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Original Research

Response rate as a potential surrogate for survival and efficacy in patients treated with novel immune checkpoint inhibitors: A meta-regression of randomised prospective studies

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Abstract ***Introduction:*** To assess the role of the tumour response rate (RR) after immune checkpoint inhibitors–based therapy as a potential surrogate end-point of progression-free survival (PFS) and overall survival (OS) in patients with solid tumours, we performed a trial-based meta-regression of randomised studies comparing different immune checkpoint inhibitors–based treatments.

Methods: The systematic literature search included the electronic databases and the proceedings of oncologic meetings. Treatment effects on PFS and OS were expressed as hazard ratios (HRs); treatment effects on RR were expressed as odds ratios (ORs). A weighted regression analysis was performed on log-transformed treatment effect estimates to test the association between treatment effects on the surrogate outcome and treatment effects on the clinical outcome.

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Results: Twenty-four trials, for a total of 11,894 patients, were included in the analysis. Using the complete set of data, the regression of either the log(HR) for PFS or the log(HR) for OS on the log(OR) for RR demonstrated weak associations ($R^2 = 0.47$; 95% confidence interval [CI], 0.03–0.77; $P = 0.001$; and $R^2 = 0.32$; 95% CI, 0.02–0.76; $P = 0.01$, respectively). The pre-planned analyses stratifying trials according to different type of disease and different mechanism of action of immune checkpoint inhibitors showed a very weak association of the RR with the OS for non–small cell lung cancer indicated and a modest association of the RR with the PFS for cytotoxic T lymphocyte–associated antigen 4 checkpoint inhibitors.
Conclusion: The results of the trial-based meta-regression analysis indicated a weak correlation between RR and OS, supporting future investigations to assess the surrogacy of RR in the patient treated with immune checkpoint inhibitors.

1. Introduction

Over the past years, the main role played by the host's immune system and the activation of the host's immune effectors against cancer was under a deep research focused on the discovery of the role of immunological agents that are able to directly or indirectly generate a potential immune response. Therefore, a new class of drugs targeting the tumour microenvironment has become available in clinic and has shown an unexpected efficacy [1]. The first identified target was the cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) receptor, and ipilimumab is the first human monoclonal antibody against CTLA-4 [2]. Recently, the discovery of new antigens as the programmed cell death 1 (PD-1) in activated T cells and its ligand PD-L1 in tumour cells are the targets for the immunotherapeutic agent as nivolumab, already tested in patients with various types of advanced cancer [3]. Moreover, also pembrolizumab, another checkpoint inhibitor, blocking the binding of PD-1 and PD-L1 as well as PD-L2, showed a clear efficacy in several solid tumours [4]. Interestingly, with the exception of ipilimumab, nivolumab and pembrolizumab seem to demonstrate objective response in solid tumours other than melanoma or renal cancer [4]. Owing to the important clinical impact in several malignancies, new immune checkpoint inhibitors are in the advanced stages of clinical development [4]. Recent evidences indicated checkpoint-blocking monoclonal antibodies not only represent a promising means to induce robust and durable responses when employed as single agents [4–8] but can also be harnessed to boost the activity of several therapeutic regimens [9]. In this scenario, the identification of a potential surrogate marker for survival in patients under treatment with novel immune checkpoint inhibitors would represent an important advance in the early identification of patients' response/resistance to a potential active therapy.

The assessment of the tumour change induced by the treatment is an important issue for the clinical evaluation of activity and efficacy of the administered therapy. The Response Evaluation Criteria in Solid Tumours (RECIST) is a set of published rules defining when tumours in cancer patients respond or not during treatment [10]. According to the RECIST criteria, the complete response and the partial response defined the tumour response rate (RR) in phase III trials. Although, in many clinical trials the tumour RR has been used as a marker to guide treatment decisions on individual patients, the overall survival (OS) remained as the main end-point for phase III trials and for the evaluation of treatment efficacy. To assess the role of RR as a potential surrogate of the clinical outcomes in patients under treatment with the novel immune checkpoint inhibitors, we performed a systematic literature search and a trial-based meta-regression analysis of randomised controlled trials comparing different immune checkpoint inhibitors in different solid tumours and the survival outcomes. The aim of this study was to assess whether the treatment effects on tumour burden are able to predict the long-term effects on survival of patients receiving immune checkpoint inhibitors.

2. Methods

We planned a literature-based meta-regression analysis of randomised controlled trials based on the use of the novel immune checkpoint inhibitors. The primary objective of the meta-analysis was the validation of the RR as a potential surrogate end-point for efficacy and survival meant as progression-free survival (PFS) or OS in patients with solid tumours receiving the new immune checkpoint inhibitors.

2.1. Identification of randomised trials

A systematic search of the literature was conducted to identify all randomised trials based on the use of the novel immune checkpoint inhibitors in solid tumours. Relevant publications from PubMed and the Central Register of Controlled Trials of the Cochrane Library were identified. The search was focused on terms describing novel immune checkpoint inhibitors; therefore, following medical subject heading terms were used: