$). The results were confirmed by bootstrapping.
Conclusions: Total tumour size and high serum AST levels were predictive factors of severe TACE-related toxicity in this hospital-based series of patients with unresectable HCC.

1. Introduction

With approximately 750,000 new cases and 690,000 deaths worldwide in 2008, hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third most common cause of cancer-related death worldwide [1]. Transarterial chemoembolisation (TACE) is the current standard treatment for intermediate stage HCC [2,3]. This recommendation is based on the results of two randomised trials and of two meta-analyses showing statistically significant increased survival with TACE in patients with unresectable HCC, compared to supportive care or suboptimal therapies [4–7].

Patients with intermediate-stage HCC are a heterogeneous population in terms of tumour burden (large or multifocal), liver function (Child–Pugh A/B) and disease aetiology (alcohol, viruses, *etc.*). This heterogeneity is amplified by the fact that, in clinical practice, patients with early stage [Barcelona Clinic Liver Cancer (BCLC) A] and contraindications to surgery or local treatment, and patients with advanced stage [BCLC C, mainly due to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥1], are both treated with TACE [8–11]. Since the earliest TACE clinical trials, it has been clearly demonstrated that not all patients with unresectable HCC obtain similar benefits; additionally, there is now evidence that some patients with intermediate-stage HCC do not obtain a clinical benefit from TACE [12]. Moreover, since TACE carries a risk of mortality and morbidity, and is a palliative treatment for HCC, it is extremely important to be able to predict TACE-related serious adverse events (AE).

* Corresponding author at: Department of Pharmacy, CHU (University Hospital), 14 rue Gaffarel, 21000 Dijon, France. Tel.: +33 380 293 796; fax: +33 380 293 275.
** Corresponding author at: Department of Hepatogastroenterology, CHU (University Hospital), 14 rue Gaffarel, 21000 Dijon, France. Tel.: +33 380 293 750; fax: +33 380 293 722.
E-mail addresses: mathieu.boulin@chu-dijon.fr, mathieuboulin@yahoo.fr (M. Boulin), come.lepage@u-bourgogne.fr (C. Lepage).

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The aim of our study was to identify predictive factors of severe TACE-related toxicity in a cohort of patients with unresectable HCC.

2. Patients and methods

2.1. Patients

All patients with HCC who received at least one TACE session at our University Hospital between January 2008 and December 2011 were included in this retrospective study. For all patients the indications for TACE were discussed during our weekly multidisciplinary meeting, which involves interventional radiologists, gastroenterologists, hepatic surgeons, radio-oncologists, and medical oncologists.

The patients' indication for TACE was based on: confirmed diagnosis of HCC according to the European Association for the Study of the Liver (EASL) criteria [3]; ECOG PS of 0 or 1; preserved liver function (Child–Pugh class A or <B7); platelet count $>50 \times 10^9\,l^{-1}$; absence of symptoms (encephalopathy, ascites), portosystemic shunts, hepatofugal blood flow, thrombus within the main portal vein, extrahepatic metastases, concomitant malignancy, renal failure (serum creatinine level $\geq$150 μmol/l), allergy to iodine-containing agents, and pregnancy.

2.2. TACE procedure

Patients underwent TACE according to a standard protocol. The femoral artery was punctured using the Seldinger technique and a 5-French catheter was inserted. According to the degree of liver involvement, selective catheterisation of the artery feeding the tumour (or tumours) was performed with selective or hyperselective injections throughout the study period. The choice of vector (lipiodol or drug eluting beads, DEB) was left to the discretion of the interventional radiologist (DEBs have been available at our institution since July 2008). For conventional TACE, a mixture of the anticancer agent and 10-ml lipiodol (Lipiodol®, Guerbet, Aulnay-sous-Bois, France) was perfused in 10 min, followed by the injection of a particulate embolic agent chosen by the radiologist (gelatin sponge; Curaspon®, Curamedical B.V., Amsterdam, Netherlands) or unloaded beads (Embozene™, Celonova Biosciences, Paris, France) until stasis. The anticancer agent-lipiodol emulsion was prepared by the interventional radiologist just before injection by passing the mixture 10 times from one 50 ml-syringe to another *via* a 3-way tap.

For DEB-TACE, the anticancer agent was loaded into 1 vial of DC Beads™ (Biocompatibles, Farnham, UK) containing 2 ml of hydrated beads measuring 300–500 μm or 100–300 μm in the pharmacy. After the addition of at least 10 ml of non-ionic contrast medium (iodixanol, Visipaque®, GE Healthcare, Velizy, France), the loaded beads were slowly injected within 10 min. When stasis was not obtained, complementary embolisation (*i.e.* additional embolisation by gelatin sponge or unloaded beads at the end of the TACE session) was used at the discretion of the interventional radiologist.

Two anticancer agents were used during the study period: doxorubicin 50 mg (Doxorubicin, Teva, Paris, France) until July 2011 and idarubicin 10 mg (Zavedos®, Pfizer, Paris, France) thereafter.

2.3. Study protocol

Patient characteristics (age, gender, aetiology of cirrhosis, ECOG PS, Child–Pugh class, BCLC stage), tumour characteristics (size, number of nodules), and biological pre-treatment data (albumin, total bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma-glutamyl transpeptidase [GGT], prothrombin time [PT], and alpha-fetoprotein [AFP]) were recorded. The following TACE characteristics were also recorded: anticancer drug (doxorubicin or idarubicin) and vector (lipiodol or DEBs).

Each patient was followed for 1 month after the TACE procedure. During this period, toxicities were recorded during the scheduled visit at 1 month or at emergency visits. The 1-month scheduled visit consisted of a complete physical examination, liver function tests, serum creatinine level, platelet count, Child–Pugh score, and electrocardiogram. Severe toxicity was defined as the occurrence of a serious AE in accordance with the National Cancer Institute Common Terminology Criteria (NCI-CTCAE) v4.0 [13]: grade 4 or 5 AE, or any other AE that caused a prolongation of the TACE-related hospitalisation of >8 days, or any additional hospitalisation, all within the first month after TACE.

2.4. Statistical analyses

The association between TACE-related severe toxicity and baseline variables was examined using the χ^2 or Fischer's exact test as appropriate for categorical variables, and the two-sided *t*-test or Wilcoxon rank sum test as appropriate for continuous variables. Due to the low number of events, only variables that were significant in univariate analysis were further examined in multivariate analysis. Multivariate analysis was performed with all possible stepwise logistic regression (LR) models [14]. ECOG PS was not introduced into the LR models because this variable was already incorporated in the BCLC staging system (all of our patients were classified BCLC C on the sole criterion of an ECOG PS $\geq$1). Highly correlated variables were not used together in the LR models in order to avoid collinearity. For continuous variables, log-linearity was checked using fractional polynomials [15]. We evaluated the discrimination of the LR models by calculating the area under the receiver operation characteristic (ROC) curve (AUC). Pseudo R^2 statistics [16] and Akaike's information criterion (AIC) were used to choose the final model. The choice of the variables to include in the final model was confirmed by random forest analysis [17]. The robustness of the final model was confirmed using bootstrapping (500 replications). All analyses were performed using Stata software version 12.0 (Stata Corporation, College Station, TX, USA). A p value below 0.05 was considered significant.

3. Results

3.1. Baseline characteristics

The study cohort consisted of 124 patients, of whom 112 were men (90%). The median age was 67 years (range 44–87 years). Sixty-nine percent of the patients had an ECOG PS of 0 and 82% had a preserved Child–Pugh A class liver function. There were 22 patients (18%) with Child–Pugh class B7. The BCLC stage of the patients consisted of stages A (23%), B (46%), and C (31%). Ninety percent of the patients were cirrhotic. Among these, the aetiology of the cirrhosis was alcohol abuse and hepatitis B or C in 69% and 14% of the patients, respectively. Sixteen patients (13%) had received previous curative treatments. The median total tumour size was 6.3 cm (range 1.6–23 cm). Before TACE, the median serum levels of total bilirubin, albumin, and AFP were respectively 13 μmol/l (range 2–81 μmol/l), 34 g/l (range 18–43 g/l), and 24 ng/ml (range 2–18,436 ng/ml).

Seventy-two patients received conventional TACE (58%) and 52 patients received DEB-TACE (42%). The anticancer agents were doxorubicin and idarubicin in 70% and 30% of the patients, respectively. The mean duration of TACE-related hospitalisation was 5.5 days.