METHODS

BACKGROUND

We used random effects model using the Mantel-Haenszel (MH) method to determine the relative risk of gastrointestinal (GI) and hepatic toxicities associated with upfront use of ICI-based regimens compared to sunitinib for aRCC.

We conducted a meta-analysis of phase 3 randomized controlled trials (RCTs) to determine the relative risk of gastrointestinal (GI) and hepatic toxicities associated with upfront use of ICI-based regimens compared to sunitinib for aRCC.

Immune checkpoint inhibitors (ICI) paired with anti-angiogenic tyrosine kinase inhibitor (VEGF-i) have been investigated as a new avenue of frontline therapy in advanced renal cell carcinoma (aRCC).

The primary outcome of our meta-analysis was relative risk of any-grade and high-grade GI and hepatic toxicities. Sunitinib was used for all the control arms.

Primary Outcome

The primary outcome of our meta-analysis was relative risk of any-grade and high-grade GI and hepatic toxicities associated with ICI-based regimens.

Heterogeneity was assessed with I^2 and P values. Forest plots were generated using R (version 3.6.1) and Metafor package. The overall weighted effects were synthesised using random effects model.

RESULTS

Search results

Two phase 3 RCTs, JAVELIN Renal 101 and KEYNOTE-426, randomizing 1727 patients were included in the analysis of GI and hepatic toxicities.

ICI regimens used in the study arms were as follows — JAVELIN Renal 101: avelumab and axitinib, and KEYNOTE-426: pembrolizumab and axitinib. Sunitinib was used for all the control arms.

Randomization was 1:1 in both studies.

Clinical characteristics of studies

The characteristics of the studies are demonstrated in Table 1.

Fig. 1 Flow diagram of the study selection process.

Fig. 2 Flowchart for grade ≥ 3 diarrhea associated with Immune Checkpoint Inhibitor based regimens.

Primary analyses

Pooled RR of any-grade dyspepsia associated with Immune Checkpoint Inhibitor based regimens.

Risk of any-grade and high-grade diarrhea, abdominal pain, vomiting, and transaminitis for both intervention and control arms were included in the analysis.

-1.38, P < 0.00001, I^2 = 0%); dyspepsia: 0.40 (95% CI: 0.30 – 0.53, P < 0.00001, I^2 = 0%); nausea: 0.87 (95% CI: 0.74 – 1.02, P = 0.19, I^2 = 0%), and reporting of GI and hepatic toxicities, e.g., diarrhea, vomiting, and transaminitis for both intervention and control arms were included in the analysis.

Data extraction

- eligibility for each study was screened by at least two authors. Two authors also independently extracted data from every eligible study before final analysis.

Primary Outcome

The primary outcome of our meta-analysis was relative risk of any-grade and grade ≥ 3 GI and hepatic toxicities associated with ICI-based regimens.

Data synthesis and analysis

We used a two-tailed test model using the inverse-variance (IV) method to calculate the pooled risk ratio (RR) with 95% confidence interval (CI).

Heterogeneity was assessed with I^2 and P values. Forest plots were generated using R (version 3.6.1) and Metafor package. The overall weighted effects were synthesised using random effects model.

Overall, the pooled RR of grade ≥ 3 and higher GI and hepatic toxicities are as follows — diarrhea: 1.36 (95% CI: 1.13 – 1.63; P = 0.0004; I^2 = 0%), dyspepsia: 0.40 (95% CI: 0.30 – 0.53, P < 0.00001, I^2 = 0%); nausea: 0.87 (95% CI: 0.74 – 1.02, P = 0.19, I^2 = 0%), and reporting of GI and hepatic toxicities, e.g., diarrhea, vomiting, and transaminitis for both intervention and control arms were included in the analysis.

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CONCLUSIONS

- Immune checkpoint inhibitors (ICI) and VEGFi combinations have significant GI and hepatic toxicities.

- The risk of any-grade and high-grade diarrhoea, abdominal pain, elevation of AST/ALT was higher in combination arms compared to the Sunitinib arm. Risk of all-grade dyspepsia and nausea was lowered in combination arms.

- The risk of high-grade diarrhoea, elevation of AST, and elevation of ALT was higher in combination arms compared to the Sunitinib arm.

- Careful monitoring of patient symptoms and liverfunction with indication of appropriate supportive care is critically important.

REFERENCES
