Research Article

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Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial

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Background & Aims: Transarterial chemoembolization with doxorubicin-eluting beads (DC Bead®; DEB-TACE) is effective in patients with Barcelona clinic liver cancer stage B hepatocellular carcinoma (HCC). The multikinase inhibitor sorafenib enhances overall survival (OS) and time-to-tumor progression (TTP) in patients with advanced HCC. This exploratory phase II trial tested the efficacy and safety of DEB-TACE plus sorafenib in patients with intermediate stage HCC.

Methods: Patients with intermediate stage multinodular HCC without macrovascular invasion (MVI) or extrahepatic spread (EHS) were randomized 1:1 to DEB-TACE (150 mg doxorubicin) plus sorafenib 400 mg twice daily or placebo. The primary endpoint was TTP by blinded central review. Secondary endpoints included time to MVI/EHS, OS, overall response rate (ORR) using modified response evaluation criteria in solid tumors, disease control rate (DCR), time to unTACEable progression (TTUP), and safety.

Results: Of 307 patients randomized, 154 received sorafenib and 153 received placebo. Median TTP for subjects receiving sorafenib plus DEB-TACE or placebo plus DEB-TACE was similar (169 *vs.* 166 days, respectively; hazard ratio (HR) 0.797, $p = 0.072$). Median time to MVI/EHS (HR 0.621, $p = 0.076$) and OS (HR 0.898, $p = 0.29$) had not been reached. The ORRs for patients in the sorafenib and placebo groups with post-baseline scans were 55.9% and 41.3%, respectively, and the DCRs were 89.2% and 76.1%, respectively. TTUP was lower with sorafenib than with placebo (HR 1.586; 95% confidence intervals, 1.200–2.096; median 95 *vs.* 224 days). No unexpected adverse events related to sorafenib were observed.

Conclusion: Sorafenib plus DEB-TACE was technically feasible, but the combination did not improve TTP in a clinically meaningful manner compared with DEB-TACE alone.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver; the sixth most common cancer, and the third most common cause of cancer-related deaths worldwide [1,2]. Resection, liver transplantation, and local ablation are considered potentially curative in carefully selected patients, with 5-year survival rates of 40–70%, compared with 20% in untreated patients [3–5].

Transarterial chemoembolization (TACE) is the standard of care for patients with intermediate stage (Barcelona clinic liver cancer (BCLC) stage B) HCC. These patients are defined as being asymptomatic, with non-invasive, multinodular, unresectable tumors and adequate preservation of liver function [3–7]. TACE can deliver higher concentrations of drug to tumors than systemic chemotherapy, while decreasing systemic exposure [8–10]. TACE has also been reported to achieve objective

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responses in 16%–61% of HCC patients, to significantly delay tumor progression and vascular invasion and to improve survival [5,11].

Despite the survival benefits of TACE in patients with unresectable HCC [7], the optimal technique is less clear [12]. TACE procedures can vary substantially, with regards to both the chemotherapeutic agent and embolization method, making these procedures quite heterogeneous [13]. Moreover, no consensus has been reached concerning the number of TACE administrations or the time between administrations. TACE with embolic doxorubicin-eluting beads (DC Bead®; Biocompatibles UK Ltd) was developed to simplify the procedure, reduce peak concentrations and total systemic exposure to doxorubicin, and ensure high concentrations in the tumor and adequate arterial occlusion [14–18]. These beads show sustained, continuous release of doxorubicin for 14 days (9), with a significantly lower systemic plasma concentration of doxorubicin compared with intra-arterial injection [9,19]. A randomized phase II trial found that TACE with doxorubicin-eluting beads (DEB-TACE) reduced the rates of systemic adverse events (AE) and liver toxicity compared with conventional TACE with Lipiodol® (Guerbet Group, Villepinte, France) and doxorubicin [10]. Median overall survival (OS) in a highly selected population (95% Child-Pugh A) was approximately 4 years [20]. Moreover, in a recent trial in 173 patients, 59% Child-Pugh class A, DEB-TACE resulted in a median survival of 43.8 months and a 5-year OS rate of 22.5% [21].

Sorafenib is a multikinase inhibitor [22–24] shown in two large, double-blind, randomized, placebo-controlled phase III clinical trials to significantly improve OS and time-to-tumor progression (TTP) in patients with advanced HCC [25,26]. Similar improvements in OS and TTP were observed in the subgroup of patients with intermediate stage HCC (BCLC B) [27]. Sorafenib is currently approved as the only systemic therapy for HCC.

Sorafenib has been reported to provide no significant benefit in TTP or OS in selected HCC patients when administered after initial response to TACE [28]. Because TACE has been shown to lead to a spike in the intratumoral concentration of vascular endothelial growth factor (VEGF), blockade of VEGF receptors prior to TACE may prevent the effects of a surge in pro-angiogenic factors [29–31]. Moreover, because both TACE and sorafenib have been shown to enhance patient survival without obvious overlapping toxicities [11,25,26,32], their combination may improve clinical outcomes. Single-arm studies combining sorafenib with various forms of chemoembolization have suggested that this combination is safe and effective [33–41]. This signal-generating phase II trial was designed to compare TTP in patients with intermediate stage HCC treated with sorafenib or placebo plus DEB-TACE.

Patients and methods

Patient characteristics

This phase II randomized, double-blind, placebo-controlled study enrolled 307 patients with intermediate stage HCC at 85 centers in 13 countries (Fig. 1). Patients were included if they had unresectable, multinodular, asymptomatic HCC (BCLC stage B) [5], with measurable lesions on CT or MRI; no macrovascular invasion (MVI) or extrahepatic spread (EHS); Child-Pugh class A and compensated liver function; an Eastern Cooperative Oncology Group (ECOG) performance status of 0; no ascites; age $\geqslant$18 years, with a life expectancy $\geqslant$12 weeks; and adequate bone marrow function (hemoglobin >9.0 g/dl; absolute neutrophil count (ANC) >1500/mm^3; platelet count $\geqslant 60 \times 10^9$/L), liver function (bilirubin <3 mg/dl; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <5 times the upper limit of normal (ULN); alkaline phosphatase <4 times ULN; prothrombin time-international normalized ratio (PT-INR) <2.3 or PT <6 seconds above control), and kidney function (serum creatinine <1.5 times ULN; amylase and lipase <3 times ULN).

Patients were excluded if they had diffuse HCC; vascular invasion (including segmental portal obstruction); extrahepatic tumor spread; advanced liver disease, as shown by Child-Pugh class B or C liver function, gastrointestinal bleeding, encephalopathy, or ascites; or contraindications for embolization, including known hepatofugal blood flow or portosystemic shunt. Patients were also excluded if the target lesion had previously undergone local treatment, including resection, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), or TACE; if they had received local therapy within 4 weeks of a baseline scan; had

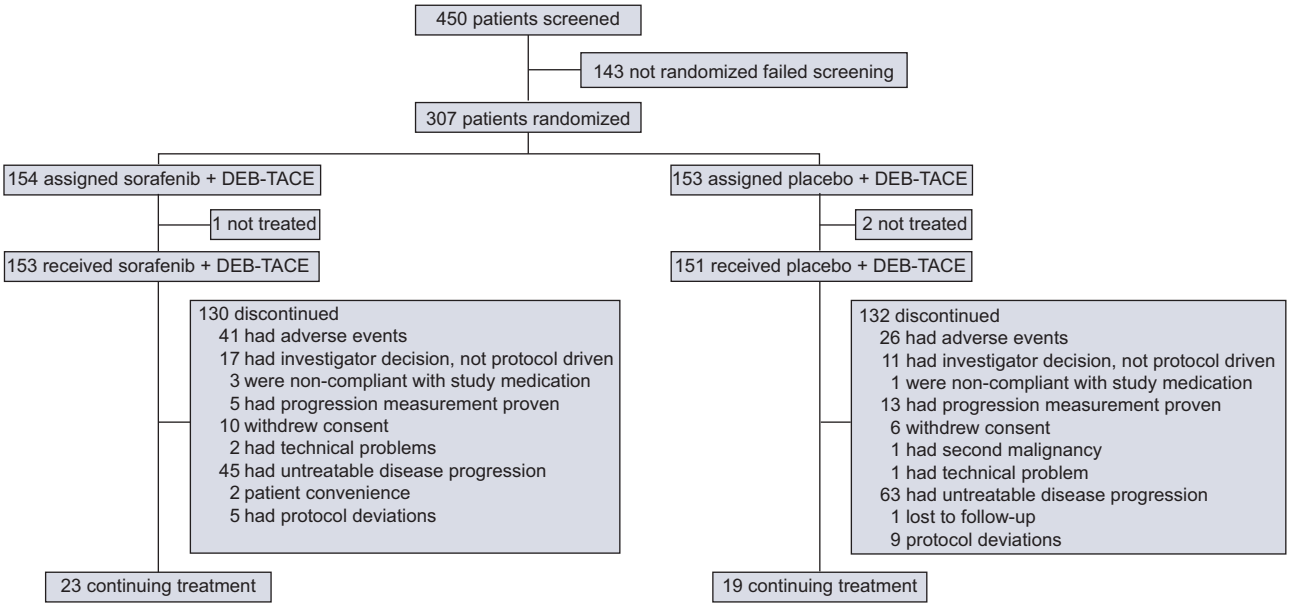

Fig. 1. Trial profile.