Anti-Tumour Treatment

Comparison of efficacy of immune checkpoint inhibitors (ICIs) between younger and older patients: A systematic review and meta-analysis

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) rely on the presence of ongoing immune response to exert their antitumor effect. Little is known whether an age-related decline in immune function negatively influences antitumor response and in so doing diminishes the efficacy of ICIs in elderly subjects. We performed a meta-analysis to compare the efficacy of ICIs between younger and older patients.

Patients and methods: PubMed and the ASCO databases were searched up to September 2015. We included randomized controlled trials (RCTs) of ICIs (ipilimumab, tremelimumab, nivolumab and pembrolizumab) reporting subgroup comparison of overall survival (OS) and/or progression-free survival (PFS) based on age cutoffs. The summary hazard ratio (HR) and 95% confidence interval (CI) were calculated.

Results: A total of 5265 patients from nine RCTs of ICI were included. When patients are dichotomized into younger and older groups with an age cut-off of 65–70 years, ICIs improved OS in both younger (HR, 0.75; 95% CI, 0.68–0.82) and older (HR, 0.73; 95% CI, 0.62–0.87) groups. An improvement in PFS was observed in younger (HR, 0.58; 95% CI, 0.40–0.84) and older (HR, 0.77; 95% CI, 0.58–1.01) patients. Subgroup analyses according to ICI and tumor type showed a consistent survival benefit in both younger and older groups except for the subgroup of older patients treated in 4 trials of anti-programmed cell death protein-1 (PD-1) monoclonal antibody (HR, 0.86; 95% CI, 0.41–1.83).

Conclusions: A benefit in OS with ICIs was significant in both younger and older patients with a cut-off age of 65–70 years.

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Introduction

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein-1 (PD-1) are the two most well studied immunoregulatory checkpoint pathways in cancer [1]. They exert their function by restricting immune cell activation in distinct phases and anatomic locations of host antitumor response [2]. Various clinical-grade monoclonal antibody therapies have been developed to target these and other immune checkpoint proteins to enhance antitumor immune responses. The monoclonal antibodies (mAbs) against CTLA-4 and PD-1 have been the best studied immunotherapies so far and shown to improve survival outcomes in various randomized controlled trials [3–5]. The mechanism of action of CTLA-4 inhibitors involves abrogation of immune tolerance leading to increases in the number and repertoire of activated T cells. PD-1 inhibitors, on the other hand, re-stimulate previously primed T cells that have lost effector and proliferative function during the course of an immune response. Underlying host anti-tumor immune response is fundamental for clinical benefit from these agents [6]. Currently, the United States Food and Drug Administration (FDA) has approved ipilimumab, nivolumab, and pembrolizumab for patients with unresectable or distant metastatic melanoma. Nivolumab and pembrolizumab have been approved as a second-line treatment of patients with advanced non-small-cell lung cancer. Recently, the FDA approved has approved nivolumab as a treatment for patients with metastatic renal cell carcinoma following prior treatment with an anti-angiogenic therapy [7–9]. Additionally, tremelimumab, an anti-CTLA-4 mAb, has been granted orphan drug designation by the FDA for the treatment of patients with malignant mesothelioma [10].

The age-related decline in the immune system has been termed immunosenescence. Of note, immunosenescence may be, at least in part, associated with higher propensity to react to

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self-antigens (autoimmunity), reduced ability of the host to defend microbes and cancer (immunodeficiency), and dysregulation between different immune system components [11–13]. T cells, the primary effectors of antitumor response, undergo significant changes with age: their absolute numbers, in particular the naïve, CD8+ T cells decline with age in part due to thymic involution and contraction of lymphopoietic stem cells [14]. In addition to numeric defects, functional defects have been described, such deficiency in CD28 co-stimulation, upregulation of co-inhibitory immune checkpoints PD-1 and Tim-3 [15], diminution of intracellular signaling important for T-cell activation, decreased cytokine production and IL-2 signaling [16]. Since ICIs exert their antitumor effects through effector T-cells, immunosenescence may have a negative impact on the efficacy of ICIs in elderly cancer patients. The clinical efficacy of immune checkpoint inhibitors in elderly cancer patients has not been fully elucidated in previous clinical trials [3–5]. Therefore, we conducted a systemic review and study-level meta-analysis of randomized controlled trials to compare the efficacy of ICIs between younger and older patients.

Methods

Data source

This analysis was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [17]. We conducted an independent review of PubMed from January 1966 to September 2015. Search terms included "ipilimumab", "tremelimumab", "nivolumab", "pembrolizumab". The search was limited to randomized controlled trial. We searched abstracts and virtual meeting presentations utilizing the same search terms from the American Society of Clinical Oncology (ASCO) conferences held up to September 2015 to identify relevant studies. An independent search of the Web of Science, Embase, and Cochrane electronic databases was also performed to ensure that no additional studies were overlooked. In cases of duplicate publications, only the most complete, recent, and updated report of the study was included.

Study selection

Clinical trials that met the following criteria were included: (1) phase II and III trials in patients with cancer; (2) random assignment of participants to treatment with ICI or a control regimen which did not include an ICI; and (3) subgroup comparisons of overall survival (OS) and/or progression-free survival (PFS) based on age using a hazard ratio (HR). Independent reviewers (T.F.N and S.S.S) screened reports that included the key terms by their titles and abstracts for relevance. Then, full texts of the relevant articles were retrieved to assess eligibility. The references of relevant reports were also reviewed manually.

Data extraction

Two investigators (T.F.N and S.S.S) independently performed data extraction. Any discrepancies between reviewers were resolved by consensus. The following information was recorded for each study: first author's name, year of publication, trial phase, masking, underlying malignancy, treatment arms, number of patients available for analysis, age, follow-up duration, OS and PFS. The quality of included trials was rated using the 5-point Jadad scale, which is based on the reporting of randomization method, blinding method, and withdrawals and dropouts [18].

Statistical analysis

The primary objective of this study was to compare overall survival between younger and older patients treated with ICIs. The secondary objective was comparison of PFS between younger and older patients. The summary measures of OS and PFS were HRs and corresponding 95% CIs which were extracted from each study. Statistical heterogeneity in results between studies included in the meta-analysis was examined using Cochrane's Q statistic, and inconsistency was quantified with I^2 statistic [$100\% \times (Q - \text{df})/Q$], which estimates the percentage of total variation across studies due to heterogeneity rather than chance [19]. The assumption of homogeneity was considered invalid for P values less than 0.10. Summary HRs were calculated using random-effects or fixed-effects models depending on the heterogeneity of included studies. When substantial heterogeneity was not observed, the pooled estimate calculated based on the fixed-effects model was reported by using inverse variance method. When substantial heterogeneity was observed, the pooled estimate calculated based on the random-effects model was reported by using the DerSimonian and Laird method, which considers both within-study and between-study variations [20]. Differences in the HRs between the younger and older groups were assessed using Q statistics. Pre-specified exploratory subgroup analyses were performed with regard to the HRs for OS according to ICI type (anti-CTLA-4 mAbs: ipilimumab and tremelimumab vs. anti-PD1 mAbs: nivolumab and pembrolizumab) and tumor type (melanoma vs. others). We evaluated publication bias regarding the primary outcome using funnel plots and with the Begg and Egger tests [21,22]. A two-tailed P value of less than 0.05 was considered statistically significant. Statistical analyses were performed by using the comprehensive meta-analysis program (Version 2, Biostat, Englewood, NJ, USA).

Results

Search results and patient characteristics

Our search strategy yielded 199 potentially relevant publications in the PubMed and ASCO databases. 190 publications were excluded. Our selection process and reasons for study exclusion are shown in Fig. 1. A total of eight phase III and one phase II randomized clinical trials were considered eligible for the meta-analysis. A total of 5265 patients (ICIs: 2925; controls: 2340) were included in the analysis from three ipilimumab trials, one tremelimumab trial, four nivolumab trials and one pembrolizumab trial. The underlying malignancies included were melanoma (5 trials) non-small cell lung cancer (2 trials), prostate cancer (1 trial) and renal cell carcinoma (1 trial). Eight trials used 65 years and one trial used 70 years as an age cut-off to conduct subgroup analyses. The baseline characteristics in each trial are presented in Table 1.

Primary outcome: overall survival

A total of 4725 patients from eight trials were included in the analysis of HRs for OS. The patients were dichotomized into younger and older groups with an age cut-off of 65–70 years. For younger patients, the pooled HR for OS showed significant difference between ICIs and controls (HR, 0.75; 95% CI, 0.68–0.82; $P < 0.001$; Fig. 2). The fixed-effects model was used because there was no significant heterogeneity ($Q = 10.46$; $P = 0.23$; $I^2 = 23.55$). For older patients, ICIs also significantly improved OS (HR, 0.73; 95% CI, 0.62–0.87; $P < 0.001$) in comparison with controls. The test for heterogeneity was significant and a random-effects model was used ($Q = 23.00$; $P = 0.03$; $I^2 = 47.83$). There was no statistically