Efficacy and safety of immune checkpoint inhibitors combined anti-angiogenic therapy in patients with unresectable hepatocellular carcinoma
A meta-analysis

Feng Xian, PhD*a,b, Cailiang Wu, Masterc, Guojun Zhang, Masterb, Guohui Xu, MDa,*

Abstract

Background: This study aimed to compare the efficacy and safety of immune checkpoint inhibitors (ICIs) combined with antiangiogenic agents in patients with unresectable hepatocellular carcinoma (HCC).

Methods: We conducted a systematic literature search of articles published between the establishment of the database and February 2022. Data were extracted and analyzed using STATA 14.0.

Results: Six randomized controlled trials (RCTs) (980 patients for combination therapy and 565 patients for monotherapy) and 5 single-arm studies (246 patients for ICIs combination therapy) were enrolled. The objective response rate (ORR) and disease control rate (DCR) were 26% and 70%, respectively, after ICIs combination therapy. Compared with monotherapy in RCTs, ICIs combination therapy resulted in higher progression-free survival (PFS) and overall survival (OS), but also increased the incidence of adverse events (AEs). Increased incidences of fatigue, hypertension, hyperbilirubinemia, proteinuria, and nausea were more common after ICIs combination therapy.

Conclusion: The analysis results reveal that ICI-combined anti-angiogenesis therapy has higher efficacy than either ICIs or anti-angiogenesis options for unresectable HCC, but it is necessary to manage the AEs.

Abbreviations: AE = adverse event, DCR = disease control rate, HCC = hepatocellular carcinoma, HR = hazard ratio, ICI = immune checkpoint inhibitor, ORR = objective response rate, OS = overall survival, PD-1 = programmed cell death protein-1, PD-L1 = programmed death ligand-1, PFS = progression-free survival, RCT = randomized controlled trial, RD = risk difference, RR = risk ratio, TRAE = treatment-related AE, VEGF = vascular endothelial growth factor.

Keywords: anti-angiogenic therapy, hepatocellular carcinoma, immune checkpoint, meta-analysis

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common types of cancer worldwide and is currently the third leading cause of cancer-related death.[1] More than 78% of liver cancer cases are related to hepatitis B virus infection in some areas, and the global incidence and mortality rates of HCC continue to increase, resulting in at least 600,000 deaths annually.[2] Because the symptoms cannot be easily detected and the treatment options for HCC are relatively limited, curative treatment is not possible at the time of diagnosis for over 80% of patients.

Thus, the treatment of HCC remains a major healthcare challenge globally, and novel diagnostic and treatment options for this fatal disease are urgently needed.[3,4]

The liver has a special immunosuppressive cell population that makes it exist in a state of “innate immune tolerance.” Therefore, during liver cancer, tumors can achieve “immune escape” through various pathways. Binding of programmed cell death protein-1 (PD-1) to programmed death ligand-1 (PD-L1) negatively regulates CD8+ cell activity, resulting in immunosuppression.[5] PD-1 and PD-L1 antibodies play a role in the treatment of liver cancer by relieving immunosuppression and overcoming the failure of
The authors declare that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, informed consent was obtained from the participants involved in investigations involving human subjects.

3. Statistical analysis

The meta-analysis results were reported as the risk ratio (RR), risk difference (RD), and hazard ratio (HR) with 95% confidence interval (CI). RRs represented the overall results of the comparison between ICIs combination therapy and monotherapy for HCC; RD represented the AE, ORR, and DCR in the single-arm trials; and HR represented the OS and PFS in all studies. A Z test was performed to determine the effect size, and statistical significance was set at \( P < 0.05 \). Heterogeneity among the studies was measured using the \( Q \) test and \( I^2 \) statistics. A random-effects model was chosen to estimate the pooled RR when the p heterogeneity was lower than 0.10 or the \( I^2 \) value was over 50%. Otherwise, a fixed effects model was used. In addition, the reliability of the results was tested using a sensitivity analysis, and the potential publication bias was investigated using the Begg/Egger test. All statistical analyses were performed using Review Manager 5.1.7 and STATA 14.0, statistical package (Stata Corp, College Station, TX).

3. Results

3.1. The included studies & characteristics

Figure 1 shows a flow diagram of the meta-analysis. A total of 2234 potentially relevant articles were enrolled through the above-mentioned search strategies, and 727 studies were excluded after careful screening of titles and abstracts. Then,
1480 articles, including conference abstracts, replies to letters, case reports, systematic reviews, meta-analyses, and unrelated research, were excluded, and 16 trials were excluded because the available data could not be extracted. Finally, 6 randomized trials\cite{16-21} and 5 single-arm studies\cite{22-26} were enrolled, including a total of 1791 patients (980 patients for combination therapy and 565 patients for monotherapy in RCTs and 246 patients for ICIs combination therapy in single-arm trials). The detailed characteristics are listed in Table 1.

### 3.2. Quality assessment

Randomization and withdrawal were mentioned in the 6 randomized trials, and the quality assessment is presented in Figure 2A and B. The Newcastle-Ottawa scale was adopted to assess the 5 single-arm studies, and the results are shown in Table 2. All these results should be considered as high-quality studies.

### 3.3. Meta-analysis of ORR

The ORR was analyzed in 559 patients treated with combination therapy in 9 studies. A fixed-effects model was applied after the heterogeneity test ($P = .20$, $I^2 = 32\%$). The ORR of ICIs combined with anti-angiogenesis agents in the treatment of HCC was 26% (95% CI:0.18-0.34), and the difference was statistically significant ($P < .001$) (Fig. 3).

The subgroup analysis regarding first-line and second- or later-line subtypes by ICIs combined with anti-angiogenesis was also reported in the 5 studies; the other 2 studies showed data as the first-line group and the second- or later-line group. Because no statistical heterogeneity was observed in these trials, a fixed-effects model was used to integrate the analysis. The ORR in the first-line group was 27% (95%CI: 0.16–0.38, $P < .001$), which was significantly higher than 16% in the second- or later-line group (95%CI: −0.06 to 0.38, $P = .16$) (Fig. 4).

In the RCTs, 559 patients from 4 trials were included to analyze the ORR, of whom 315 were treated with ICIs and anti-angiogenesis agents and 244 were treated with ICIs or anti-angiogenesis agents. The ORR was 29.8% (94/315) for the combination therapy cases and 16.4% (40/244) for the monotherapy cases. The difference in ORR between the groups was statistically significant (RR = 1.87, 95%CI: 1.31–2.66, $P < .001$) (Fig. 5).

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**Figure 1.** Flow diagram of the meta-analysis process.

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**PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only**

- **Records identified from:** Pubmed, Embase, Web of science, Clinical trials (n = 2234 )
  - Records removed before screening: Duplicate records removed (n = 727)

- **Records screened (n = 1507 )**
  - Records excluded (n = 794)

- **Reports sought for retrieval (n = 713 )**
  - Reports not retrieved (n = 686)

- **Reports assessed for eligibility (n = 27 )**
  - Reports excluded: Basic research (n = 3) Data cannot be extracted (n = 13)

- **Included**
  - Studies included in review (n = 11)
3.4. Meta-analysis of DCR

The DCR in the ICIs-combined with anti-angiogenic therapy group was estimated in 9 research studies. The results of the fixed-effects model showed that DCR was 70% (95%CI: 0.62–0.79, \( P < .001 \)) (Fig. 6) in the combination therapy group.

Data regarding the first-line and second- or later-line subtypes were also available for 5 studies, and the other 2 studies reported results as the first-line group and the second- or later-line group. The results showed that the DCR was 70% (95%CI: 0.59–0.81, \( P < .001 \)) in the first-line group, which was significantly higher than 61% (95%CI: 0.38–0.83, \( P < .001 \)) in the second-line group, and the difference was statistically significant (Fig. 7).

The DCR from the 4 RCT studies were also assessed. The pooled analysis revealed a higher DCR (RR = 1.51, 95%CI: 1.29–1.76, \( P < .001 \)) using the fixed-effects model in the combination therapy group than in the monotherapy group (Fig. 8).

3.5. Meta-analysis of OS and PFS

Comparisons of OS between the ICIs combination and monotherapy groups were reported in 4 RCT studies, and the median follow-up time was 6.8 to 17 months. Pooled analysis showed that the OS after ICI-combined anti-angiogenesis therapy was significantly higher than that after monotherapy (HR = 0.52, 95%CI: 0.41–0.64, \( P < .001 \)) (Fig. 9).

Meanwhile, PFS was analyzed from 5 RCTs, and the median follow-up time was between 6.8 and 17 months. The difference in PFS between the 2 groups was statistically significant (HR = 0.56, 95%CI: 0.48–0.66, \( P < .001 \)) (Fig. 10).

3.6. Meta-analysis of AEs

The overall AEs rate was reported in 5 studies (615 evaluable patients). A pooled prevalence of 94% (95%CI: 0.86–1.02, \( P < .001 \)) (Fig. 11) was observed among patients treated with ICI-combined anti-angiogenesis therapy. Meanwhile, no significant difference in the overall AEs rate between the ICI-combined...
anti-angiogenesis and monotherapy groups from RCTs was found in the fixed-effects model ($P = .40$) (Fig. 12). AEs ≥ grade 3 were reported in 7 trials (733 evaluable patients). A pooled prevalence of 33% (95% CI: 0.16–0.51, $P < .001$) (Fig. 13) was demonstrated among patients treated with ICIs plus anti-angiogenesis therapy using the random-effect model ($I^2 = 78%$). Moreover, subgroup analysis of sorafenib and anti-PD-1 subtypes used in monotherapy groups was reported in 4 RCTs. The rate of AEs ≥ grade 3 in the ICI-combined anti-angiogenesis group was significantly higher than that in the anti-PD-1 alone group but similar to that in the sorafenib group. The rate of AEs ≥ grade 3 was slightly higher in the combination group than in the monotherapy group, but the difference was not significant (Fig. 14).

Decreased appetite was reported in 7 studies. A pooled prevalence of 25% (95% CI: 0.18–0.32, $P < .001$) was observed among patients treated with ICIs plus anti-angiogenesis therapy (Table 3a). A pooled prevalence of 16% (95% CI: 0.09–0.23, $P < .001$) was observed among patients treated with ICI-combined anti-angiogenesis. Three of the 7 RCT studies, and a pooled analysis revealed that the nausea rate was significantly higher in the combination group than in the monotherapy group (RR = 1.21, 95% CI: 0.81–1.80, $P = .35$), but the difference was not significant (Table 3a).

Hypertension was reported in 9 studies (832 evaluable patients) (Table 3a). A pooled prevalence of 16% (95% CI: 0.04–0.28, $P = .01$) was demonstrated among patients treated with ICI-combined anti-angiogenesis.

Nausea was reported in 5 studies (743 evaluable patients), as shown in Table 3b. A pooled prevalence of 18% (95% CI: 0.10–0.26, $P < .001$) was observed among patients treated with ICI-combined anti-angiogenesis. Three of the 5 studies were RCTs, and a pooled analysis revealed that the nausea rate was significantly higher in the combination therapy group than in the monotherapy group (RR = 1.52, 95% CI: 1.08–2.15, $P = .02$) in the fixed-effect model (Table 3b).

Proteinuria was reported in 7 studies (472 patients) (Table 3b). A pooled prevalence of 28% (95% CI: 0.19–0.37, $P < .001$) was demonstrated among patients treated with ICI-combined anti-angiogenesis. Three of the 7 studies were RCTs, and the difference in proteinuria rate between the combination therapy and monotherapy groups was statistically significant (RR = 2.79, 95% CI: 1.73–4.52, $P < .001$) (Table 3b).

| Study or Subgroup | Risk Difference | SE | Weight | IV, Fixed, 95% CI | Risk Difference | SE | Weight | IV, Fixed, 95% CI |
|------------------|----------------|----|--------|------------------|----------------|----|--------|------------------|
| Chun Han 2021    | 0.3103448      | 0.1641149 | 5.2% | 0.31 [0.05, 0.57] | 0.1641149 | 0.31 [0.05, 0.57] |
| Kang Chen 2021   | 0.4153846      | 0.1235646 | 11.6% | 0.42 [0.17, 0.66] | 0.1235646 | 0.42 [0.17, 0.66] |
| Makoto Chuma 2021| 0.1806651      | 0.1028696 | 16.8% | 0.18 [0.02, 0.38] | 0.1028696 | 0.18 [0.02, 0.38] |
| Michael S Lee 2020| 0.2666667     | 0.1285649 | 10.7% | 0.27 [0.01, 0.52] | 0.1285649 | 0.27 [0.01, 0.52] |
| San-Chi Chen 2022| 0.2241739     | 0.1307441 | 10.4% | 0.22 [0.03, 0.48] | 0.1307441 | 0.22 [0.03, 0.48] |
| Shukui Qin 2021  | 0.2876788     | 0.0668744 | 23.5% | 0.29 [0.12, 0.46] | 0.0668744 | 0.29 [0.12, 0.46] |
| Xioozhun Huang 2021| 0.2413793    | 0.1841149 | 5.2% | 0.24 [0.12, 0.60] | 0.1841149 | 0.24 [0.12, 0.60] |
| Yuka Hayakawa 2021| 0.225         | 0.1571348 | 7.2% | 0.23 [0.08, 0.53] | 0.1571348 | 0.23 [0.08, 0.53] |
| Yuwa Ando 2021   | 0.1538462     | 0.1380131 | 9.3% | 0.15 [0.12, 0.42] | 0.1380131 | 0.15 [0.12, 0.42] |

| Total (95% CI)  | 0.26 [0.18, 0.34] | 0.026 |
|-----------------|-------------------|-------|

Heterogeneity: $Chi^2 = 3.08, df = 8 (P = .93); I^2 = 0%$
Test for overall effect: $Z = 8.11 (P < 0.000001)$

Figure 3. Forest plot of ORR of ICIs plus anti-angiogenesis treatment in the included studies. ICI = immune checkpoint inhibitor, ORR = objective response rate.
Thrombocytopenia was reported in 4 studies (232 evaluable patients), as shown in Table 3b. A pooled prevalence of 11% (95% CI: −0.02 to 0.24, P = .10) was observed among patients treated with ICI-combined anti-angiogenesis. A rash was reported in 8 studies (317 evaluable patients), as shown in Table 3b. A pooled prevalence of 26% (95% CI: 0.18–0.35, P < .001) was observed among patients treated with ICI-combined anti-angiogenesis. Three of the 8 studies were RCTs, and the rash rate was higher in the combination therapy group than in the monotherapy group (RR = 0.29, 95% CI: 0.76–2.19, P = .34), but the difference was not significant (Table 3b).

Elevated transaminase levels, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were reported in 8 studies (503 evaluable patients) (Table 3b). A pooled prevalence of 24% (95% CI: 0.16–0.33, P < .001) was demonstrated among patients treated with ICI-combined anti-angiogenesis. Three of the 8 studies were RCTs, and the difference in the elevated transaminase rates between the combination and

| Study or Subgroup | Risk Difference | SE | Weight | M-H. Fixed, 95% CI |
|-------------------|----------------|----|--------|--------------------|
| Chun Han 2021     | 0.6275662      | 0.1841149 | 5.2% | 0.83 [0.47, 1.19] |
| Kang Chen 2021    | 0.7230769      | 0.1235604 | 11.6% | 0.72 [0.48, 0.97] |
| Makoto Chuma 2021 | 0.7872241      | 0.1028889 | 16.8% | 0.79 [0.59, 0.99] |
| Michael S Lee 2020| 0.6833333      | 0.1285649 | 10.7% | 0.68 [0.43, 0.94] |
| San-Chi Chen 2022 | 0.6896552      | 0.1307441 | 10.4% | 0.69 [0.43, 0.95] |
| Shukui Qin 2021   | 0.6818162      | 0.0966744 | 23.5% | 0.68 [0.51, 0.85] |
| Xiaozhun Huang 2021| 0.6551724   | 0.1841149 | 5.2% | 0.66 [0.40, 1.02] |
| Yuwa Ando 2021    | 0.7259231      | 0.1360131 | 9.3% | 0.58 [0.31, 0.90] |

Total (95% CI) | 100.0% | 0.70 [0.62, 0.79] |
monotherapy groups was not significant (RR = 0.88, 95% CI: 0.39–1.97, \( P = .75 \)) (Table 3b) in the random-effects model.

### 3.7. Sensitivity analysis & publication bias

Funnel plots were established to estimate publication bias and the funnel plots showed no evidence of obvious asymmetry among the studies in this meta-analysis (Fig. 15). Sensitivity analyses were performed to calculate the influence of individual data on the combined RRs and hazard ratios. The pooled RRs and hazard ratios did not change remarkably, indicating the stability of this meta-analysis.

### 4. Discussion

Multi-kinase inhibitors, such as sorafenib, sunitinib, and regorafenib, have been used as first- and second-line treatments for HCC. There are obvious benefits of multi-kinase inhibitors in clinical trials; however, resistance and adverse effects have limited the use of these treatments to only a few patients. These studies highlight the strongly immunosuppressive nature of HCC and indicate the critical need for combination strategies to address immune defects beyond PD-L1. Co-targeting of the PD-L1 and VEGF signaling axes is the most extensively studied combination approach for advanced HCC. Recently, combination approaches have become the standard treatment...
ICI-combined anti-angiogenesis therapy has been increasingly proven to have both local and systemic effects, providing a survival benefit through potentially synergistic effects. However, the optimal combination therapy for unresectable HCC remains controversial. Thus, an in-depth analysis was performed to evaluate whether the survival rate of patients with HCC could be effectively and safely improved with ICI combined anti-angiogenesis therapy.

The findings of this study showed that both OS and PFS could be improved by monotherapy. Similarly, a multicenter phase Ib/II trial by Kuimin Mei et al.[27] showed median PFS and OS were 3.7 months (95%CI: 2.0–5.8) and 13.2 months (95%CI: 8.9 to unreached level), respectively. Moreover, the ORR and DCR were higher than those of the monotherapy group. Further analysis revealed that the ORR was better in the first-line group that received combination therapy, but unfortunately, no clear advantage was observed in the second- or later-line group (P = .16).

similar results in some studies showed response rates with nivolumab and pembrolizumab of 20% and 17% in patients previously treated with sorafenib, respectively[6,28]; however,
randomized Phase III trials of anti-PD-1 monotherapy in either the first-line or second-line settings did not demonstrate statistically significant improvements in OS. In addition, the present analysis demonstrated that the DCR in the combination therapy group was 70%, which was higher than that in the monotherapy group. The subgroup analysis suggested that the DCR in the first-line group was higher than that in the second- or later-line groups. Similar results from single-arm studies showed that combinations of VEGF and PD-L1 inhibitors were associated with a manageable safety profile and promising antitumor activity, with ORRs of 11% to 50%. In Arm F of another study GO30140, a confirmed ORR of 36% – including a complete response rate of 12% – was reported in patients with unresectable HCC treated with atezolizumab and bevacizumab, and a statistically and clinically significant improvement in PFS was observed in the combination group compared with the atezolizumab monotherapy (HR = 0.55; \( P = .0108 \)), with a median of 5.6 months versus 3.4 months, respectively. Surprisingly, ORR was not markedly higher in the combination arm than in the atezolizumab arm (20% vs 17%); however, DCR was improved in favor of the combination group (67% vs 49%). These data show that anti-angiogenic therapy significantly enhances the efficacy of PD-L1 inhibition, and that a combination of PD-L1 and angiogenesis inhibitors is likely required to augment anticancer immunity in patients with unresectable HCC. Moreover, the results of IMbrave150 showed that atezolizumab-combined bevacizumab significantly improved both PFS (HR = 0.59, \( P < .0001 \)) and OS (HR = 0.58, \( P = .0006 \)) compared with sorafenib, and the ORR more than doubled in the atezolizumab-combined bevacizumab group compared with the sorafenib alone group (27% vs 12%, \( P < .0001 \)). These studies were consistent with the present result, which is a clinical manifestation of the mutually promotional pharmacological mechanism between immune checkpoint inhibitors and anti-angiogenic medicines.

The incidence of AEs was 94% in the combination therapy group, similar to that in the monotherapy group. However, AEs \( \geq \) grade 3 were more severe in the combination group

| Study or Subgroup | Experimental Events | Control Events | Weight | Risk Ratio | M-H Fixed 95% CI | Risk Ratio |
|-------------------|---------------------|---------------|--------|------------|------------------|------------|
|                  | Total               |               |        |            |                  |            |
| 5.1.1 control(sorafenib) | 186 | 329 | 86 | 156 | 72.4% | 1.03 [0.86, 1.22] |
| Richard S. Finn 2020 | 78 | 132 | 27 | 58 | 23.3% | 1.27 [0.93, 1.73] |
| Shukui Qin 2021 | 461 | 214 | 95.7% | 1.08 [0.93, 1.26] |
| Total events | 264 | 113 |
| Heterogeneity: \( \chi^2 = 1.40, df = 1 \ (P = 0.24); \ P = 29% \) |
| Test for overall effect: \( Z = 1.97 \ (P = 0.29) \) |
| 5.1.2 control(anti-PD-1) | 7 | 60 | 2 | 59 | 1.3% | 3.44 [0.75, 15.89] |
| Michael S Lee 2020 | 6 | 58 | 6 | 82 | 3.1% | 1.41 [0.48, 4.17] |
| Subtotal (95% CI) | 118 | 141 | 4.3% | 2.00 [0.84, 4.76] |
| Total events | 13 | 8 |
| Heterogeneity: \( \chi^2 = 0.68, df = 1 \ (P = 0.35); \ P = 0% \) |
| Test for overall effect: \( Z = 1.56 \ (P = 0.12) \) |
| Total (95% CI) | 579 | 355 | 100.0% | 1.12 [0.97, 1.31] |
| Total events | 277 | 121 |
| Heterogeneity: \( \chi^2 = 3.94, df = 3 \ (P = 0.27); \ P = 24% \) |
| Test for overall effect: \( Z = 1.54 \ (P = 0.12) \) |
| Test for subgroup differences: \( \chi^2 = 1.85, df = 1 \ (P = 0.17); \ P = 45.9% \) |

Figure 14. Forest plot of comparison of overall AEs \( \geq \) grad3 between ICIs plus anti-angiogenesis group and monotherapy group in the included RCT studies. AE = adverse event, ICI = immune checkpoint inhibitor, RCT = randomized controlled trial.

Table 3a
Subgroup analysis of pooled HRs for each AE in HCC.

| AEs | No. of studies | RD (95% CI) | RR (95% CI) | P value | I2 (%) | P value |
|-----|----------------|-------------|-------------|---------|--------|---------|
| Decreased appetite | 7 | 0.25 [0.18, 0.32] | - | <.00001 | 32 | .18 |
| Compare with monotherapy group | 3 | 0.91 [0.71, 1.16] | .43 | 0 .78 |
| Diarrhea | 8 | 0.16 [0.09, 0.23] | - | <.00001 | 0 | .90 |
| Compare with monotherapy group | 4 | 0.61 [0.30, 1.25] | .18 | 85 | .0002 |
| Anti-PD-1 for monotherapy | 2 | 1.26 [0.75, 2.12] | .38 | 0 | .99 |
| Sorafenib for monotherapy | 2 | 0.34 [0.16, 0.73] | .006 | 82 | .02 |
| Fatigue | 9 | 0.32 [0.20, 0.43] | - | <.00001 | 57 | .02 |
| Compare with monotherapy group | 4 | 1.09 [0.91, 1.30] | .34 | 0 | .59 |
| Anti-PD-1 for monotherapy | 2 | 1.36 [0.85, 2.17] | .20 | 4 | .31 |
| Sorafenib for monotherapy | 2 | 1.04 [0.86, 1.26] | .34 | 0 | .99 |
| Hyperbilirubinemia | 5 | 0.31 [0.23, 0.43] | <.00001 | 43 | .13 |
| Compare with monotherapy group | 3 | 1.21 [0.81, 1.80] | .35 | 51 | .13 |
| Hypertension | 9 | 0.29 [0.19, 0.39] | <.00001 | 45 | .07 |
| Compare with monotherapy group | 3 | 1.52 [1.08, 2.15] | .02 | 51 | .13 |

AE = adverse event, HR = hazard ratio, PD-1 = programmed cell death protein-1, RD = risk difference, RR = risk ratio.
than in the anti-PD-1 monotherapy group, but with a similar incidence rate in the monotherapy group. In the combination therapy group, the most common AEs were decreased appetite, diarrhea, fatigue, hyperbilirubinemia, hypertension, nausea, proteinuria, thrombocytopenia, myelotoxicity, rash, and elevated transaminase levels. The incidences of diarrhea, hypertension, nausea, and proteinuria in the combination therapy group were higher than those in the monotherapy group. This could be explained by the superimposition of AEs between the 2 medicines. Moreover, analysis of patient-reported outcomes showed significant and consistent benefits in key symptoms, quality of life, and functioning with atezolizumab-combined bevacizumab compared with sorafenib, further supporting the overall clinical benefit of this combination. The effective reduction in the incidence of AEs is a hot topic for future research. These results suggest that special attention should be paid to the digestive system, blood pressure, and kidney function of patients before administering ICI-combined anti-angiogenesis agents. In summary, our meta-analysis results suggest that ICI-combined anti-angiogenesis medicine approaches are more suitable for patients with advanced HCC, especially for first-line treatment, whereas anti-PD-1 or anti-angiogenesis medicines alone are more beneficial for patients with poor physical fitness.

This meta-analysis has some limitations. First, information on the tumor-node-metastasis stage and chemotherapy regimens could not be obtained, which further limited subgroup analysis. Second, the eligible studies were retrospective in nature. Thus, large randomized controlled clinical trials are urgently required to overcome these problems and to provide more advanced evidence.

5. Conclusion

Our meta-analysis revealed that ICIs combined with anti-angiogenesis agents could provide OS. PFS, ORR, and DCR were advantageous to monotherapy, which was mainly reflected in the first and second- or later-line treatment. Although the incidence of AEs ≥ grade 3 was higher in the combination group, the total rate of AEs was similar between the combination and monotherapy groups. Overall, ICIs plus anti-angiogenesis may be the standard preoperative first-line treatment for advanced HCC as 1st-line treatment, meanwhile, the combination treatment approach was also effective as 2nd-line.

Acknowledgments

Significant support was provided by the authors’ clinical and technical colleagues during the protocol design, data collection and analysis, and writing of the manuscript.

Author contributions

Conceptualization: Feng Xian, Guojun Zhang, Guohui Xu. Data curation: Feng Xian.
Formal analysis: Feng Xian, Cailiang Wu, Guojun Zhang, Guohui Xu.
Funding acquisition: Guohui Xu.
Investigation: Feng Xian, Cailiang Wu.
Methodology: Feng Xian.
Project administration: Feng Xian, Cailiang Wu, Guojun Zhang.
Resources: Feng Xian, Cailiang Wu, Guojun Zhang.
Software: Feng Xian.
Supervision: Feng Xian, Guojun Zhang, Guohui Xu.
Validation: Feng Xian, Guojun Zhang, Guohui Xu.
Visualization: Feng Xian, Guohui Xu.
Writing – original draft: Feng Xian.
Writing – review & editing: Feng Xian.

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