Risk of Musculoskeletal Complications in Cancer Patients Treated with Nivolumab

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Abstract

Object: We performed a meta-analysis of the risk of selected musculoskeletal toxicities associated with the PD-1 inhibitor Nivolumab versus other drugs.

Methods: Several databases were searched. We assess the relevant articles and relative risks (RRs) with 95% confidence intervals (95% CIs) were estimated regarding the risk of arthralgia, asthenia, myalgia and extremity pain and Nivolumab versus control. Heterogeneity, sensitivity analysis and publication bias of the included studies were also analyzed.

Results: There were 5 eligible studies, including 2220 patients that were considered in the present meta-analysis. The RRs of arthralgia, asthenia, myalgia and extremity pain were 1.116 (95% CI: 0.669, 1.860; p=0.675), 0.846 (95% CI: 0.657, 1.090; p=0.197), 0.658 (95% CI: 0.141, 3.062; p=0.593), 1.037 (95% CI: 0.647, 1.662; p=0.882), respectively.

Conclusion: Our results suggested that PD-1 inhibitor Nivolumab was not associated with an increased risk of musculoskeletal toxicities including arthralgia, asthenia, and myalgia and extremity pain compared with control.

Keywords: Musculoskeletal complications; Cancer patients; Nivolumab; Meta-analysis

Introduction

Immunotherapy has been considered to be one of the most important breakthroughs in cancer treatments in the last decade. Immune checkpoint inhibitors against T lymphocyte antigen-4 (CTLA-4) and programmed death 1 (PD-1) topped the list of the most noticeable and encouraging cancer therapies [1,2]. As PD-1 is able to limit T-cells’ cytokine secretion, function and proliferation especially in cancer-bearing hosts or chronic viral infections, PD-1 inhibitors have been developed and have achieved many achievements [3]. On the surface of tumor-infiltrating T-cells and circulating T-cells from melanoma patients, high level of PD-1s have been tested, indicating that PD-1 inhibition might prevent cancer-correlated T-cells’ exhaustion [4]. The first batch of PD-1 inhibiting agents includes pembrolizumab (also named lambrolizumab) and Nivolumab. Nivolumab, scientifically named BMS-936558/MDX-1106, is a fully human immunoglobulin G4 (IgG4) monoclonal PD-1-blocking antibody that abrogates its interaction with PD-L2 and PD-L1 [5]. In an amount of phase III studies regarding non-small cell lung cancer (NSCLC), renal cancer and melanoma, Nivolumab administration has shown survival benefit. Because of this, in 2015, US Food and Drug Administration (FDA) approved its marketing [6]. Different from traditional antineoplastic chemotherapies, Nivolumab can potentially lead to some side-effects, such as gastrointestinal, hepatotoxic, orthopedic and mucocutaneous toxicities [7]. Nevertheless, large variations in the incidence of musculoskeletal adverse events among clinical trials such as asthenia, arthralgia, myalgia, et al still exist [8-10]. Until now, there is still no comprehensive review and analysis to synthesize those data, thus the overall musculoskeletal risks caused by Nivolumab needs to be further clarified. We conducted a meta-analysis of randomized clinical trials to determine the overall risk of musculoskeletal disorders in cancer patients treated with Nivolumab.

Material and Methods

Search strategy and study selection

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, two authors independently searched the database of Embase, PubMed, Chinese National Knowledge Infrastructure (CNKI), and Web of Knowledge (time: September 1st, 2016) to enroll studies which met the criteria. The search term was “Nivolumab”. Search results were limited to randomized clinical studies without language limitation. If there were duplicate literatures, only the most updated and complete ones were adopted. If there were disagreements between the two investigators, a discussion would be carried out or a third investigator would...
intervene. Inclusion criteria and exclusion criteria have been listed in (Table 1). We also reviewed related references to find out other potentially eligible studies.

Figure 1: Literature search and selection of articles.

Data extraction and clinical endpoints

We extracted the data independently. We generally gathered the following data: author name, publication year, phase of the trial, total number of patients enrolled for analysis, number of events for inclusion. We also reviewed related references to find out other potentially eligible studies.

Table 1: Inclusion and exclusion criteria for study selection in this meta-analysis.

**Data synthesis**

Differences were expressed as RRs with 95% CIs. The Labbe plot, I2 test and Cochran’s Q-test (Table 2) were all conducted to estimate the heterogeneity among the studies [11,12]. In case no evidence of statistical heterogeneity was detected, we chose to use a fixed-effects model. Otherwise, Laird’s and DerSimonian’s random-effects model would be adopted. To access the stability of the pooled values, we also performed sensitivity analyses (explanation in Table 2) [12]. Potential publication bias was assessed by contour-enhanced funnel plots [13] (Table 2). Since only 5 studies were included, meta-regression analyses were not performed. P<0.05 was deemed as statistical significance. The statistical analysis was done through Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK) and STATA 13.0 (StataCorp LP, College Station, TX, USA) software.

Table 2: The statistical methods used in this meta-analysis and their explanation.
Results

Search results and characteristics of the studies

The article search process was performed as presented in (Figure 1). A total of 5 articles involving 2220 patients eventually met the inclusion criteria [8-10,14,15]. All the 5 studies were written in English and were randomized phase III trials. Four studies were done in the US [8-10,14] and 1 in France [15]. Their baseline characteristics including treatment arms, interventions and clinical indications are shown in (Table 3).

| Study   | Year | Country | Study type | Treatment arms                                                                 | Indication                                                                                                                                  | Arthralgia | Asthenia | Myalgia | Extremity pain |
|---------|------|---------|------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------|----------|---------|---------------|
| Robert  | 2014 | France  | Phase III  | Arm A: Nivolumab 3 mg/kg of body weight every 2 weeks (206 pts) Arm B: dacarbazine (205 pts) | Stage III or IV unresectable melanoma without a BRAF mutation                                                                             | 12 (5.8%)  | 21 (10.2%)| 9 (4.4%)| 6 (2.9%)     |
| Weber   | 2015 | USA     | Phase III  | Arm A: Nivolumab 3 mg/kg of body weight every 2 weeks (288 pts) Arm B: investigator choice chemotherapy (102 pts) | Patients with advanced melanoma who progressed after anti-CTLA-4 treatment                                                               | 14 (5.2%)  | 12 (11.7%)| -       | -             |
| Larkin  | 2015 | USA     | Phase III  | 945 patients were randomized in a 1:1:1 fashion into: 1) Nivolumab 3 mg/kg combined with placebo (316 pts) 2) Ipilimumab (3 mg/kg) combined with Nivolumab (1 mg/kg) (314 pts) 3) Ipilimumab (3 mg/kg) combined with placebo (315 pts) | Advanced melanoma                                                                                                                          | 24 (7.7%)  | 19 (6.1%) | -       | -             |
| Borghaei| 2015 | USA     | Phase III  | Arm A: Nivolumab 3 mg/kg of body weight every 2 weeks (292 pts) Arm B: docetaxel (290 pts) | Advanced non squamous cell NSCLC                                                                                                          | 46 (16%)   | 32 (12%) | 18 (6%) | 27 (9%)       |
| Brahmer | 2015 | USA     | Phase III  | Arm A: Nivolumab 3 mg/kg of body weight every 2 weeks (131 pts) Arm B: docetaxel (129 pts) | Advanced squamous cell NSCLC                                                                                                              | 7 (5%)     | 9 (7%)   | 13 (10%)| 2 (2%)        |

CTLA-4: Cytotoxic T Lymphocyte Antigen-4; NSCLC: Non-Small Cell Lung Cancer; BRAF: B-Raf.

Table 3: Baseline characteristics of included studies comparing Nivolumab to other drugs.

Quality of the included studies

(Table 4) shows various items of the Jadad scale for all included literatures, including blindings, randomizations and accounts of included patients in addition to the overall score [16].

| Study   | Year | Country | Study type | Randomization | Blinding | An account of all patients | Overall score |
|---------|------|---------|------------|---------------|----------|---------------------------|---------------|
| Robert  | 2014 | France  | Phase III  | 2             | 2        | 1                         | 5             |
| Weber   | 2015 | USA     | Phase III  | 2             | 0        | 1                         | 3             |
| Larkin  | 2015 | USA     | Phase III  | 2             | 2        | 1                         | 5             |
| Borghaei| 2015 | USA     | Phase III  | 2             | 0        | 1                         | 3             |
| Brahmer | 2015 | USA     | Phase III  | 2             | 0        | 1                         | 3             |

Table 4: Jadad quality assessment of the included studies.
Meta-analysis regarding nivolumab and musculoskeletal toxicities

Arthralgia was reported in all 5 studies and it ranged from 11 to 51%; asthenia and myalgia were reported in 3 out of the 5 studies and they ranged from 3 to 32% and 3 to 32%, respectively; Extremity pain was reported in 2 out of the 5 studies and it ranged from 1 to 16%. A meta-analysis of the OR of all-grade adverse events was performed on the included randomized trials. Take arthralgia as an example. From the Labbe figure (Figure 2A), we can see the points did not present as a linear distribution, which can be taken as evidence of heterogeneity among these studies (Q=10.16, d.f.=4, I²=95.8%, p=0.038). Consequently, we summarized the data with a random effects model. As revealed in (Figure 3A), the forest plot demonstrated that Nivolumab administration did not increase the risk of arthralgia (RR 1.116, 95% CI 0.669, 1.860; p=0.675). We also tested the correlation between the risk of arthralgia, asthenia, myalgia and extremity pain and Nivolumab versus other drugs on the according effect models. The results also suggest no significant differences (asthenia: RR 0.846, 95% CI 0.657, 1.090; p=0.197; myalgia: RR 0.658, 95% CI 0.141, 3.062; p=0.593; extremity pain: RR 1.037, 95% CI 0.647, 1.662; p=0.882) as shown in (Figures 3B-3D).

Sensitivity analysis and publication bias

To access if a single literature can affect the final RRs, each individual study was removed one time and re-pool the data. The analysis results demonstrated that the pooled RRs were not affected by deleting every single study (Figures 2D-2F). The contour-enhanced funnel plots were employed to reveal the publication bias, showing that the studies had missing areas for high statistical significance (in the right-hand side of the plot), indicating no publication bias in the study (Figures 2G-2I). The results of our study should be interpreted with caution because the meta-analysis is at a study level and thus limiting variables at patient levels might not be worked out. So, we couldn't confirm if there are any additional potential risk factors correlated to developments of musculoskeletal toxicities.

Discussion

To the best of our knowledge, this is the most updated meta-analysis to provide an evaluation of selected musculoskeletal toxicities including arthralgia, asthenia, myalgia and extremity pain in patients with solid tumors receiving Nivolumab. Our analysis of data from 5 III randomized controlled trials did not demonstrate any increased or decreased risks of these musculoskeletal disorders with Nivolumab treatment compared with control. Normally, T-cells have the capacity to attack cancer cells; meanwhile, T-cells have to be regulated properly through certain inhibitory checkpoints to be controlled not to attack normal cells and normal tissues [17]. According to this theory, inhibiting these checkpoints is likely to activate T-cells and lead them to stronger anticancer responses [18]. At the moment, PD-1 as an inhibitory receptor, is one of the most fashionable and hottest research directions in the cancer immunotherapy field [2]. Its antagonist Nivolumab has been developed as a US-FDA approved anticancer drug for melanomas, which is based on the findings of a mount of Phase II–III studies [6]. Moreover, Nivolumab has been evaluated for its effects on anti-gastrointestinal cancer, prostate cancer and lung cancer.
Generally, if studies appear to be missing in areas of low statistical significance, then it is very possible that the asymmetry is due to publication bias. Conversely, if the area where studies are perceived to be missing are areas of high statistical significance, then publication bias isn’t the cause of funnel asymmetry [19]. In the present meta-analysis, the funnel plot indicated no publication bias.

The musculoskeletal adverse effects have been regarded as an emerging reason for treatment discontinuation or interruption in some studies. Although hematological toxicities are not common, at present no effective methods have been developed to predict high-risk patients, hence careful monitoring of laboratory and clinical parameters being necessary. Hematological toxicities have been reported also in a number of other targeted anticancer therapeutics and have been linked to noncompliance with many of them [7-10,14,15]. Therefore, we combined Wanfang, PubMed, Google Scholar, Embase, Sinomed and CNKI databases to analyze the correlation between the risk of arthralgia, asthenia, myalgia and extremity pain and Nivolumab versus other drugs systematically. The results of our study demonstrated that in comparison with controls, Nivolumab did not significantly increased the risk of selected musculoskeletal toxicities (arthralgia: RR 1.116, 95% CI 0.669, 1.860; p=0.675; asthenia: RR 0.846, 95% CI 0.657, 1.090; p=0.197; myalgia: RR 0.658, 95% CI 0.141, 3.062; p=0.593; extremity pain: RR 1.037, 95% CI 0.647, 1.662; p=0.882).

Conclusions

Summarily, our analysis supported that PD-1 inhibitor Nivolumab did not cause an increased or decreased risks of musculoskeletal toxicities including arthralgia, asthenia, myalgia and extremity pain in patients with solid tumors compared with control. These outcomes indicated that in term of musculoskeletal side effects, Nivolumab is safe.

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