Regorafenib compared to nivolumab after sorafenib failure in patients with hepatocellular carcinoma: A systematic review and meta-analysis

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Abstract

Which systemic therapy should be administered following sorafenib failure for patients with advanced hepatocellular carcinoma (HCC) is still a debated issue in clinical practice. This study aimed to compare regorafenib with nivolumab after sorafenib failure in patients with HCC. MEDLINE via PubMed, Scopus and Embase databases were searched for studies published until December 2021. The risk of bias (RoB) was evaluated using the Cochrane Collaboration tool for assessing risk of bias in randomized trials. From a total of 2120 articles, 3 papers were included in this meta-analysis. We found a statistically significant difference in the patient's objective response rate between the regorafenib and nivolumab groups (odds ratio (OR): 0.296, 95% confidence interval (95% CI): 0.161–0.544, p = 0.000). A statistically significant difference between regorafenib and nivolumab was not found for disease control rate after sorafenib failure in patients with advanced HCC (OR: 1.111, 95% CI: 0.793–1.557, p = 0.541) nor the number of progressive disease events (OR: 0.972, 95% CI: 0.693–1.362, p = 0.867). Overall survival (OS) and progression-free survival (PFS) were not calculable. The heterogeneity of the included data was low. Nivolumab monotherapy appears superior to regorafenib after sorafenib failure in patients with advanced HCC.

Key words: hepatocellular carcinoma, sorafenib, regorafenib, nivolumab, meta-analysis

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Introduction

Hepatocellular carcinoma (HCC) is the 6th most common type of malignancy and the most frequent type of liver cancer. It is also the 3rd leading cause of cancer-related deaths worldwide, resulting in nearly 745,000 deaths annually.[1] Hepatitis B virus (HBV), hepatitis C virus (HCV) and other non-viral chronic liver diseases leading to cirrhosis are the most well-known risk factors for HCC.[2] Although factors such as alcohol use, diabetes and smoking are also considered risk factors for developing HCC, this is less broadly accepted.[2,3]

Hepatocellular carcinoma is asymptomatic in the early stages; thus, most HCC cases are not recognized until advanced stages which renders this disease incurable in clinical practice.[4] The best therapy for resectable HCC without portal hypertension is surgery.[5] In patients who were not ideal candidates for resection according to the Barcelona Clinic Liver Cancer (BCLC) classification, surgical resection was linked to higher survival than locoregional or systemic therapeutic strategies.[6] However, the majority of patients with HCC do not benefit from surgery and will ultimately need further medical treatment. Sorafenib, a small-molecule multikinase inhibitor, is the most commonly used systemic therapy in patients with HCC. However, it improves the median overall survival (OS) for no more than 2–3 months.[5,7] Furthermore, at least half of the patients who receive sorafenib as a treatment fail to respond. The lack of second-line treatment for these patients is thus a serious issue.[8]

Multiple immunologic pathways contribute to HCC development by impairing the antitumor immune surveillance of the host.[9] Nivolumab, a Programmed-Death-1 (PD-1) immune checkpoint inhibitor, has modest single-agent activity in advanced HCC with a favorable 6-month OS rate (72%) and without any significant side effects.[10,11] An objective response rate of 15–20% was achieved using nivolumab (as opposed to 2–3% in sorafenib) in patients with advanced HCC, irrespective of the line of therapy (CheckMate 040 study).[12]

The hypervascular nature of most HCC tumors and the involvement of multiple angiogenic pathways suggests that these mechanisms may be associated with the progression and pathogenesis of HCC.[13] Regorafenib, an oral multikinase blocker, inhibits the protein kinases associated with oncogenesis, metastasis, angiogenesis, and tumor immunity.[14] Moreover, regorafenib has a wider range of inhibitory effects compared to other tyrosine kinase inhibitors, and can alter the tumor microenvironment.[15] The RESORCE trial showed that treatment of advanced HCC patients who failed to respond to sorafenib with regorafenib improved median OS compared with placebo (10.6 compared to 7.8 months, respectively).[16]

Objectives

This meta-analysis aimed to assess the therapeutic effects of regorafenib compared to nivolumab after sorafenib failure in patients with HCC.

Methods

Data sources and searches

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] An electronic search of MEDLINE via PubMed, Scopus and Embase databases was performed for studies published until December 2021. The search terms were "regorafenib," "STIVARGA," "nivolumab," "OPDIVO," "hepatocellular carcinoma," and "HCC". The search strategy was as follows: TITLE-ABS-KEY (regorafenib) OR TITLE-ABS-KEY (stivarga) AND TITLE-ABS-KEY (nivolumab) OR TITLE-ABS-KEY (opdivo) AND TITLE-ABS-KEY (hepatocellular AND carcinoma) OR TITLE-ABS-KEY (hcc) AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (SRCTYPE, "j")).

Study selection

The inclusion criteria for the primary analysis were as follows: all clinical trials that were performed on humans and compared the effects of second-line regorafenib therapy with nivolumab therapy after failure of first-line sorafenib therapy in patients with advanced HCC. Because regorafenib is approved only for HCC patients who have tolerated first-line sorafenib, we only included studies in which such a criterion was considered. Studies that assessed the effects of either only regorafenib or nivolumab therapy (and thus provided no comparison) in advanced HCC were excluded. All duplicate, non-English-language and animal (in vivo) or cell lines (in vitro) papers were excluded as well. Independent data collection was performed by 2 authors and all potentially relevant citations were retrieved in full. These citations were independently evaluated by the same 2 authors for eligibility. Disagreement was resolved by consensus or consultation with the 3rd author.

Data extraction

Predesigned electronic forms were used to extract all the relevant data from the included articles. Last name of the first author, publication year, study design, mean age of the patients, sex, Child–Pugh class, study outcome(s), and related adverse events (grade III/IV) were extracted from the included studies. The p-value for complete response, partial response, stable disease, objective response (complete response + partial response), progressive

disease, disease control rate (complete response + partial response + stable disease), objective response rate, and odds ratios (ORs) and related 95% confidence intervals (95% CIs) were also extracted. The primary objective of this study was to compare the effects of regorafenib compared to nivolumab after sorafenib failure in patients with HCC using complete response, partial response stable disease, progressive disease, as well as objective response rate, and the secondary objective was to compare the side effects of these 2 regimens.

Study quality

The risk of bias (RoB) was evaluated using the Cochrane Collaboration tool for assessing risk of bias in randomized trials. This tool consists of performance, detection, selection, and attrition assessment, and of reporting bias items.[18]

Statistical analyses

All statistical analyses were conducted using Comprehensive Meta-Analysis software v. 2 (Biostat Inc, Englewood, USA). A fixed-effects model was used to pool the study outcomes. Median as well as 95% CI and response rates were used to report time-to-event data and categorical outcomes, respectively. The heterogeneity of the included publications was evaluated using χ^2 and I^2 tests. A value of $I^2 < 25\%$ was considered as low-level heterogeneity. Funnel plots and Begg and Mazumdar's test were not used to assess publication bias as the number of included studies was lower than 10. A two-tailed p-value of less than 0.05 was regarded as statistically significant for all comparisons.

Results

Search results

An initial electronic search of the included databases yielded a total of 2120 articles; as a first step of their evaluation, 387 duplicate citations were excluded. Accordingly, the title, abstract and keywords of the remaining 1733 articles were screened. This resulted in the exclusion of a further 1700 publications. Finally, the full texts of the 33 remaining articles were screened and 3 papers were chosen for this meta-analysis (Fig. 1).

General study characteristics

The main characteristics of the included studies are presented in Table 1. All of the included studies were retrospective cohort studies. A total of 676 patients were included in this meta-analysis, with 140 males and 536 females; 383 patients received regorafenib and 230 patients received nivolumab. Most patients had a Child–Pugh class of A or B. The etiology of HCC was predominantly HBV and HCV.

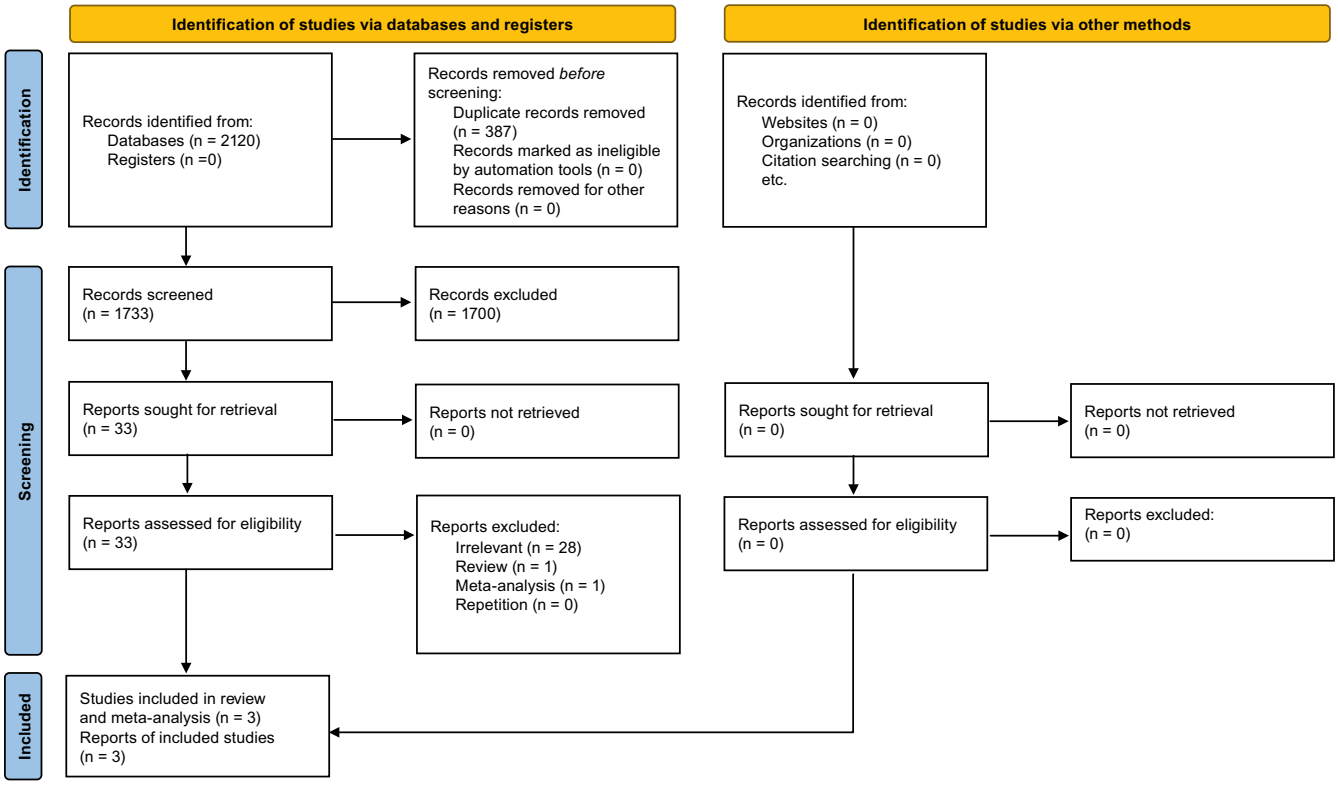

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of study inclusion (From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:10.1136/bmj.n71. More information: http://www.prisma-statement.org/)

Table 1. Main characteristics of the included studies (all 3 were retrospective cohort studies)

Study	Number of patients	Gender (male)	Regorafenib (nivolumab)	Child–Pugh class	Etiology	Outcome(s)	Adverse events
Choi et al., 2020[27]	436	109 (327)	223 (150)	A and B	mainly HBV and HCV	Survival outcomes in patients treated with regorafenib and nivolumab after sorafenib failure did not differ significantly.	NM
Lee et al., 2020[28]	150	28 (122)	102 (48)	A, B and C	mainly HBV	The use of nivolumab may be associated with improved OS and better objective response rate as compared to using regorafenib.	Both drugs were well tolerated.
Kuo et al., 2021[29]	90	23 (67)	58 (32)	A and B	mainly HBV and HCV	After sorafenib failure, using nivolumab or regorafenib both resulted in promising treatment outcomes.	The most frequent related adverse event was hand to-food skin reaction.
Total	676	140 (536)	383 (230)	–	–	–	–

HBV – hepatitis B virus; HCV – hepatitis C virus; NM – not mentioned; OS – overall survival.

Regorafenib compared to nivolumab after sorafenib failure

Objective response

The objective response rate included complete response and partial response. We found a statistically significant difference in the patients' objective response rate between the regorafenib and nivolumab groups, with regorafenib having a better response. The pooled OR was 0.296 (95% CI: 0.161–0.544, p = 0.000; Fig. 2). The heterogeneity of the included articles was low (χ^2 = 0.10, T^2 = 0.000, df = 2, I^2 = 0.00%, p = 0.951).

Disease control rate

Disease control rate included complete response, partial response and stable disease. No statistically significant difference in the patients' disease control rate between the regorafenib and nivolumab groups was found. The pooled OR was 1.111 (95% CI: 0.793–1.557, p = 0.541; Fig. 3). The heterogeneity of the included articles was low (χ^2 = 2.70, T^2 = 0.041, df = 2, I^2 = 26.04%, p = 0.259).

Progressive disease

No statistically significant difference between the groups based on the number of progressive disease events was found; the pooled OR was 0.972 (95% CI: 0.693–1.362, p = 0.867; Fig. 4). The heterogeneity of the included articles was low (χ^2 = 1.47, T^2 = 0.000, df = 2, I^2 =0.00%, p = 0.478).

Study quality

Due to the nature of included studies (retrospective cohort studies), none of these publications were randomized or blinded. Allocation concealment was not employed

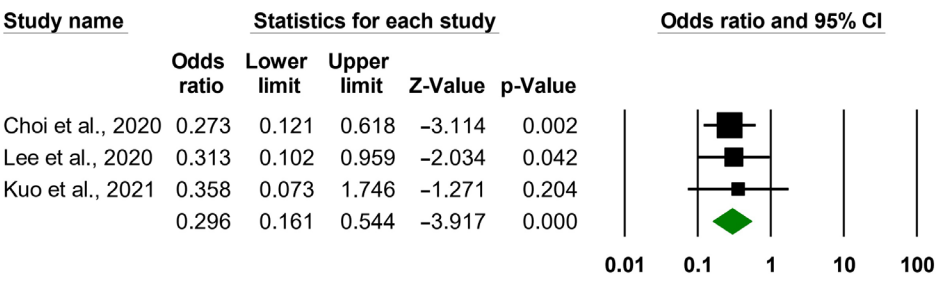

Fig. 2. Forest plot of standardized mean difference (SMD) for the objective response for regorafenib therapy compared to nivolumab therapy in patients with advanced hepatocellular carcinoma (HCC). The green diamond shows the overall pooled effect. Black squares indicate the SMD in each study. Horizontal lines represent 95% confidence interval (95% CI)

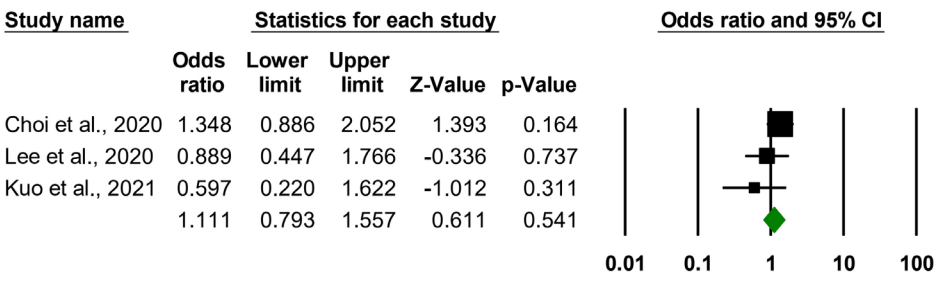

Fig. 3. Forest plot of standardized mean difference (SMD) for the disease control rate for regorafenib therapy compared to nivolumab therapy in patients with advanced hepatocellular carcinoma (HCC). The green diamond shows the overall pooled effect. Black squares indicate the SMD in each study. Horizontal lines represent 95% confidence interval (95% CI)

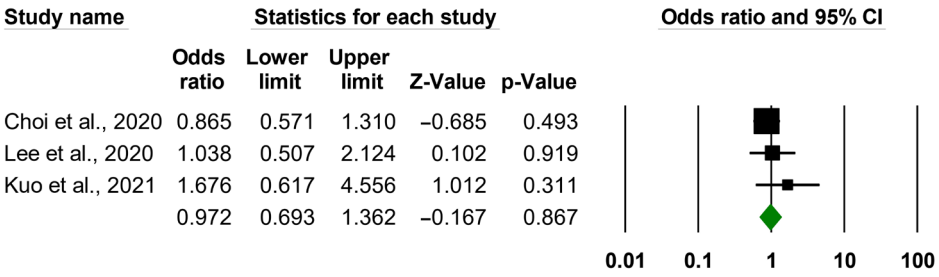

Fig. 4. Forest plot of standardized mean difference (SMD) for progressive disease for regorafenib therapy compared to nivolumab therapy in patients with advanced hepatocellular carcinoma (HCC). The green diamond shows the overall pooled effect. Black squares indicate the SMD in each study. Horizontal lines represent 95% confidence interval (95% CI)

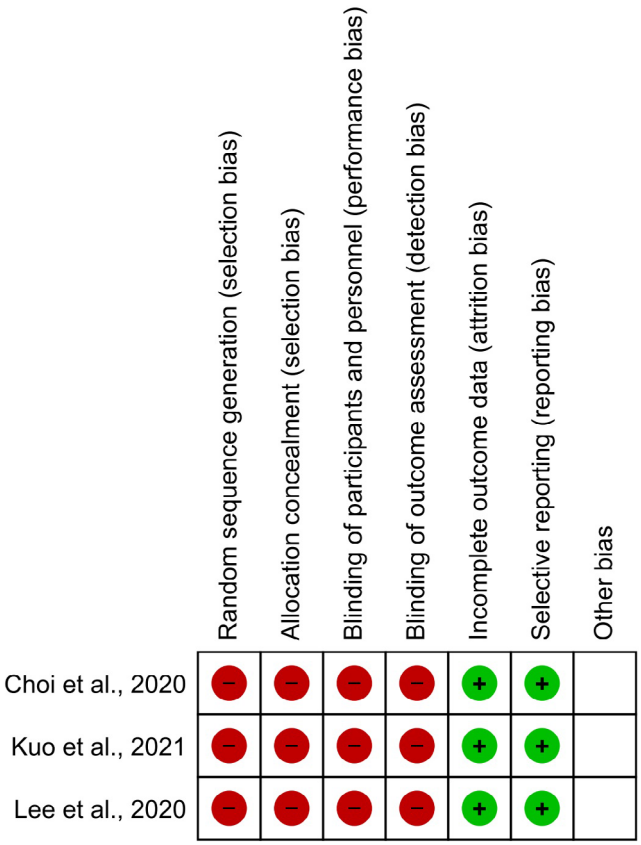

Fig. 5. Different levels of risk of bias for each item in included studies. The risk of bias (RoB) was evaluated using the Cochrane Collaboration tool for assessing risk of bias in randomized trials

in any of the analyzed papers. There was no evidence of attrition nor reporting bias in this set of articles (Fig. 5).

Discussion

This meta-analysis found that nivolumab monotherapy had an objective response rate superior to regorafenib monotherapy after sorafenib failure in patients with advanced HCC. However, we failed to find a difference in disease control rate between the 2 groups. Safety analysis of these medications could not be performed due to incomplete data.

Hepatocellular carcinoma has a poor prognosis because most patients are diagnosed in the advanced stages of the disease. These late diagnoses limit the efficacy of locoregional therapies such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA) or hepatic resection. Accordingly, systemic therapy is the main therapeutic strategy in this set of patients.[19]

The first agent that was approved for systemic therapy in patients with advanced HCC was sorafenib, based on the results from 2 randomized, double-blind, phase III clinical trials.[20,21] Sorafenib is a multi-targeted tyrosine kinase inhibitor (mTKI) that largely acts against vascular angiogenesis by inhibiting platelet-derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR). Tumor proliferation is also prohibited by sorafenib through inhibition of Raf-1, B-Raf and kinase activity in the Ras/Raf/MEK/ERK signaling pathways.[22] In 2017, 2 second-line medications, namely regorafenib (RESORCE trial) and nivolumab (CheckMate 040), were approved for the treatment of patients who fail to respond to sorafenib as a first-line medication.[12,16] Based on the RESORCE trial, in which 567 patients were randomized to regorafenib (n = 374) or placebo (n = 193) groups, sequential treatment with regorafenib after sorafenib failure improved OS (hazard ratio (HR) of 0.63 (95% CI: 0.50–0.79; one-sided $p < 0.001$)), and increased both median survival (26.0 months compared to 19.6 months) and progression-free survival (PFS) (3.1 months compared to 1.5 months, $p < 0.001$). The most common treatment-related adverse events were hypertension, hand-foot skin reaction (HFSR), fatigue, and diarrhea.[16] The CheckMate 040 trial showed that sequential administration of nivolumab after sorafenib failure in patients with advanced HCC improved PFS by 4.1 months. In the CheckMate 040 trial, the objective response rate was 20% and the disease control rate was 64%.[12] These results were further replicated for other anti-PD-1 agents, namely pembrolizumab and tislelizumab. Patients with advanced HCC who had previously been treated with sorafenib both responded well to and tolerated pembrolizumab.[23] Single-agent tislelizumab also provided a clinically meaningful OS benefit over sorafenib, with a favorable safety profile as a first-line treatment option for patients with unresectable HCC.[24] Thus, both regorafenib and nivolumab have shown to be superior to placebo in HCC patients after sorafenib failure. When the results from the RESORCE and CheckMate 040 studies were compared, it was found that the objective response in the regorafenib group (11%) was lower than in the nivolumab group (19%). Further, the disease

control rate for both medications in these 2 studies was almost the same (64% for nivolumab compared to 65% for regorafenib).[12,16] These previous findings are in line with the results of our study. However, a question remains unanswered: Which treatment should be sequentially administered in patients with sorafenib failure?

According to current guidelines, both regorafenib and nivolumab are approved only for HCC patients with Child–Pugh B class. Presently, after sorafenib failure, the only systemic therapy that provides efficacy and has an acceptable safety profile for patients with compromised liver function (Child–Pugh B class) is metronomic capecitabine.[25,26]

In a recent retrospective study by Choi et al., 373 patients with advanced HCC were enrolled, and the efficacy of regorafenib (n = 223) or nivolumab (n = 150) monotherapy was evaluated after sorafenib failure. That study found no significant difference in PFS, time to progression (TTP) and OS between these 2 treatment modalities. However, the objective response rate was significantly higher in patients treated with nivolumab than in those treated with regorafenib (13.3% compared to 4.0%; p = 0.002). Progression-free survival (p = 0.001), TTP (p < 0.001) and OS (p = 0.013) were significantly longer in the 59 nonprogressors (patients who achieved complete response, partial response or stable disease after first response evaluation) following nivolumab administration than in the 104 nonprogressors to regorafenib.[27]

In another recent study by Lee et al., performed on 150 patients (102 received regorafenib and 48 received nivolumab), it was found that nivolumab monotherapy was associated with a higher objective response rate compared with regorafenib monotherapy (16.7% and 5.9%, respectively) in advanced HCC patients. Median OS and TTP were not significantly different between the treatment groups.[28] Another study by Kuo et al., in which 90 patients were recruited (32 patients in the nivolumab group and 58 patients in the regorafenib group), no difference was found in the objective response rate, disease control rate, OS, and TTP between treatments. Improvements in OS in patients with advanced HCC was similarly observed in treatment modalities.[29] The regorafenib group had significantly higher rates of treatment-related adverse events than the nivolumab group (68% compared to 37.5%, p = 0.006). The rate of adverse events did not significantly differ between treatment modalities in the study by Lee et al. (p = 0.34).[28] The most common adverse events observed in patients who received regorafenib were HFSR (in 23.8% of the patients), diarrhea, fatigue, and elevated alkaline aminotransferase (ALT) level, while 37.5% of patients who received nivolumab experienced a treatment-related adverse events, including fatigue in 12.1%, dermatitis in 9.3% and hyperbilirubinemia in 6.2%.[29] It is unknown if prophylactic/therapeutic measures had been applied to prevent or treat these adverse reactions.

Limitations

This meta-analysis was not previously registered and has no previously published protocols. It has several shortcomings that should be addressed in future studies. First, this meta-analysis was only hypothesis-generating, meaning that it was based on the existing data. The main issue with the data used in this meta-analysis is that they are from retrospective cohort studies. Due to this, several vital statistics could not be determined in the included studies, leading to significant bias in the selection of controls. The retrospective nature of these studies predisposes them also to selection bias. Furthermore, there is an absence of common information on potential confounding factors in the included studies. Thus, well-designed randomized clinical trials (RCTs) should be conducted to assess and compare the effects of regorafenib with nivolumab in patients with advanced HCC. Second, only a limited number of studies were included in this meta-analysis. With the completion of more research, future meta-analyses should include a higher number of publications to address this important issue. Third, the included papers were from Taiwan and South Korea (Eastern Asian race) and from a single center each. This limits the generalizability of the results. Fourth, the results of this study may not be generalizable to etiologies other than HBV and HCV, as most of the patients in these studies had HCC due to these viruses. This may also worsen the prognosis of the disease and response to medications. Fifth, due to the lack of data, it was impossible to obtain accurate information about adverse events that occurred during the study period and perform safety analysis. Sixth, if both treatments are available for particular patients, regorafenib is more likely to be used after sorafenib failure in patients with advanced HCC; this introduces an important bias that should be addressed in future studies.

Conclusions

Both regorafenib and nivolumab have been shown to exhibit significant therapeutic efficacy compared with a placebo in patients with HCC. However, which systemic therapy should be administered following sorafenib failure for patients with advanced HCC is still unknown. This study showed that nivolumab is superior to regorafenib in terms of objective response rate after sorafenib failure in patients with advanced HCC. However, both treatments achieved similar disease control rate. Due to the retrospective nature of the studies and the limited number of studies included in this meta-analysis, future RCTs should be designed to directly determine which treatment is superior.

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