Efficacy and safety of lenvatinib versus sorafenib for unresectable hepatocellular carcinoma: A meta-analysis

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Research

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Abstract

Background

Although sorafenib was recommended as a first-line systemic therapy to prolong overall survival time in unresectable hepatocellular carcinoma (HCC), two randomized phase 3 noninferiority trials demonstrated that lenvatinib was noninferior to sorafenib in unresectable HCC.

Methods

This study included three trials containing 1462 patients identified by a database search using standard terms. We conducted the data analysis in Review Manager version 5.3 software.

Results

The outcomes showed that there were nonsignificant differences in OS of 6, 12, 18, 30 and 36 months, PFS of 18, 24, 30 and 36 months and AEs (grade < 3) between the lenvatinib group and the sorafenib group, and there were significant differences in OS of 24 months ($p = 0.01$), PFS of 6 ($p < 0.00001$) and 12 ($p < 0.00001$) months, ORR ($p < 0.00001$) and DCR ($p < 0.00001$) between the lenvatinib group and the sorafenib group.

Conclusions

Lenvatinib was not superior to sorafenib in terms of OS and AEs, and lenvatinib was superior to sorafenib in terms of secondary endpoints, including PFS, ORR and DCR, in unresectable HCC.

Background

Hepatocellular carcinoma (HCC), as the most common type of liver cancer, is the sixth most common cancer worldwide[1]. Most HCC patients have accompanying chronic liver disease and have lost the chance for surgical resection. Originally, sorafenib, as an inhibitor of multiple protein kinases, was recommended as a first-line systemic therapy to prolong the overall survival time in unresectable HCC[2, 3]. Moreover, all phase 3 trials, including of sunitinib, brivanib and linifanib, had demonstrated that these oral targeted drugs were inferior to sorafenib in the first-line treatment of unresectable HCC[4–6]. However, low response rate and toxicities limited the clinical application of sorafenib[7].

Lenvatinib is an antiangiogenic oral target drug acting as a multikinase inhibitor of VEGFR1–3, FGFR1–4, PDGFR- α , RET, and KIT[8–10]. Lenvatinib is approved for antiangiogenic therapy in the treatment of radioiodine-refractory differentiated thyroid cancer and advanced renal cell carcinoma[11, 12]. Lenvatinib was demonstrated to be noninferior to sorafenib in overall survival in unresectable HCC in a phase 3, multicenter, randomized, open-label, noninferiority trial[13]. Furthermore, subsequent systemic therapy of lenvatinib also showed clinical efficacy and acceptable safety in unresectable HCC[14].

Given the observations from previous studies and the lack of data to assess the efficacy and safety of lenvatinib versus sorafenib for unresectable HCC, we conducted a meta-analysis to provide clinically useful information about the efficacy and safety of lenvatinib versus sorafenib for unresectable HCC.

Methods

Systematic literature review

We performed a systematic search of the PubMed and Cochrane Central Register of Controlled Trials databases from their establishment to 1 March 2020. The search used the following keywords: hepatocellular carcinoma, lenvatinib and sorafenib. A comparison between lenvatinib and sorafenib in unresectable HCC must have occurred in the included studies.

Data extraction and quality assessment

The following characteristics of the included studies were extracted by two reviewers: author, year of publication, study design, number of patients in the experimental and control groups, follow-up period and outcomes. Additionally, the qualities of the included studies were assessed by the Cochrane Collaboration risk of bias tool.

Statistical analysis

Statistical analysis was performed using Review Manager version 5.3 software. First, we compared outcomes, including overall survival (OS) and progression-free survival (PFS) after 6, 12, 18, 24, 30, and 36 months, objective response rate (ORR), disease control rate (DCR) and adverse effects (AEs, grade < 3). The p value of the Z test was used to evaluate the overall effect size, with a $p < 0.05$ signifying a significant difference between the observed and control groups. Heterogeneity was quantitatively assessed by I^2 statistics, with an $I^2 \geq 50\%$ signifying that heterogeneity existed. Second, to explore the source of heterogeneity, subgroup and sensitivity analyses were conducted. Finally, funnel plots were used to evaluate publication bias. A symmetrical funnel plot signified that no publication bias existed.

Results

Systematic literature review

A total of 169 records were identified through the database search. A total of 152 studies were excluded after eligibility screening, and the full texts of 17 potentially eligible studies were assessed. Consequently, 3 trials[13–15] were included in the quantitative analysis (Fig. 1).

Data extraction and quality assessment

Table 1 shows the characteristics of the included studies. Study design, dosage of target therapy, and follow-up were the same in all three included studies. Nation was the same in two studies[13, 14]. Outcomes were the same in two studies[13, 15]. The study design of the three studies was a phase 3, multicenter, randomized, open-label, noninferiority trial. The dosages of lenvatinib and sorafenib were the same in all three studies.

The results of the quality assessment in the three studies are shown in Fig. 2. Figure 2 summarizes the assessment of random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias. The investigations identified as low risk, unclear risk or high risk are represented as green, yellow and red colors, respectively. In this meta-analysis, the three included studies were proved to be of high quality.

Statistical analysis

The forest plot indicated that there were nonsignificant differences in the OS of 6, 12, 18, 30 and 36 months between the lenvatinib group and the sorafenib group (Fig. 3A-C,E,F). The forest plot also indicated that there was a significant difference in an OS of 24 months (OR, 95%CI, 1.38[1.08, 1.77], $p = 0.01$) between the lenvatinib group and the sorafenib group (Fig. 4D). No heterogeneity was found ($I^2=0$).

The forest plot indicated that there were significant differences in a PFS of 6 (OR, 95%CI, 2.11[1.65, 2.70], $p < 0.00001$) and 12 months (OR, 95%CI, 2.32[1.66, 3.32], $p < 0.00001$) between the lenvatinib group and the sorafenib group (Fig. 4A,B). The forest plot also indicated that there were nonsignificant differences in a PFS of 18, 24, 30 and 36 months (Fig. 4C-F). No heterogeneity was found ($I^2<50\%$).

The forest plot indicated that there were significant differences in the ORR (OR, 95%CI, 5.01[3.70, 6.77], $p < 0.00001$) and DCR (OR, 95%CI, 2.04[1.58, 2.62], $p < 0.00001$) between the lenvatinib group and the sorafenib group (Fig. 5). No heterogeneity was found ($I^2=0$).

The forest plot indicated that there was a nonsignificant difference in AEs (grade < 3) between the lenvatinib group and the sorafenib group (Fig. 6). Heterogeneity was found ($I^2=72\%$). Due to the limited number of included studies, the source of heterogeneity was not explored.

The funnel plot was symmetrical, indicating that no publication bias existed (Fig. 7).

Discussion

This meta-analysis provided data from three randomized phase 3 noninferiority trials to evaluate the efficacy and safety of lenvatinib versus sorafenib for unresectable HCC. The results indicated that the objective responses, including ORR, DCR and PFS, were better with lenvatinib than with sorafenib, consistent with previous studies. However, the results of OS and AEs indicated that the efficacy and safety of lenvatinib were not markedly better than those of sorafenib.

As an oral multikinase inhibitor, lenvatinib selectively acts on more kinase activities and proangiogenic and oncogenic pathways than sorafenib, particularly fibroblast growth factor (FGF) signaling. Recent research demonstrated that FGF signaling might be a cause of acquired resistance to sorafenib posttreatment[16, 17]. Hence, lenvatinib was considered to have theoretically better performance in improving OS and tumor responses, including ORR and DCR[8–10]. However, in practice, lenvatinib was not superior to sorafenib in terms of OS.

OS is regarded as the primary endpoint to evaluate the efficacy of all types of anticancer therapies according to mRECIST[18]. Our meta-analysis emphasized that lenvatinib was not superior to sorafenib in improving the OS in unresectable HCC, consistent with previous studies[13–15]. Based on reviewing the patients in the selected trials, we may generalize the following reasons for these findings. First, multimodality therapies may be efficacious and were performed after systemic therapies such as lenvatinib or sorafenib treatment[19], which could make OS as an endpoint alone unable to completely capture the full extent of anticancer efficacy. Second, the heterogeneity of the baseline characteristics of unresectable HCC patients, such as serum AFP, BCLC stage[20] and ECOG PS[21], could dilute the treatment benefit of the observed OS. Third, the relatively small number of included studies in this meta-analysis might affect the treatment outcomes.

PFS, ORR and DCR were treated as the secondary endpoints according to mRECIST. Our meta-analysis highlighted that lenvatinib improved PFS, ORR and DCR compared with sorafenib, similar to previous research[13–15].

The result regarding AEs in this meta-analysis indicated that the safety of lenvatinib was not superior to that of sorafenib. Our results were consistent with previous research[11, 22]. The most common AEs of lenvatinib in the selected studies were hypertension, diarrhea, decreased appetite and weight reduction. The most common AEs of sorafenib were palmar-plantar erythrodysesthesia syndrome (PPES), diarrhea, hypertension and decreased appetite. These AEs were class effects of VEGF-targeted therapies and were manageable. The AEs were associated with dose, and they were managed by dose modifications.

HCC is distinct from other cancer types. HCC patients usually experience hepatic impairment to various degrees, and increased systematic therapies can aggravate hepatic impairment[23]. Furthermore, the metabolism of lenvatinib occurs mainly in the liver[24], and lenvatinib pharmacokinetics have been shown to be affected by bodyweight[25]. Hence, the initial and subsequently modified dosages of lenvatinib were of significance to preserve the balance between efficacy maintenance and toxicity reduction. Based on previous studies[13,15,], currently, doses of 8 mg for bodyweight less than 60 kg and 12 mg for bodyweight greater than or equal to 60 kg is optimal for lenvatinib treatment in unresectable HCC.

We should acknowledge the limitations in our meta-analysis. First, there were not enough high-quality prospective studies included. Second, due to the number of selected studies, the source of heterogeneity was not found. Third, although no significant publication bias existed, the potential publication bias could not be neglected.

Conclusions

This meta-analysis showed that lenvatinib was not superior to sorafenib in terms of OS and AEs and that lenvatinib was superior to sorafenib in terms of the secondary endpoints, including PFS, ORR and DCR, in unresectable HCC.

Abbreviations

HCC: hepatocellular carcinoma; OS:overall survival; PFS:progression-free survival; ORR:objective response rate; DCR:disease control rate; AEs:adverse effects; FGF:fibroblast growth factor; PPES:palmar-plantar erythrodysesthesia syndrome

Declarations

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Not applicable

Consent for publication:

Not applicable

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Not applicable

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WFS wrote the first draft of the manuscript and contributed to the data collection and analysis. JYL and JHF contributed to the study design. Acknowledgements: None

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Tables

Table 1. The characteristics of the included studies

Author(year)	Nation	Study design	Number of patients(M/F)		Dosage		Follow-up	Outcomes
			len group	sor group	len group	sor group		
Masatoshi Kudo(2018)	Western Asia-Pacific	randomised phase 3 non-inferiority trial	405/73	401/75	12 mg/day (for bodyweight ≥60 kg)	400mg twice daily	42 month	OS,PFS,TTP,ORR,DCR, AEs
Tatsuya Yamashita(2020)	Japan		65/16	72/15	8 mg/day			OS,PFS,TTP,ORR,DCR, AEs
Angel Alsina(202)	Western Asia-Pacific		156	184	(for bodyweight <60 kg)			OS

len: lenvatinib, sor: sorafenib, OS:overall survival, PFS: progression-free survival, TTP: time to progression, ORR: objective response rate, DCR: disease control rate, AEs: adverse events.

Figures

Figure 1

Flowchart showing the flow of information through the different phases of the systematic review toward a meta-analysis

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Angel Alsina 2020	+	?	+	+	+	+	?
Masatoshi Kudo 2018	+	+	+	+	+	+	?
Tatsuya Yamashita 2020	+	+	+	+	+	+	?

Figure 2

Risk of bias summary: review of authors' judgments about each risk of bias item for each included study. – high risk, +: low risk, ?: unclear risk.

Figure 3

(A–F): Forest plot for OS of 6,12, 6, 12, 18, 30 and 36 months.

Figure 4

(A–F): Forest plot for PFS of 6,12, 6, 12, 18, 30 and 36 months.

Figure 5

(A,B): Forest plot for ORR and DCR.

Figure 6

Forest plot for AEs.

Figure 7

Funnel plot of publication bias