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Original Article

Treatment-related Death in Cancer Patients Treated with Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis

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Abstract

Aims: We carried out a meta-analysis to determine the risk of treatment-related death associated with immune checkpoint inhibitor use in cancer patients.
Materials and methods: We examined data from the Medline and Google Scholar databases. We also examined original studies and review articles for cross-references. Eligible studies included randomised phase II and phase III trials of patients with cancer treated with ipilimumab, pembrolizumab; nivolumab; tremelimumab and atezolizumab. The authors extracted relevant information on participants, characteristics, treatment-related death and information on the methodology of the studies.
Results: After exclusion of ineligible records, 18 clinical trials were included in the analysis. The odds ratio for treatment-related death for CTLA-4 inhibitors (ipilimumab and tremelimumab) was 1.80 (95% confidence interval 1.25, 2.59; $P = 0.002$) and for PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab and atezolizumab) was 0.63 (95% confidence interval 0.31, 1.30; $P = 0.22$). Treated cancer seems to have no effect on the risk of treatment-related death.
Conclusions: Analysis of our data showed that CTLA-4 inhibitors (ipilimumab and tremelimumab) in a higher dose (10 mg/kg) seem to be associated with a higher risk of treatment-related death compared with control regimens, whereas PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab and atezolizumab) do not cause the same risk. Clinicians have to be fully aware of these differential risks and council their patients appropriately.
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Key words: Atezolizumab; ipilimumab; nivolumab; pembrolizumab; treatment-related death; tremelimumab

Introduction

Immune checkpoint inhibitors are unequivocally one of the most important breakthroughs in cancer therapy in the past 10 years [1]. They work by releasing the brakes of the immune system that limit the activation of T-cells, thus boosting the self-immune response against cancer cells [2]. A number of checkpoint inhibitors have already been approved and have been in practice for years. Ipilimumab (an anti-CTLA-4 monoclonal antibody) was the first to be approved in melanoma management in the adjuvant and metastatic settings [3,4]. Nivolumab and pembrolizumab are two PD-1 targeted monoclonal antibodies that have been approved in advanced melanoma management and in previously treated non-small cell lung cancer (NSCLC) [5–7]. Atezolizumab is a novel anti-PD-L1 monoclonal antibody that has shown impressive activity in advanced urothelial carcinoma and previously treated NSCLC [8].

However, the consequence of the activation of the immune system was not only against cancer cells but also bystander effects against some healthy tissues [9]. Thus, a new pattern of adverse events, called immune-related adverse events, has been recognised, including characteristic cutaneous,

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gastrointestinal, hepatic, pulmonary, endocrine and renal events [10–14]. Thus, a question has always been asked about whether these agents are accompanied by a higher risk of treatment-related death compared with cytotoxic chemotherapy or other control regimens?

Therefore, the aim of this study was to conduct a meta-analysis of available clinical trials to determine the risk of treatment-related death in patients treated with different immune checkpoint inhibitors.

Materials and Methods

Data Source

A literature review of major citation databases including Medline and Google Scholar from January 2005 to March 2016 was conducted using the following search terms: ('nivolumab' [Supplementary Concept] OR 'nivolumab' [All Fields]) OR ('pembrolizumab' [Supplementary Concept] OR 'pembrolizumab' [All Fields]) OR ('ipilimumab' [Supplementary Concept] OR 'ipilimumab' [All Fields]) OR ('tremelimumab' [Supplementary Concept] OR 'tremelimumab' [All Fields]) OR 'atezolizumab' [All Fields]. The search was limited to randomised clinical trials involving human solid tumour patients published in English. Trials were selected and reviewed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [15].

Study Selection

Inclusion criteria for the clinical trials in the meta-analysis included randomised controlled trials of patients with solid tumours; participants were allocated to treatment with an immune checkpoint inhibitor; and events and sample size were available for treatment-related deaths. Exclusion criteria included meeting abstracts without subsequent full-text publication and phase I studies.

Independent reviewers screened reports that included the key terms by their titles and abstracts for potential relevance. Then, full texts of the relevant articles were retrieved to assess eligibility. The references of relevant papers were also reviewed.

Data Extraction and Clinical End Points

Review authors conducted extraction of data. The following information was recorded for each trial: first author's name, year of publication, trial phase, underlying diagnosis, immune checkpoint inhibitor used, treatment arms, total number of patients and number of events described as treatment-related death.

Statistical Analysis

Odds ratios and corresponding 95% confidence interval of treatment-related deaths were the principal measures. The number of events of each adverse event in participants randomised to immune checkpoint inhibitors was compared with those randomised to control treatment in each trial. Outcome heterogeneity between assessed studies in the analysis was evaluated through Cochrane's Q statistic. The fixed effect model was used in all the subanalyses because of the homogeneity of the results [16]. Publication bias was assessed through the use of funnel plots. Data analyses were carried out by using Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Search Results

The search strategy yielded 274 potentially relevant records on immune checkpoint inhibitors from PubMed/Medline and other databases. The reasons for exclusion of studies are shown in Figure 1. Accordingly, 18 clinical trials were included in the analysis, including 14 phase III trials and four phase II trials [3,4,6,8,17–30]. Six trials evaluated ipilimumab, seven trials evaluated nivolumab (two of which evaluated a ipilimumab/nivolumab combination), one trial evaluated tremelimumab, one trial evaluated atezolizumab, two trials evaluated pembrolizumab and one trial evaluated pembrolizumab in addition to one trial that compared pembrolizumab to ipilimumab. Ten studies evaluated malignant melanoma, five studies evaluated NSCLC, one study evaluated renal cell carcinoma, one study evaluated advanced prostate cancer and one study evaluated small cell lung cancer. The non-checkpoint inhibitor control used in some of the studies included placebo, everolimus and chemotherapy (including dacarbazine and docetaxel).

Population Characteristics

In total, 10 849 patients were available for the analysis. According to the inclusion criteria of most of the trials, patients with impaired renal, hepatic, bone marrow function were not included and most patients had Eastern Cooperative Oncology Group performance status from 0 to 2. The baseline characteristics and the number of treatment-related deaths in each trial are presented in Tables 1 and 2.

Overall Incidence of Treatment-related Deaths

For the analysis of the incidence, we considered only arms receiving one of the immune checkpoint inhibitors. The incidence of treatment-related death ranged from no cases to 66 cases (17%). The most frequently reported aetiologies for treatment-related death included severe diarrhoea/colitis, neutropenic sepsis and acute hepatic toxicity. The time to develop treatment-related deaths has been detailed in Tables 1 and 2.

Odds Ratio of Treatment-related Death

To evaluate the odds ratios for treatment-related deaths, only studies evaluating immune checkpoint inhibitors

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