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A systematic review and network meta-analysis of second-line therapy in hepatocellular carcinoma

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ABSTRACT

Background In patients with advanced hepatocellular carcinoma (HCC) following sorafenib failure, it is unclear which treatment is most efficacious, as treatments in the second-line setting have not been directly compared and no standard therapy exists. This systematic review and network meta-analysis (NMA) aimed to compare the clinical benefits and toxicities of these treatments.

Methods A systematic review of randomized controlled trials (RCTs) was conducted to identify phase III RCTs in advanced HCC following sorafenib failure. Baseline characteristics and outcomes of placebo were examined for heterogeneity. Primary outcomes of interest were extracted for results, including overall survival (OS), progression-free survival (PFS), objective response rate (ORR), grade 3/4 toxicities, and subgroups. An NMA was conducted to compare both drugs through the intermediate placebo. Comparisons were expressed as hazard ratios (HRs) for OS and PFS, and as risk difference (RD) for ORR and toxicities. Subgroup analyses for OS and PFS were also performed.

Results Two RCTs were identified (1280 patients) and compared through an indirect network; CELESTIAL (cabozantinib vs. placebo) and RESORCE (regorafenib vs. placebo). Baseline characteristics of patients in both trials were similar. Both trials also had similar placebo outcomes. Cabozantinib, compared with regorafenib, showed similar OS [hazard ratio (HR): 1.21; 95% confidence interval (CI): 0.90 to 1.62], PFS (HR: 1.02; 95% CI: 0.78 to 1.34) and ORR (–3.0%; 95% CI: –7.6% to 1.7%). Both treatments showed similar toxicities, but there were marginally higher risks of grade 3/4 hand–foot syndrome (5%; 95% CI: 0.1% to 9.8%), diarrhea (4.8%; 95% CI: 1.1% to 8.5%), and anorexia (4.4%; 95% CI: 0.8% to 8.0%) for cabozantinib. Subgroup results for OS and PFS were consistent with overall results.

Conclusions Overall, this NMA determined that cabozantinib and regorafenib have similar clinical benefits and toxicities for second-line HCC.

Key Words Liver cancer, regorafenib, cabozantinib, sorafenib

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer worldwide and is rising in incidence in North America[1,2]. For patients with advanced disease, who are not amenable to resection, or who are not candidates for transplant, no curative treatment exists[3]. Among patients with portal vein tumour thrombus or extrahepatic metastases, treatment options have been limited and outcomes poor[4]. The development of sorafenib, an oral tyrosine kinase inhibitor targeting the vascular endothelial growth factor (VEGF) pathway, provided a therapeutic option for such patients, albeit with modest survival benefits[5,6]. Until recently, sorafenib was the only systemic therapy approved by the U.S. Food and Drug Administration for patients with HCC, and no effective second-line treatment was available[7]. In the past years, two new tyrosine kinase inhibitors have been approved for patients with HCC progression following

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sorafenib: regorafenib and cabozantinib[8,9]. Both have reported improved survival compared with placebo, but these agents have not been compared with each other[10,11].

Meta-analyses are traditionally used to directly compare trials with the same intervention and comparator[12]. In the absence of a direct comparison between treatments, a network meta-analysis (NMA) allows synthesis of data from different trials while maintaining the randomized structure of the data within each study[13]. Because a clinical trial comparing treatments after sorafenib failure has yet to be conducted, an NMA is a useful tool to directly and indirectly compare randomized controlled trials (RCTs) by constructing a network of all available treatments and bridging them together using existing comparisons, thereby increasing the precision of the comparison[12,14,15]. Network meta-analyses are gaining popularity and have effectively been used to investigate optimal treatments for cancers by synthesizing and incorporating direct and indirect evidence, including breast cancer, pancreatic cancer, and advanced colorectal cancer[12,14,16–18].

In this study, we aimed to identify second-line treatments for advanced HCC following sorafenib failure by conducting a systematic review and to compare the efficacy and toxicity of those treatments using an NMA.

METHODS

Literature Search and Study Selection

A systematic review was performed using the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases and American Society of Clinical Oncology (ASCO) Meeting Library from 2007 (the year sorafenib was approved) to February 2018. The search strategies can be found in supplemental Table 1. For the ASCO Meeting Library search, "hepatocellular carcinoma" was searched. Studies were limited to phase III RCTs, which enrolled patients with advanced HCC who had failed sorafenib treatment and investigated a second-line systemic therapy. Randomized controlled trials that demonstrated a statistically significant overall survival (OS) or progression-free survival (PFS) benefit were included in the NMA. Titles of the citations were first read to assess eligibility for inclusion. Abstracts and full texts of potentially eligible citations were then examined to determine eligibility or possible exclusion. The results from the literature review were recorded following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using the Review Manager software application (RevMan 5.3: The Cochrane Collaboration, Copenhagen, Denmark).

Outcomes

Outcomes of interest were overall survival (OS), progression-free survival (PFS), objective response rate (ORR), toxicities [grade 3/4 toxicities, hand–foot syndrome, hypertension, aspartate aminotransferase (AST) elevation, fatigue, diarrhea, anorexia, and anemia], OS and PFS subgroups for regions (Asians vs. others), extrahepatic spread with or without macrovascular invasion [extrahepatic spread (EHS) or macroscopic vascular invasion (MVI), yes vs. no], and cause [hepatitis B (HBV) vs. hepatitis C (HCV)].

Data Extraction

Reported outcomes from eligible RCTs were extracted and used to construct an indirect network and to compare second-line treatments through the placebo arm. The placebo arm in each trial was examined for substantial clinical heterogeneity. We compared the baseline characteristics and performance of placebo in the eligible trials. The hazard ratios (HRs) for outcomes of interest were extracted from published reports. In the case in which HRs were not reported, HRs from forest plots were digitized from reported results using Digitizeit (version 2.3.3: I. Bormann, Braunschweig, Germany). Toxicities and ORR were extracted from the reported results in manuscripts or accompanying supplemental materials. Data were independently extracted by 2 authors to ensure accuracy. Using the netmeta package in the R software application (version 3.3.1: The R Foundation for Statistical Computing, Vienna, Austria), an NMA to maintain randomization within each trial was conducted.

Statistical Analysis

Overall survival and PFS outcomes for comparing cabozantinib and regorafenib were analyzed using HRs. Toxicity outcomes and ORR were analyzed using risk difference [RD (difference between the percentages)]. Subgroup analyses were performed for OS and PFS for regions, EHS/MVI, and cause. Review Manager (version 5.3) was used to generate forest plots.

RESULTS

Literature Review and Trials Included

The literature search yielded 2582 citations in MEDLINE, EMBASE, Cochrane Central, and ASCO Meeting Library. This search is summarized in the PRISMA diagram (Figure 1). All citations were reviewed, and 2529 were excluded based on screening of the title or abstract. Of the remaining fifty-three citations, after removal of duplicates, the full texts of twenty-eight studies were retrieved for further review. Of these, ten were not RCTs, two were not specific to the population under study, nine had negative results, one had no outcomes of interest, two trials included patients who were not post-sorafenib, and two trials were still in progress. Characteristics of the negative trials can be found in supplemental Table 2. Of the two trials with positive results, both were eligible for inclusion in the NMA[19,20].

Characteristics of Included Trials

The RESORCE trial[19], which compares regorafenib with placebo as second-line therapy in patients who progressed on sorafenib treatment, and the CELESTIAL trial[20], which compares cabozantinib and placebo as a second-line therapy in patients who received prior sorafenib, were identified. Baseline characteristics of patients in both trials were similar in region; EHS or MVI, or both; and cause (Table I). One recognized difference was that for the RESORCE trial, patients had to have had progressive disease during sorafenib therapy, where patients in the CELESTIAL trial could have discontinued sorafenib due to toxicity before disease progression. In addition, a small number of patients

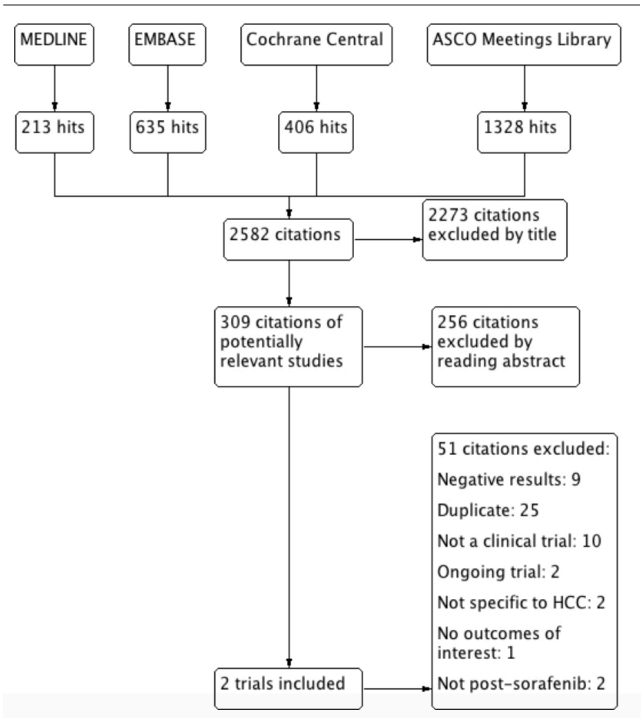

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the literature search.

TABLE I Patient demographics and baseline characteristics for the included clinical trials

Variable	CELESTIAL trial	RESORCE trial
Comparators	Cabozantinib vs. placebo	Regorafenib vs. placebo
Primary outcome	Overall survival	Overall survival
Participants *(n)*	707	573
Median age (years)	64	63
Sex (%)		
Men	81	88
Women	19	12
Region (%)		
Asia	25	38
Others	75	62
Cause (%)		
HBV	38	38
HCV	24	21
Other	38	41
EHS or MVI, or both (%)		
Yes	85	81
No	15	19

HBV = hepatitis B virus; HCV = hepatitis C virus; EHS = extrahepatic spread; MVI = microvascular invasion.

in CELESTIAL had more than 1 prior systemic therapy before study entry. The placebo arms in both trials also had similar median OS (8.0 months in CELESTIAL vs. 7.8 in RESORCE) and PFS (1.9 months in CELESTIAL vs. 1.5 in RESORCE). Both trials included adult patients with HCC with previous sorafenib therapy and compared treatment of HCC with cabozantinib or regorafenib versus placebo (Table I). The trials were similar with respect to the choice of primary outcome and trial design (double-blind and placebo-controlled). In the CELESTIAL trial, patients received cabozantinib orally at 60 mg once daily or placebo until toxicity or lack of clinical benefit. In the RESORCE trial, patients received best supportive care plus regorafenib orally at 160 mg or placebo once daily during weeks 1–3 of each 4-week cycle. Among a combined 1280 patients, 470 were randomized to receive cabozantinib, 379 were randomized to regorafenib, and 431 were randomized to placebo.

Efficacy of Regimens

Both trials reported better OS among patients treated with investigational agents than those treated with placebo; the HR for cabozantinib was 0.76 [95% confidence interval (CI): 0.63 to 0.92] and for regorafenib was 0.63 (95% CI: 0.50 to 0.79)[19,20]. For PFS, the HR for cabozantinib was 0.44 (95% CI: 0.36 to 0.52) and for regorafenib was 0.43 (95 % CI: 0.35 to 0.52)[19,20]. In the assessment of radiographic response, cabozantinib treatment resulted in a higher ORR than placebo (RD: 3.6%; 95% CI: 1.7% to 5.6%), as did regorafenib (RD: 6.6%; 95% CI: 2.3% to 10.8%)[19,20].

Using the indirect comparison of cabozantinib and regorafenib through an NMA, both drugs had similar OS results [HR: 1.21; 95% CI: 0.90 to 1.62; Figure 2(A)]. Cabozantinib and

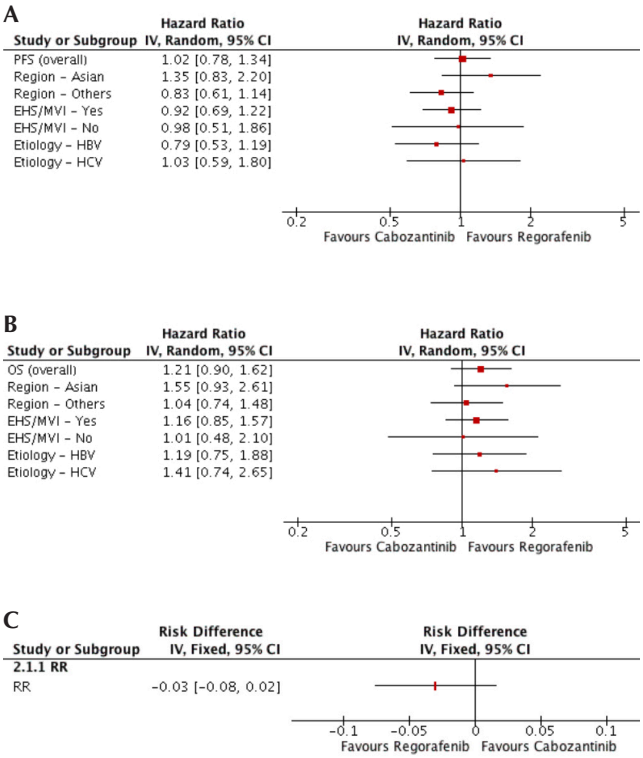

FIGURE 2 (A) Overall survival (OS) and (B) progression-free survival (PFS) subgroup analyses of trial results. (C) Risk difference response rates (RRS) for cabozantinib and regorafenib. CI = confidence interval; EHS = extrahepatic spread; MVI = microvascular invasion; HBV = hepatitis B virus; HCV = hepatitis C virus.

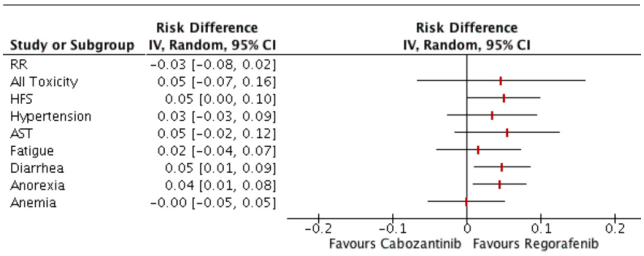

FIGURE 3 Analysis of toxicities as risk difference response rates (RRs). CI = confidence interval; HFS = hand–foot syndrome; AST = aspartate aminotransferase.

regorafenib were also similar in PFS [HR: 1.02; 95% CI: 0.78 to 1.34; Figure 2(B)] and ORR (RD: –3.0% 95% CI –7.6% to +1.7%, Figure 2C).

Subgroup analyses of OS and PFS results for region, EHS/MVI, and cause were consistent with overall results [Figure 2(A,B), supplemental Figure 1].

Toxicities

In the CELESTIAL trial, the most common grade 3/4 toxicities for cabozantinib were hand–foot syndrome (HFS), hypertension, increased AST, fatigue, diarrhea, asthenia, and decreased appetite. In the RESORCE trial, the most common toxicities of regorafenib were hypertension, HFS, fatigue, and diarrhea[19,20].

All 1280 patients were included for the toxicity analysis. The grade 3/4 toxicities that were compared were HFS, hypertension, AST, fatigue, diarrhea, anorexia, and anemia. An NMA of cabozantinib and regorafenib showed similar frequencies of hypertension, AST, fatigue, and anemia (Figure 3). Compared with regorafenib, cabozantinib appeared to have slightly more risk of grade 3/4 HFS (RD: 5%; 95% CI: 0.1% to 9.8%) as well as higher risks of diarrhea (4.8%; 95% CI: 1.1% to 8.5%) and anorexia (4.4%; 95% CI: 0.8% to 8.0%).

Details of the findings of both trials and the results of the NMA can be found in supplemental Tables 3–5.

DISCUSSION

Systemic therapy for HCC has developed from largely ineffective cytotoxic chemotherapy regimens to anti-angiogenic tyrosine kinase inhibitors, which have shown survival benefits in patients with advanced disease[21]. For several years, sorafenib remained the only drug licensed for use in patients with advanced or metastatic HCC, and no approved second-line treatments were available following progression on this drug[7]. The recent positive results of RCTs of regorafenib and cabozantinib have provided new options for the second-line setting[10]. However, given the lack of comparative studies between these new drugs, clinicians have limited guidance for their choice of treatment.

Clinicians can benefit from useful indirect evidence provided by NMAs by using pairwise comparisons between an intervention and control[22]. An NMA of two RCTs was conducted to evaluate the efficacy of regorafenib compared with cabozantinib in terms of improved survival and response outcomes to address the knowledge gap in the most effective regimen in the second-line setting. At the time of this analysis, this is the third meta-analysis of RCTs comparing second-line treatments of HCC after sorafenib failure and the second NMA[23,24]. However, to our knowledge, this is the first NMA of RCTs to specifically address the efficacy and tolerance of second-line treatments that have been proven to work.

The results of our systematic review and NMA found no significant difference in OS, PFS, or ORR between regorafenib and cabozantinib in the second-line treatment of HCC following sorafenib failure. Although toxicities were similar between the drugs, there were marginally higher toxicity risks for patients treated with cabozantinib—namely, HFS, diarrhea, and anorexia. Overall, both drugs were similar in their side-effect profiles.

A 2017 pairwise meta-analysis by Kim *et al.* suggested that second-line targeted therapy (including regorafenib, among others) improved time-to-progression ($p < 0.0001$) and OS ($p = 0.06$)[23]. However, this analysis was conducted before the publication of cabozantinib as a second-line treatment and did not evaluate treatments individually but rather as a whole, compared with best supportive care. This forms a basis for the use of second-line treatment in general, but does not assist clinicians in decision-making between targeted therapies. Following this, a recent NMA by Bakouny *et al.* reported that regorafenib followed by cabozantinib demonstrated the best efficacy and safety profile among multiple second-line treatments, most of which did not show efficacy benefits over placebo[24]. In contrast, our study restricted comparison to second-line treatments with proven survival benefit and found similar efficacy and toxicity profiles between regorafenib and cabozantinib. Thus, our study is able to guide discussions regarding efficacy and safety of proven second-line treatments, in the absence of an RCT directly comparing the two regimens.

The validity of an NMA relies on the similarity of the patient populations in the individual trials[25]. In this case, patients treated in both studies had comparable baseline characteristics and had progressive disease after prior sorafenib therapy. In both studies, median treatment duration in the placebo group was similar (2 months in CELESTIAL and 1.9 months in RESORCE), as was median OS (8 months in CELESTIAL and 7.8 months in RESORCE)[19,20]. These factors suggest that the similarity of the study populations was sufficient to allow an accurate comparison.

Since work on this NMA began, five phase III studies on second-line therapy in HCC after first-line sorafenib, namely the REACH, REACH-2, KEYNOTE-224, and the ongoing KEYNOTE-240 and KEYNOTE-394 trials, have been initiated. In the phase III REACH study, 565 patients with advanced HCC were randomized to either ramucirumab or placebo following first-line therapy with sorafenib[26]. Compared with placebo, ramucirumab showed a significant improvement in PFS (median: 2.8 months vs. 2.1 months; HR: 0.63; 95% CI: 0.52 to 0.75; $p < 0.0001$). However, the study did not meet its primary endpoint, as the median OS in the ramucirumab group was 9.2 months compared with 7.6 months in the placebo group (HR: 0.87; 95% CI: 0.72 to 1.05; p = 0.14)[26]. This is hypothesized to be due to the relationship between high alpha-fetoprotein concentration and prognosis in advanced HCC and was the basis for the recently conducted REACH-2 study[26,27]. In this phase III study, 292 patients with

alpha-fetoprotein concentrations of 400 ng/mL or greater following first-line therapy with sorafenib were randomized to either ramucirumab or placebo[27]. The study met its primary endpoint, as the median OS in the ramucirumab group was 8.5 months compared with 7.3 months in the placebo group (HR: 0.710; 95% CI: 0.531 to 0.949; $p = 0.0199$).[27] Despite the significant improvement in median OS shown with ramucirumab, this study was not included in this NMA because of its biomarker-selective patient population[27].

A nonrandomized phase II study (KEYNOTE-224) evaluated the efficacy and safety of pembrolizumab in patients with advanced HCC who had previously been treated with sorafenib[28]. The trial results showed an objective response of 17% (95% CI: 11% to 26%) among 104 patients with 1% (n = 1) achieving complete response and 16% (n = 17) achieving partial response[28]. The study demonstrated a tolerable safety profile, with 24% (n = 25) of patients reporting grade 3 adverse events and 1% (n = 1) of patients reporting grade 4 adverse events[28].

Pembrolizumab is currently being assessed in two ongoing phase III, randomized trials for patients with HCC who previously received treatment with sorafenib. Both studies (KEYNOTE-240 and KEYNOTE-394) will compare pembrolizumab plus best supportive care with placebo plus best supportive care. Recently, it was announced that KEYNOTE-240 did not meet its co-primary endpoints, because adding pembrolizumab to best supportive care failed to improve OS or PFS[29]. These studies were excluded in this analysis as they are currently ongoing.

This analysis has a few limitations that have to be noted. First, only two studies were included in this meta-analysis, which could lead to bias. Additionally, although this meta-analysis addresses treatment options in the second-line setting after failure of sorafenib, the CELESTIAL trial included a small number of patients treated with more than 1 prior systemic therapy, while the RESORCE trial did not include patients who received first-line therapy other than sorafenib. Patients who had discontinued sorafenib due to toxicity were also excluded in the RESORCE trial, but not in the CELESTIAL trial. Health-related quality of life was also not accounted for due to the lack of available data at the time of analysis to make a comparison between the two drugs. However, the quality-of-life (QOL) analysis of the CELESTIAL trial was recently presented, reporting that cabozantinib resulted in an improved QOL, while the RESORCE trial reported no clinically meaningful differences in QOL between the regorafenib and placebo groups[19,20,30]. The costs and cost-effectiveness differences between cabozantinib and regorafenib were also not addressed. Furthermore, sequential use of these agents may be viable, but was not explored in this analysis. Nonetheless, this present study analyzes efficacy and tolerance of cabozantinib and regorafenib in published trials in the absence of a direct comparison.

CONCLUSIONS

In this indirect comparison, cabozantinib and regorafenib demonstrated similar efficacy in survival in patients with HCC after failure of first-line treatment with sorafenib. Slightly higher toxicities were seen with cabozantinib. In the future, direct assessments between second-line therapies would benefit treatment decisions for patients with advanced HCC.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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