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Review

Immune-related adverse events from combination immunotherapy in cancer patients: A comprehensive meta-analysis of randomized controlled trials

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ABSTRACT

Background: Although available evidence from clinical trials has shown that immune checkpoint inhibitors (ICIs) combination therapy can lead to a series of immune-related adverse events (irAEs), the overall risk of irAEs on combination therapy has yet not been systematically reported. Therefore, we performed a meta-analysis to comprehensively explore the overall risks for irAEs on combination immunotherapy.

Methods: PubMed, Embase, and Google Scholar were systematically searched for relevant randomized controlled trials (RCTs) comparing combination immunotherapy to monotherapy. The meta-analysis was conducted by using Review Manager 5.3.

Results: A total of 11 RCTs involving 5307 patients were eligible for this meta-analysis. The risk ratio for all-grade diarrhea and all-grade colitis for combination therapy was 1.95 (95% CI 1.54, 2.46; $P < 0.00001$) and 4.45 (95% CI 3.04, 6.51; $P < 0.00001$), respectively. The risk ratio for all-grade hyperthyroidism and all-grade hypothyroidism for combination therapy was 2.84 (95% CI 1.71, 4.72; $P < 0.0001$) and 1.71 (95% CI 1.38, 2.13; $P < 0.00001$), respectively. The risk ratio for all-grade increased AST and all-grade increased ALT was 3.87 (95% CI 2.74, 5.47; $P < 0.00001$) and 4.29 (95% CI 3.05, 6.04; $P < 0.00001$), respectively. The risk ratio for all-grade hypophysitis and all-grade pneumonitis was 4.24 (95% CI 2.26, 7.98; $P < 0.00001$) and 2.92 (95% CI 1.60, 5.33; $P = 0.0005$), respectively.

Conclusions: Patients receiving combination immunotherapy are at increased risk of selected all-grade irAEs. Although fatal high-grade irAEs is rare, AEs caused by combination immunotherapy should be recognized promptly in order to avoid more serious complications.

1. Introduction

Cancer is one of the most serious diseases and one of the major causes of death all over the world [1]. Traditional cancer treatments mainly include surgical operation, chemotherapy and radiotherapy, but the overall survival rates remain far from ideal [2]. Immune checkpoint inhibitors (ICIs) are undoubtedly a major breakthrough in cancer therapy in recent years [3]. Currently, programmed death-1 (PD-1) and Cytotoxic T-lymphocyte antigen-4 (CTLA-4) are the most widely used immune checkpoint [4]. PD-1 and CTLA-4 have been identified as effective targets for killing tumor cells. The immunosuppressive CTLA-4 and PD-1 receptor pathways help tumor cells evade the immune attack by immune regulatory [5]. PD-1 receptor is highly expressed on activated T cells and interacts with its ligand PD-L1 to prevent overactivation of T cells and inhibit the immune system, thus inducing immune tolerance of tumor cells [6,7]. CTLA-4 receptor interacting with its ligand CD28 inhibits the activation of cytotoxic T cells and down-regulates antitumor immunity [8]. Ipilimumab, a fully human immunoglobulin G subclass 1 (IgG1) monoclonal antibody, has demonstrated great efficacy for the treatment of metastatic melanoma by blocking binding of CTLA-4 with its ligands. Nivolumab, a fully human IgG4 monoclonal antibody, improves significantly overall survival and response rate in multiple malignancies by inhibiting PD-1 [9–22]. ICIs combination therapy has demonstrated a significant overall survival benefit compared to monotherapy [8,23–24]. Although combination therapy has demonstrated an inspiring efficacy against different malignancies, they lead to a series of immune-related adverse events (irAEs) associated with ICIs therapy and some of the adverse events can be fatal. These adverse events can be available from many clinical trials [24–27]. Despite the demonstrated overall survival benefit, whether

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ICIs combination therapy increases toxicity still remains controversial [28–29]. Therefore, we conducted a meta-analysis of randomized controlled trials (RCTs) to systematically explore the overall incidence and risk of irAEs in cancer patients mainly from five aspects: dermatologic irAEs, gastrointestinal irAEs, hepatic irAEs, pulmonary irAEs and endocrine irAEs.

2. Material and methods

Our work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines.

2.1. Search strategy and study selection

PubMed, Embase, and Google Scholar were systematically searched for relevant RCTs comparing ICIs combination therapies to monotherapy, from database inception to April 2018. The search terms we used were as follows: nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, ipilimumab, tremelimumab, PD-1, PD-L1, CTLA-4, combination immunotherapy, and adverse events. The RCTs that we included were only published in English. We also examined the relevant reviews and the references of the included studies.

Study selection was required to meet the following inclusion criteria: (a) The studies must be RCTs. (b) The studies compared ICIs combination therapy to monotherapy. (C) The studies reported irAEs. (d) The studies were limited to clinical trials published in English. (e) Patients were diagnosed with cancer.

Studies were excluded according to the following criteria: (a) Review articles. (b) Case reports. (c) Studies without relevant data.

2.2. Data extraction

Two authors conducted data extraction independently and any discrepancies were resolved by consensus. The following information was extracted from the included studies: first author, year of publication, phase of trials, cancer types, participant characteristics, treatment arms, number of patients in the experimental groups and the control groups. The severity of irAEs was graded according to version 3 or 4 of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

2.3. Risk of bias assessment

According to the Cochrane risk of bias assessment [41], we assessed the risk of bias for included study in terms of the following criteria: [1] randomized Sequence Generation, [2] allocation concealment, [3] blinding of participants, personnel, [4] blinding of outcome assessment, [5] incomplete outcome data, [6] selective outcome reporting, and [7] other sources of bias. Two authors (Bo Zhang and Qiong Wu) assessed the risk of bias for each RCT independently. Each item was described as low risk, high risk or unclear risk. Any disagreements were resolved by discussion with other authors.

2.4. Statistical analysis

All data was analyzed by Review Manager 5.3 software (Nordic Cochrane Center, Copenhagen, Denmark). We calculated risk ratio (RR) and 95% confidence interval (CI) of irAEs (all grades and high grades) in each RCT. The Q test and I^2 statistic were used to assess statistical heterogeneity among included studies. $P < 0.05$ for the Q test indicated a significant heterogeneity and $I^2 > 50\%$ was considered statistically significant heterogeneity. If the I^2 value was < 50%, we performed the meta-analysis using the fixed-effects models. Otherwise, we used the random-effects models. The stability of the combined results was examined by sensitivity analysis. If a significant heterogeneity existed, we also explored sources of heterogeneity by the sensitivity analysis. Potential publication bias was detected by using funnel plots. If there was no obvious asymmetry in funnel plots' shapes, no significant publication bias existed among the included studies. $P \leq 0.05$ was considered statistically significant.

3. Results

3.1. Search results and study characteristics

A total of 12,102 potential articles were initially in line with our requirements based on search terms. 11,637 articles were excluded by screening the titles and abstracts. 437 articles were excluded due to duplicates. 11 articles were finally identified in strict inclusion and exclusion criteria. This included 3 phase 1 studies, 3 phase 2 studies, 4 phase 3 studies and 1 phase 1/2 study. All studies belonged to RCTs. 2209 patients received ICIs combination therapy and 3098 patients received monotherapy. 6 studies evaluated advanced melanoma or metastatic melanoma. 1 study evaluated non-small cell lung cancer. 1 study evaluated small-cell lung cancer. 1 study evaluated recurrent glioblastoma. 1 study evaluated advanced renal-cell carcinoma. And 1 study evaluated recurrent metastatic sarcoma. All studies reported the irAEs of ICIs combination therapy. A total of 5307 patients were included in our meta-analysis, of whom 2194 had been diagnosed with melanoma, 1750 had lung cancer, 40 had recurrent glioblastoma, 85 had metastatic sarcoma and 1096 had advanced renal-cell carcinoma. Patients who received monotherapy served as the control group and who received combination therapy as the experimental group. Grade3–5 was considered as high grade or severe grade. The process of study selection is shown in Fig. 1, and the details of the included study characteristics are presented in Table 1.

3.2. Quality assessment

We generated risk of bias graphs to identify the risk of bias of all included studies. The graphs indicated that the studies included in our meta-analysis presented generally good methodological quality. The section bias of all studies experienced low risk especially random sequence generation. Unclear risk of bias was mainly focused on performance bias (Blinding of participants and personnel). In summary, the included studies generally experienced good quality. The results of the risk of bias assessment are presented in Fig. 2.

3.3. Dermatologic irAEs

The most frequent dermatologic irAEs during clinical trials were pruritus and rash. 10 studies reported the incidence of rash for all grades and 9 studies reported the incidence of pruritus. Based on the random-effects models, the risk ratio for all-grade rash and all-grade pruritus for combination therapy was 1.73 (95% CI 1.39, 2.16; $P < 0.00001$) and 1.80 (95% CI 1.38, 2.35; $P < 0.00001$), respectively. The risk ratio for high-grade rash and high-grade pruritus for combination therapy was 5.62 (95% CI 2.84, 11.11; $P < 0.00001$) and 4.98 (95% CI 1.67, 14.87; $P = 0.004$), respectively (Table 2). Compared to patients who received monotherapy, patients who received ICIs combination therapy had significantly higher risk of developing pruritus and rash, whether all grades or high grades.

3.4. Gastrointestinal irAEs

The most frequent gastrointestinal irAEs during clinical trials were diarrhea and colitis. The incidence of all-grade diarrhea was reported in ten studies. Using the random-effects models, we observed a significant increase in the risk of developing all-grade diarrhea on combination therapy (RR = 1.95; 95% CI 1.54, 2.46). The difference between combination regimen and monotherapy was statistically significant ($P < 0.00001$). The incidence of colitis for all grades was evaluated in