Research Article

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Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: Subanalyses of a phase III trial ☆,☆☆

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Background & Aims: The Sorafenib Hepatocellular Carcinoma (HCC) Assessment Randomized Protocol (SHARP) trial demonstrated that sorafenib improves overall survival and is safe for patients with advanced HCC. In this trial, 602 patients with well-preserved liver function (>95% Child–Pugh A) were randomized to receive either sorafenib 400 mg or matching placebo orally b.i.d. on a continuous basis. Because HCC is a heterogeneous disease, baseline patient characteristics may affect individual responses to treatment. In a comprehensive series of exploratory subgroup analyses, data from the SHARP trial were analyzed to discern if baseline patient characteristics influenced the efficacy and safety of sorafenib.

Methods: Five subgroup domains were assessed: disease etiology, tumor burden, performance status, tumor stage, and prior therapy. Overall survival (OS), time to progression (TTP), disease control rate (DCR), and safety were assessed for subgroups within each domain.

Results: Subgroup analyses showed that sorafenib consistently improved median OS compared with placebo, as reflected by hazard ratios (HRs) of 0.50–0.85, similar to the complete cohort (HR = 0.69). Sorafenib also consistently improved median TTP (HR, 0.40–0.64), except in HBV-positive patients (HR, 1.03), and DCR. Results are limited by small patient numbers in some subsets. The most common grade 3/4 adverse events included diarrhea, hand-foot skin reaction, and fatigue; the incidence of which did not differ appreciably among subgroups.

Conclusions: These exploratory subgroup analyses showed that sorafenib consistently improved median OS and DCR compared with placebo in patients with advanced HCC, irrespective of disease etiology, baseline tumor burden, performance status, tumor stage, and prior therapy.

Keywords: Hepatocellular carcinoma; Sorafenib; Subset analyses; Overall survival; Time to progression; Disease control rate.

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Introduction

Hepatocellular carcinoma (HCC) is often diagnosed at an advanced stage, when most potentially curative therapies, such as resection, transplantation, and percutaneous ablation, are of limited utility [1–3]. Only approximately 30–40% of patients are diagnosed at an early stage and can benefit from such curative

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therapies [1,2], and up to 70% of patients who undergo these procedures will have recurrent disease within 5 years and reach a more advanced tumor stage [4,5]. Patients diagnosed at an intermediate stage can benefit from transarterial chemoembolization (TACE) but after an initial therapeutic benefit, most patients progress to advanced stage.

Sorafenib is a multitargeted tyrosine kinase inhibitor that blocks the activity of Raf serine/threonine kinase isoforms, as well as the receptor tyrosine kinases vascular endothelial growth factor receptors (VEGFR)-2 and -3, platelet-derived growth factor receptor (PDGFR) β, c-KIT, FLT-3, and RET, to inhibit tumor angiogenesis and tumor cell proliferation [6–8]. Results from the multinational, randomized, placebo-controlled, phase III Sorafenib HCC Assessment Randomized Protocol (SHARP) trial demonstrated that sorafenib significantly improved overall survival (OS) in patients with advanced HCC and well-preserved liver function (>95% Child–Pugh A), and that drug-related adverse events (AEs) were manageable [9]. Median OS in the sorafenib and placebo groups was 10.7 and 7.9 months, respectively (hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.55–0.87; p <0.001), median time to progression (TTP) was 5.5 and 2.8 months, respectively (HR 0.58, 95% CI 0.45–0.74; p <0.001), and disease control rate (DCR) was 43% and 32%, respectively (p = 0.002) [9]. The positive impact of sorafenib in improving survival and delaying tumor progression was confirmed in the phase III Sorafenib Asia–Pacific trial, performed in China, South Korea, and Taiwan [10]. Together, these trials provided evidence for the effectiveness of sorafenib across a range of disease etiologies, leading to its approval as first-line systemic therapy for patients with advanced HCC [3,11–16].

Baseline characteristics may affect individual responses to treatment. To discern whether baseline patient characteristics influenced the efficacy and safety of sorafenib in patients with HCC, we performed a comprehensive series of exploratory subgroup analyses to evaluate whether patient and/or tumor characteristics at baseline affected response to sorafenib in the SHARP trial. Five subgroup domains were selected for analysis: HCC etiology (hepatitis C virus (HCV), hepatitis B virus (HBV) or alcohol-related), tumor burden (defined as macroscopic vascular invasion (MVI) and/or extrahepatic spread (EHS)), Eastern Cooperative Oncology Group performance status (ECOG PS), tumor stage according to the Barcelona Clínic Liver Cancer (BCLC) system, and treatment received prior to sorafenib. We did not include gender, as this had already been reported in the original study [9].

Patients and methods

Study design

The SHARP study design has been described [9]. Briefly, SHARP was a multinational, randomized, double-blind, placebo-controlled, phase III trial evaluating the clinical benefits of sorafenib in patients with measurable, unresectable, advanced HCC who had not received prior systemic therapy and with a Child–Pugh A classification of liver function, an ECOG PS of 0–2, and a life expectancy of at least 12 weeks. Patients were randomized 1:1 to sorafenib 400 mg or matching placebo twice daily. The primary end points included OS (measured from the date of randomization to date of death from any cause) and patient-reported quality of life [17], and safety. Tumor size was measured by computed tomography or magnetic resonance imaging at screening, every 6 weeks during treatment, and at the end of treatment. TTP was measured from the date of randomization to the date of disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST). DCR was defined as the percentage of patients who had a best response of complete response (CR), partial response (PR), or stable disease (SD) for ⩾4 weeks, based on independent radiologic review. Safety was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

The 602 patients in the SHARP trial were stratified by tumor burden (presence or absence of MVI and/or EHS), ECOG PS (0 or 1–2), and geographic region (North America; Central/South America; or Europe/Australia/New Zealand) and randomized to receive sorafenib or placebo in a double blinded fashion [9]. For the subset analyses, patients were subgrouped by tumor burden (MVI/EHS absent; MVI/EHS present) and ECOG PS (0, 1–2); and *post hoc* by etiology (HCV, HBV, alcohol); BCLC stage (B, C/D); and prior therapy (curative treatment, TACE). Designation of alcohol as an etiologic factor was made by the investigator based on history. Laboratory screening for HBV or HCV antigen was performed at least 7 days prior to initial treatment. Any previous local therapy must have been completed at least 4 weeks prior to the baseline scan and any treatment-naïve target lesion was identified for proper assessment of tumor progression.

Statistical analysis

The population for efficacy analysis in each subgroup was the intent-to-treat population (defined as all randomized patients). OS and TTP were estimated by Kaplan–Meier analysis. Because the SHARP study was not powered for subgroup analysis, the sorafenib and placebo subgroups were compared descriptively rather than statistically. Furthermore, as in any *post hoc* subgroup analysis, statistical strength decreases as sample size decreases, thereby obviating a formal assessment of statistical significance in cohorts with small sample sizes. We report HR and 95% CI only, calculated from a Cox regression with only treatment in the model.

The safety population included all patients who received at least one dose of study drug. AEs were summarized descriptively. The sorafenib and placebo groups were compared for the incidence of drug-related, treatment-emergent AEs, and serious AEs (SAEs).

Results

Baseline demographics, the major etiology of HCC, and disease characteristics of patients in the SHARP subgroups are shown in Table 1. Table 2 shows a summary of the efficacy results (OS, TTP, and DCR) of the subgroup analyses, as well as the results in the overall population.

The mean daily doses in the sorafenib and placebo groups were 710.5 ± 142.1 and 774.8 ± 65.4 mg, respectively, and the median daily doses were 797.2 and 800.0 mg, respectively. Overall, 227 (75.7%) and 284 (93.8%) patients in the sorafenib and placebo groups, respectively, received average daily doses ⩾80%, and 204 (68.0%) and 269 (88.8%) patients, respectively, received average daily doses ⩾90%, of the planned daily dose.

OS, TTP, and DCR by subgroups

Tumor etiology

Three subsets were included in the analysis of etiology (Fig. 1): patients positive for anti-HCV antibody (n = 167), those positive for HBV surface antigen (HBsAg; n = 60), and those classified as presenting with alcohol-related HCC (n = 159). HCV-infected patients treated with sorafenib had superior median OS (14.0 *vs.* 7.4 months), TTP (7.6 *vs.* 2.8 months), and DCR (44.2% *vs.* 29.6%) than those who received placebo. Among HBV-positive patients, those treated with sorafenib had a longer median OS (9.7 *vs.* 6.1 months), but a shorter median TTP (2.7 *vs.* 4.2 months) and a similar DCR (34.4% *vs.* 32.1%) as those who received placebo. This subset, however, was much smaller than the other subsets and was not well balanced, in that 18 of 32 (56.3%) of those treated with sorafenib had an ECOG PS of 1 or 2, compared with 11of 28 (39.3%) who received placebo (Table 1). Among patients with