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Geographic difference in survival outcome for advanced hepatocellular carcinoma: Implications on future clinical trial design

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ABSTRACT

In clinical trials of systemic therapy for advanced hepatocellular carcinoma (HCC), Asian trials almost always reported poorer survival than non-Asian trials. This study sought to identify contributory factors for this geographic difference. A systematic review was done on randomized trials for unresectable HCC that used systemic therapy as an experimental arm and placebo or supportive care as control. Meta-analysis was performed with the consideration of fixed and random effects. Then, meta-regression was performed to identify predictors of patient survival in the control arm and the treatment effects (improvement in median survival). Fourteen trials (6 Asians, 8 non-Asians) were eligible for meta-analysis. The median survival of patients in the control arm, which indicated natural history of advanced HCC patients, was 3.57 ± 1.88 months in Asian trials and 5.96 ± 1.46 months in non-Asian trials ($p = 0.02$). Independent predictors of better survival included non-Asian trials ($p = 0.0007$), higher percentage of Child A cirrhosis ($p = 0.01$) and hepatitis B (HBV)-related HCC ($p = 0.02$). Sub-group analysis suggested that Asian trials tended to enroll patients with more advanced diseases. Independent predictors of better treatment effect included non-Asian trials, higher percentage of extra-hepatic metastasis, HBV-related HCC, and poorer trial quality. The quantitative estimation of the geographic difference can help design of future clinical trials of advanced HCC.

1. Introduction

Advanced hepatocellular carcinoma (HCC) remains a huge unmet medical need globally. Molecular targeted therapy (MTT), which aims at specific molecular derangements in cancer cells or their microenvironment, has recently shed new light on the treatment of advanced HCC [1]. The multi-kinase inhibitor sorafenib is the first agent approved for the treatment of advanced HCC because of its survival benefit demonstrated by two randomized, placebo-control trials [2,3]. The success of the sorafenib trials has spurred enormous interest in development of novel MTT for the treatment of advanced HCC [4].

In the published clinical trials of systemic therapy for HCC, Asian trials almost always reported poorer survival than their Western counterparts [5–7]. The two sorafenib trials, which were done in Western and Asian populations, respectively, using identical eligibility criteria and treatment, provide the most direct evidence of the geographic difference. The overall survival in the Western trial was 10.7 and 7.9 months, respectively, for patients who received sorafenib or placebo. In the Asian trial it was 6.5 and 4.2 months, respectively. The

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difference in survival outcome, especially that for patients who received placebo or best supportive care only, implies that Asian and Western trials enrolled patients with different prognostic features, despite very similar eligibility and staging criteria used in these trials. These differences will have important implications in future clinical trial design for HCC.

Both patient factors and practice factors may contribute to the different prognosis between Asian and Western HCC patients. The major etiology of the underlying liver disease in Asian patients is chronic hepatitis B infection, whereas that in Western and Japanese patients is chronic hepatitis C infection or alcoholic liver disease [8,9]. The different etiologies have been found to be associated with different genetic and epigenetic aberrations, which may help predict prognosis [10–12]. In addition, Asian doctors tended to be more aggressive in surgical resection and loco-regional therapy [13–16]. Therefore, only patients who have failed all available loco-regional therapy will be referred to trials of systemic therapy. This geographic difference in treatment guidelines will continue to influence the patterns of HCC patients enrolled into future trials.

In this study a systematic review of published randomized trials of systemic therapy for advanced HCC was done. The purpose of this study is to identify pertinent factors that can explain the geographic difference in patient outcome in clinical trials for advanced HCC. Meta-analysis and meta-regression were performed according to the Cochrane guidelines [17]. The meta-regression method has the following advantages in exploring the heterogeneity issue, compared with the conventional sub-group analysis [17]. Sub-group analysis can analyze categorical variables only, while meta-regression can analyze both continuous and categorical variables. Moreover, meta-regression analyzes simultaneously the effects of multiple pertinent variables on the outcome as well as the potential interaction among these variables. Thus, meta-regression is more efficient statistically than conventional sub-group analysis, which may suffer significant loss in statistical power due to decrease in sample size in each sub-group.

2. Methods

2.1. Study eligibility and identification

The meta-analysis and meta-regression conducted in this study were based on a systematic search of the published clinical trials for advanced HCC. The electronic databases searched included Medline, Cancerlit, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Database of Abstracts of Reviews of Effect. In addition, the abstracts presented in the annual meetings of the American Society of Clinical Oncology (ASCO) from 2005 to 2008 were covered. To identify unpublished but relevant clinical trials, the website http://www.clinicaltrials.gov was also searched for clinical trials of advanced HCC that have completed patient recruitment.

The main focus of this review study was the clinical characteristics and outcomes of the HCC patients who received either placebo/supportive care or experimental treatments. The search strategy was a combination of the keywords (1) 'hepatocellular carcinoma' or 'liver cancer' or 'HCC', and (2) 'randomized controlled trial' or 'randomized controlled study'. The studies were selected for review if they fulfilled the following inclusion criteria: (1) randomized controlled trials for HCC patients who were not resectable and not suitable for local therapies (e.g., ablation therapy, trans-arterial chemoembolization), (2) systemic therapy as the experimental arm, and (3) placebo or best supportive care as the control arm. No language or ethnics was restricted. The scientific reports of the studies published since January 1996 were selected for systematic review because older trials might have different standards and quality of supportive care from the newer ones.

2.2. Data extraction

Two authors (C.H. and Y.C.S.) did the literature search, data extraction, evaluation, and summary independently. Any disagreement between them was resolved through discussion. The primary efficacy endpoint was median overall survival time. To accommodate the variation in precision across different trials, the estimated inverse variances of the treatment efficacy and the survival outcome of the control arm were used as the weights for computing the weighted mean of the treatment efficacy and the survival outcome of the control arm [18]. Some trials did not report the variances of the median survival times and we imputed them in two steps. First, the pooled estimate of the common variance was computed by pooling the reported variances using the weighted average method, with the weight proportional to sample size. Then, we estimated the variance for each of the trials in which the variances were missing with the pooled estimate of the common variance multiplied by the ratio between the average sample size and the sample size of the targeted one. The data of the following potential prognostic factors, if available, were extracted from the published reports: patient age, male/female ratio, etiologies of underlying liver diseases (HBV, HCV, alcoholic, and others), Child–Pugh classification, stage, proportion of patients with vascular invasion and/or extrahepatic metastasis, and prior treatments of HCC. To evaluate the quality of individual trials, eight criteria derived from the Cochrane guidelines were used (Supplementary Table 1). The quality score of each trial was the summed score of these 8 items with higher quality scores indicating poorer trial quality.

There was no consensus in the staging criteria among the 14 trials. Because most trials (5 Asian and 3 non-Asian trials) used the Okuda staging system [15], a staging score for each trial was calculated using the following formula:

$$\text{Staging score} = \frac{\text{Okuda I \%} \times 1 + \text{Okuda II \%} \times 2 + \text{Okuda III \%} \times 3}{3}$$

where Okuda I %, Okuda II %, and Okuda III % denoted the percentages of patients in a specific trial with Okuda stage I, stage II, and stage III diseases, respectively. Higher staging score in a particular trial indicated a higher percentage of the patients in that trial with more advanced diseases.

2.3. Data synthesis

Statistical analysis proceeded in two steps [18]. First, meta-analysis was conducted with the consideration of both fixed