Review

Haematological toxicities with immunotherapy in patients with cancer: a systematic review and meta-analysis

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Abstract *Introduction:* Programmed cell death-1 or ligand 1 (PD-(L)1) inhibitors are associated with immune-related adverse events. Conversely, little is known about the incidence of haematological toxicities across published trials. We have performed a systematic review and meta-analysis to evaluate the incidence of immunotherapy-related anaemia, neutropenia and thrombocytopenia among different tumour types, trials phases and anti-PD-(L)1 agents.
Material and methods: A PubMed, Embase and Cochrane library search on 23rd December 2017 and a review of references from relevant articles were done. Studies regarding haematological diseases were excluded. The pooled incidence rates weighted for the individual sample sizes were calculated according to fixed or random effect models. Incidence of all-grade and grade (G) III or higher anaemia were the primary end-points. Neutropenia, febrile neutropenia and thrombocytopenia were secondary end-points.
Results: Forty-seven studies of PD-(L)1 inhibitors for a total of 9324 evaluable patients were included in the meta-analysis. The overall incidence of anaemia during PD-(L)1 inhibitor was 9.8% (95% confidence interval [CI], 6—13.6%) for all-grade and 5% (95% CI, 3.3—6.7%) for G3-5 anaemia. The incidence was higher in diseases different from genitourinary, lung and melanoma, with avelumab and in phase II studies. In randomised trials, relative risk of all-grade anaemia for patients receiving anti-PD-(L)1 agents compared with control arms was 0.25 (95% CI, 0.16—0.39; p < 0.001). Incidence of all grades and G3-5 neutropenia and thrombocytopenia were 0.94%, 1.07%, 2.8% and 1.8%, respectively. Febrile neutropenia was 0.45%.

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Conclusions: The incidence of PD-(L)1 inhibitor-related anaemia was not negligible. Severe neutropenia, thrombocytopenia and febrile neutropenia were rare. These findings are useful for clinicians and suggest that blood cell count should be checked before every cycle and support should be given when severe toxicity appears.

1. Introduction

Several anti-programmed cell death (ligand) protein 1 (anti-PD-[L]1) monoclonal antibodies have been recently approved for the treatment of advanced cancers such as non-small-cell lung cancer, genitourinary tumours and melanoma. They are generally more tolerated than chemotherapy, and their toxicities are manageable with appropriate supportive therapies [1]. The use of agents that block co-inhibitory immune checkpoint molecules, such as PD-1, unleashes the immune system to control malignancy [2]. However, this can lead to imbalances in immunologic tolerance that result in an unexpected immune response against self-tissues. This may clinically manifest with autoimmune-like side-effects, such as dermatological, gastrointestinal, hepatic, pulmonary and endocrine toxicities [3,4]. Such adverse events, named 'immune-related adverse events,' are principally linked to a dysregulated T-cell effect [5].

Although most clinical trials have reported haematological toxicities (e.g. anaemia and neutropenia) of immunotherapy, no systematic review or meta-analysis reports the incidence of PD-(L)1 inhibitor-related haematological toxicity across different solid tumours.

Because this is a relatively rare adverse event, aggregated data from several prospective studies are noteworthy for clinical practice. Given the increasing number of published trials of PD-(L)1 inhibitors, such information may provide valuable knowledge of these rare but clinically significant toxicities. Anaemia, in fact, can worsen fatigue, a very commonly reported adverse event of immunotherapy, and similarly to neutropenia and thrombocytopenia, has been described as a result of bone marrow hypoplasia due to an autoimmune process [6]. We conducted a systematic review and meta-analysis of trials of PD-(L)1 inhibitors in patients with cancer and calculated the incidence of haematological toxicities among different tumours types, agents and study phases.

2. Material and methods

2.1. Search methods and study selection

Original articles that have published the results of clinical trials of PD-(L)1 inhibitors (either monotherapy or combination immunotherapy) including at least 20 patients with solid tumours were identified by a PubMed,

EMBASE and Cochrane Library search. Also, references of published trials, review articles and editorials were examined for other relevant articles. For the PubMed search, the following terms were used: *(PD-1[All Fields] OR PD-L1[All Fields]) AND (('anaemia'[All Fields] OR 'anemia'[MeSH Terms] OR 'anemia'[All Fields]) OR ('thrombocytopaenia'[All Fields] OR 'thrombocytopenia'[MeSH Terms] OR 'thrombocytopenia'[All Fields]) OR ('neutropenia'[All Fields] OR 'neutropenia'[MeSH Terms] OR 'neutropenia'[All Fields]) OR ('haemoglobin'[All Fields] OR 'hemoglobins'[MeSH Terms] OR 'hemoglobins'[All Fields] OR 'hemoglobin'[All Fields]) OR ('blood platelets'[MeSH Terms] OR ('blood'[All Fields] AND 'platelets'[All Fields]) OR 'blood platelets'[All Fields] OR 'platelets'[All Fields]) OR ('febrile neutropenia'[MeSH Terms] OR ('febrile'[All Fields] AND 'neutropenia'[All Fields]) OR ('febrile neutropenia'[All Fields]))*. The databases were searched for articles published from inception to 23rd December 2017. Meeting abstracts without published full-text original articles other than letters/case reports/commentaries and articles not written in the English language were not eligible for this study.

2.2. Data extraction

The total number of patients treated with PD-(L)1 inhibitors, the number of patients with anaemia for all grades and for grade III or higher (G3-5), severe neutropenia (G3-5), febrile neutropenia and severe thrombocytopenia (G3-5) were collected from the eligible articles. Cases listed as both anaemia and haemoglobin decrease were included in the number of anaemia events. The trial phase, disease type and stage and types of specific agents, doses and frequency of drug administration were recorded. Treatment regimen was classified as PD-(L)1 inhibitor monotherapy or combination therapy. The data extraction were performed by one primary reviewer (F.P.) and then independently reviewed by two secondary reviewers (R.A. and S.B.) following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

2.3. Statistical analysis

We extracted the number of patients experiencing anaemia (primary end-point), neutropenia, febrile