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Original Article

Sorafenib for the Treatment of Advanced Hepatocellular Cancer – a UK Audit

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Abstract

Aims: Sorafenib is the current standard treatment for advanced hepatocellular carcinoma. We carried out a national audit of UK patients treated with sorafenib as standard-of-care and those treated with systemic therapy in first-line trials.
Materials and methods: Sorafenib-treated and trial-treated patients were identified via the Cancer Drugs Fund and local databases. Data were collected retrospectively from medical records according to a standard case report form. The primary outcome measure was overall survival, estimated by the Kaplan–Meier method.
Results: Data were obtained for 448 sorafenib-treated patients from 15 hospitals. The median age was 68 years (range 17–89) and 75% had performance status $\leq$ 1. At baseline, 77% were Child-Pugh A and 16.1% Child-Pugh B; 38% were albumin–bilirubin grade 1 (ALBI-1) and 48% ALBI-2; 23% were Barcelona Clinic Liver Classification B (BCLC-B) and 72% BCLC-C. The median time on sorafenib was 3.6 months, with a mean daily dose of 590 mg. The median overall survival for 448 evaluable sorafenib-treated patients was 8.5 months. There were significant differences in overall survival comparing Child-Pugh A versus Child-Pugh B (9.5 versus 4.6 months), ALBI-1 versus ALBI-2 (12.9 versus 5.9 months) and BCLC-B versus BCLC-C (13.0 versus 8.3 months). For trial-treated patients ($n = 109$), the median overall survival was 8.1 months and this was not significantly different from the sorafenib-treated patients.
Conclusion: For Child-Pugh A patients with good performance status, survival outcomes were similar to those reported in global randomised controlled trials. Patients with ALBI grade > 1, Child-Pugh B or poor performance status seem to derive limited benefit from sorafenib treatment.

Key words: ALBI; Child-Pugh; hepatocellular carcinoma; prognosis; sorafenib

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Introduction

Hepatocellular carcinoma (HCC) is the second most common cause of cancer death worldwide and accounted for 746 000 deaths in 2012 [1]. Overall, the prognosis is poor and the 5 year age-standardised net survival for adults with liver cancer in the UK is 9.3% [2]. To date, sorafenib remains the only drug licenced for the systemic treatment of HCC based on the results of two randomised clinical trials, which showed an improvement in median overall survival of between 2 and 3 months compared with placebo [3,4]. On this basis, sorafenib was approved for HCC by the European Agency for the Evaluation of Medicinal Products in 2007 and is recommended in international guidelines [5].

The National Institute for Health and Care Excellence and Scottish Medicines Consortium both published guidance in 2010 and recommended against the use of sorafenib for advanced HCC on the basis of cost-effectiveness. However, in England, the Cancer Drug Fund, which was established in April 2011, has provided funding for sorafenib as first-line therapy for patients with advanced HCC with Child-Pugh A liver impairment or Child-Pugh grade B7 liver impairment.

The clinicopathological characteristics and clinical outcome of patients with advanced HCC treated in the UK has not been previously reported and we therefore undertook a retrospective national audit to define the patient population treated with sorafenib in the UK and the outcome in terms of overall survival.

Patients and Methods

This was an investigator-initiated collaborative study without industry support. UK centres that treat HCC were identified via the UK database of cancer networks, through which cancer care is geographically coordinated in the UK. The Patient Advice and Liaison Office for each Hospital Trust provided contact details for all clinicians who managed patients with HCC, and they were invited to participate in the study. For each hospital, HCC patients who had received sorafenib as first-line systemic therapy were identified via local Cancer Drugs Fund records or locally held databases. Only patients treated within the National Health Service were included. In addition, we identified first-line drug trials for HCC that were recruiting in the UK during the study period. Anonymised clinical and treatment data were collected from medical and pharmacy records according to a study-specific case report form. Although toxicity was not recorded according to CTC grade, we recorded the adverse events that resulted in dose reduction, interruption or termination of treatment and thereby captured toxicity of clinical relevance to patient management. The primary outcome measure was overall survival. Ethics approval was granted for this research (REC reference 12/LO/1088).

Statistics

Analyses were carried out using Stata version 12.1. Overall survival curves were generated using Kaplan–Meier methods from the start of sorafenib to the date of death or to the date of last follow-up. The Log-rank test was used for comparisons between survival curves. Cox proportional hazards regression analysis was used to obtain univariate hazard ratios. All variables in Table 1 were considered for inclusion in the multivariable model, except where there was colinearity with existing variables or where there was greater than 10% missing data. Continuous variables were analysed as categorical variables, with the cut-offs decided as: lower limit of normal range for albumin and bilirubin, and alphafetoprotein (AFP) 400 ng/ml. Eastern Cooperative Oncology Group (ECOG) performance status was included as a categorical variable with three levels (0; 1; 2 or 3). Baseline variables that were associated with overall survival in a univariable Cox model ($P < 0.1$) were included in the multivariable model. Kaplan–Meier estimated survival curves were used to compare sorafenib and trial-treated patients and the effect of Child-Pugh grade, albumin-bilirubin (ALBI) grade [6] and Barcelona Clinic Liver Classification (BCLC) stage [7] among sorafenib-treated patients. The mean daily dose of sorafenib was established by calculating the mean daily dose per patient during the course of their treatment and reporting the median mean dose for the whole population.

Results

Sorafenib-treated Patients

Overall, 17 hospitals were invited to participate and 15 provided data by the agreed deadline. In total, 448 sorafenib-treated patients were started on sorafenib from 1 July 2007 to 24 July 2013. Baseline characteristics are shown in Table 1. Most patients were ECOG performance status ≤ 1 (75%), 77% were Chuld-Pugh A and 72% were BCLC-C. Extrahepatic disease was reported in 38%, of which the most common site was lymph node followed by lung and then bone. There was a high rate of missing data for vascular invasion, but among the 252 patients in whom it was recorded, 39% had vascular invasion. The most common single aetiology of background liver disease was alcohol in 25%, and 42% had previously received prior local therapy for HCC, of whom 74% had undergone transarterial (chemo) embolisation and 12% had received radiofrequency ablation.

Treatment Dose and Toxicity

Full treatment data were available for 436 patients. The median time on sorafenib treatment was 3.6 months, with a mean daily sorafenib dose of 590 mg. Overall, 271 (62%) started at 800 mg daily, 143 (33%) started at 400 mg daily and the remainder started at 200 mg (4%) or 600 mg (1%) daily. A dose reduction was required in 140 (52%) patients and 84 (31%) had their treatment temporarily interrupted due to toxicity. The main toxicities leading to a dose reduction or treatment interruption are shown in Table 2. Fatigue, deterioration in performance status and diarrhoea were the most common listed. The frequency of adverse

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