Review Article

Therapeutic effects and associated adverse events of PD-1 and CTLA-4 pathway inhibitors in the treatment of non-small-cell lung cancer: meta-analyses of clinical phase II/III randomized controlled trials

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Abstract: Objective: To summarize and compare the therapeutic efficacy of programmed death 1 (PD-1) and cytotoxic T lymphocyte associated antigen 4 (CTLA-4) pathway inhibitors in the treatment of non-small-cell lung cancer (NSCLC). Methods: Traditional and network meta-analysis of clinical phase II/III randomized controlled trials of PD-1 and CTLA-4 pathway inhibitors vs. controls (general chemotherapy or best support therapy) in the treatment of NSCLC was performed by RevMan and ITC programs. The data of progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and grade 3/4 AE were extracted to evaluate the prognosis, tumor responses, and toxicity, respectively. Results: Among patients with NSCLC, when compared with controls, PD-1 pathway inhibitors had longer median OS, higher ORR, and lower incidence of grade 3 or 4 AE; further CTLA-4 pathway inhibitors had higher ORR. When compared with CTLA-4 pathway inhibitors, PD-1 pathway inhibitors had significant higher OS and lower incidence of grade 3 or 4 AE. Conclusion: Because the PD-1 pathway inhibitors have more advantages in patients’ survival, tumor response, and adverse events than CTLA-4 pathway inhibitors and traditional treatment, this agents could prioritize to use for the treatment of NSCLC.

Keywords: Programmed death 1 (PD-1), cytotoxic T lymphocyte associated antigen 4 (CTLA-4), non-small-cell lung cancer (NSCLC), meta-analysis

Introduction

Non-small-cell lung cancer (NSCLC) accounted for about 85% of all lung cancers [1]. As a class, NSCLCs are relatively insensitive to chemotherapy compared to small cell carcinoma [2]. However, the efficacy of traditional chemotherapy for advanced NSCLC over the last decade has been modest [3]. Molecularly targeted therapy, a major modalities of medical treatment, which developed in the recent years, has benefited to a small proportion of patients with NSCLC whose tumors contain anaplastic lymphoma kinase (ALK) gene rearrangements or epidermal growth factor receptor (EGFR) mutations [4]. Unfortunately, the agents of molecularly targeted therapy have been evaluated in clinical trials with limited success, a large part of patients with advanced NSCLC still die within one year of diagnosis [5].

Recent cancer molecularly targeted therapy efforts have focused on immune checkpoint targeted inhibitors, which are considered as the “brakes” on immune system with the goal of inducing immune cell proliferation and activation against cancer cells [6, 7]. Cytotoxic T lymphocyte associated antigen 4 (CTLA-4) was the first immune checkpoint targeted therapeutically [8]. Previous phase III trials have demonstrated that CTLA-4 antagonists have definite effects on improving the overall survival (OS) of patients with advanced melanoma [9, 10]. For NSCLC, CTLA-4 antagonists have shown minimal single-agent activity [11]; however, when combined with cytotoxic chemotherapy, these agents may have more promising results [12].

The programmed death 1 (PD-1) is an immune checkpoint receptor expressed on activated T
cells [13]. Nivolumab and Pembrolizumab, fully human IgG4 PD-1 immune checkpoint inhibitor antibodies, were previously reported in the treatment of NSCLC [14, 15]. Clinical phase I and II trials of these agents suggest that second line treatment with these agents has clinically meaningful activity and a manageable safety profile in previously treated patients with advanced, refractory NSCLC [5, 16]. Moreover, the Atezolizumab, a fully humanized, engineered monoclonal antibody of IgG1 isotype against the protein PD-L1, is currently in clinical trials as an immunotherapy for several types of solid tumors [17, 18]. For NSCLC, a second line treatment prolonged the median overall survival for patients with locally advanced/metastatic NSCLC to 16 months [19] safety and predictive biomarkers of the engineered antibody MPDL3280A (anti-PDL1).

To date, the evidence of the efficacy of CTLA-4 inhibitors on NSCLC is still limited. Further, although the PD-1 and PD-L1 inhibitors, such as Nivolumab [20, 21], Pembrolizumab [22], and Atezolizumab [23], exhibited significant advantages on the tumor response and survival for patients with NSCLC, the conclusions of these clinical trials were not entirely consistent. In addition, there is still lack of the direct evidence of the efficacy difference between CTLA-4 and PD-1 pathway inhibitors on NSCLC. In this scenario, two traditional meta-analyses of clinical phase II/III randomized controlled trials was performed to evaluate the therapeutic effect and associated adverse events of the CTLA-4 and PD-1 inhibitors for NSCLC, respectively. Furthermore, we conducted a network meta-analysis for detecting the efficacy and safety difference between these two agents.

Materials and methods

Study design

This study was meta-analyses based on data collected from previous clinical phase II/III randomized controlled trials (RCTs) of immunotherapy with PD-1 or CTLA-4 pathway inhibitors versus traditional chemotherapies or conservative treatments for patients with NSCLC. Two reviewers (HZ, YY) selected and reviewed the evidence respectively. Dilemmas were handled through group discussion.

Search strategy

Studies were search among PubMed/Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) by using the terms: “programmed death-1/PD-1 inhibitor” OR “programmed death-1 ligand/PD-L1 inhibitor” OR “programmed death-1/PD-1 agent” OR “programmed death-1 ligand/PD-L1 agent” OR “Nivolumab” OR “Pembrolizumab” OR “Atezolizumab” OR “cytotoxic T lymphocyte associated antigen 4/CTLA-4 inhibitor” OR “cytotoxic T lymphocyte associated antigen 4/CTLA-4 inhibitor agent” OR “Tremelimumab” OR “Ipilimumab” AND “non-small-cell lung cancer/NSCLC” AND “randomized trials (random* trials)” in title and abstract. The databases were searched for studies published till July 2016. Only trails published in English were involved. Reference lists of related articles were manually checked to search for additional eligible publications. All references of relevant articles were scanned and all additional studies of potential interest were retrieved for further analysis.

Selection criteria

Eligible trails have to meet the following criteria: (1) patients involved were diagnosed with NSCLC through cytological diagnosis or pathological diagnosis; (2) clinical phase II/III randomized controlled trials using PD-1 or CTLA-4 pathway inhibitors versus traditional chemotherapies or conservative treatment to treat NSCLC; (3) individual use traditional chemotherapies or conservative treatment was used as control. The exclusion criteria is: (1) trails not in RCT or clinical phase II/III; (2) without adequate data for use; (3) the former paper of the duplicated studies.

The bias risk of included publications was evaluated based on Cochrane handbook for systematic reviews of interventions, version 5.1.0 [24]. The major quality components include “(1) sequence generation of the allocation; (2) allocation concealment; (3) blinding of participants, personnel, and outcome assessors; (4) incomplete outcome data; (5) selective outcome reporting; and (6) other sources of bias” [24]. Trails were classified into three levels according to the bias risk. Trials with appropriate and sufficient support of index of outcome assessment that with minimal risk of bias are classified into A level; trials with one or more high or unclear risk for bias among the quality components and with middle level risk of bias are in B level; trials with three or more high or unclear risk for bias among the quality compo-
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Data extraction

Two reviewers (HZ, BZ) separately and independently exacted data from the trials. Disagreements were handled with consensus. All data were checked for internal consistency. The trials were identified with the first author and the year of publication. For the trials that did not report the required data to determine the outcomes, the reviewers contacted the authors to obtain required information. The baseline information of patients and details of intervention of each trial were extracted to assess the heterogeneity. The prognosis data including progression free survival (PFS) and overall survival (OS) were evaluated in the meta-analysis. The tumor responses assessed by overall response rate (ORR). In addition, toxicity data, typically the number of patients who suffered grade 3/4 adverse events (AE) were retrieved and extracted to assess the adverse effect of treatments.

Statistical analysis

Traditional meta-analysis was conducted with Review Manager5.3 (RevMan5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Odds ratio (OR) or Hazard ratio (HR) was used for evaluation and 95% confidence intervals (CI) was calculated for each estimate. \( P \leq 0.05 \) was used to denote statistical significance. Heterogeneity of the results of the trials was assessed with the \( I^2 \) statistic by using the chi-square (\( X^2 \)) test at \( \alpha = 0.1 \) [25]. Primary assessment was done with a fixed model. When \( P \geq 0.05 \) and \( I^2 \leq 50\% \), it was considered the trials are without heterogeneity and a fixed effect model was used to perform meta-analysis. When \( P < 0.05 \) and \( I^2 > 50\% \), it was considered that the trials are with significant heterogeneity [26]. The source of the heterogeneity was further analyzed. If there was no significant clinical heterogeneity, a secondary confirmatory analysis was done with a random effects model. Otherwise, descriptive analysis was performed. Where necessary, sensitivity analyses were performed to test the stability of identified outcomes. The network meta-analysis was conducted with Indirect Treatment Comparison (ITC) software (https://www.cadth.ca/resources/itc-user-guide/). Funnel plots were performed to evaluate the possibility of publications bias.

Results

Literature search

The whole search process is as described in the QUOROM-type flowchart (Figure 1). Overall six studies [11, 12, 20-23] with 2466 patients were included. The trials were all multicenter, randomized, controlled and phase II or III trails. Four studies [20-23] assessed the PD-1 pathway inhibitors (Nivolumab, Pembrolizumab, or Atezolizumab) versus Controls (Docetaxel), and two studies [11, 12] evaluated CTLA-4 pathway inhibitors (Tremelimumab or Ipilimumab plus general chemotherapy) versus Controls (best supportive care or general chemotherapy). The methodological details relevant to bias and characteristics of the selected studies are described in Table 1.

Progression free survival

Four studies [20-23] evaluated the median PFS of patients underwent PD-1 pathway inhibitor treatment, and only one [12] assessed the median PFS of patients underwent CTLA-4 pathway inhibitor treatment. According to the traditional meta-analysis, when compared with controls, both the PD-1 pathway inhibitors (HR=0.98, 95% CI: 0.77 to 1.25, \( P = 0.87 \), Figure 2) and CTLA-4 pathway inhibitors (HR=1.28, 95% CI: 0.99 to 1.67, \( P = 0.06 \), Figure 2) had the similar median PFS among patients with...
<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial name</th>
<th>Phase Line of treatment</th>
<th>Group</th>
<th>Drugs and dose</th>
<th>Patients (n)</th>
<th>Sex (M; n)</th>
<th>Median age (years)</th>
<th>Median OS (months)</th>
<th>Median PFS (months)</th>
<th>Quality level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borghaei 2015</td>
<td>CheckMate 057</td>
<td>III Second/Third</td>
<td>Experimental</td>
<td>Nivolumab 3 mg/kg</td>
<td>292</td>
<td>151</td>
<td>61</td>
<td>12.2</td>
<td>2.3</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>Docetaxel 75 mg/m²</td>
<td>290</td>
<td>168</td>
<td>64</td>
<td>9.4</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Brahmer 2015</td>
<td>CheckMate 017</td>
<td>III Second</td>
<td>Experimental</td>
<td>Nivolumab 3 mg/kg</td>
<td>135</td>
<td>111</td>
<td>62</td>
<td>9.2</td>
<td>3.5</td>
<td>B</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>Docetaxel 75 mg/m²</td>
<td>137</td>
<td>97</td>
<td>64</td>
<td>6.0</td>
<td>2.8</td>
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<tr>
<td>Herbst 2016</td>
<td>Keynote 010</td>
<td>II/III Second</td>
<td>Experimental</td>
<td>Pembrolizumab 2 mg/kg</td>
<td>345</td>
<td>212</td>
<td>63</td>
<td>10.4</td>
<td>3.9</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>Pembrolizumab 10 mg/kg</td>
<td>346</td>
<td>213</td>
<td>63</td>
<td>12.7</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Fehrenbacher 2016</td>
<td>POPLAR</td>
<td>II Second</td>
<td>Experimental</td>
<td>Atezolizumab 1200 mg</td>
<td>144</td>
<td>93</td>
<td>62</td>
<td>12.6</td>
<td>2.7</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>Atezolizumab 75 mg/m²</td>
<td>143</td>
<td>76</td>
<td>62</td>
<td>9.7</td>
<td>3.0</td>
<td></td>
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<td>Zatloukal 2009</td>
<td></td>
<td>II Second</td>
<td>Experimental</td>
<td>Tremelimumab 15 mg/kg</td>
<td>44</td>
<td>Not state</td>
<td>Not state</td>
<td>Not state</td>
<td>Not state</td>
<td>B</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>Best supportive care</td>
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<td>Lynch 2012</td>
<td></td>
<td>II First</td>
<td>Experimental</td>
<td>Concurrent Ipilimumab 10 mg/kg + Paclitaxel 175 mg/m² + Carboplatin AUC 6</td>
<td>70</td>
<td>53</td>
<td>59</td>
<td>9.7</td>
<td>4.1</td>
<td>B</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Experimental</td>
<td>Phased Ipilimumab 10 mg/kg + Paclitaxel 175 mg/m² + Carboplatin AUC 6</td>
<td>68</td>
<td>49</td>
<td>61</td>
<td>12.2</td>
<td>5.1</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>Paclitaxel 175 mg/m² + Carboplatin AUC 6 + Placebo</td>
<td>66</td>
<td>49</td>
<td>62</td>
<td>8.3</td>
<td>4.2</td>
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</table>
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NSCLC. Furthermore, according to the network meta-analysis, the PD-1 and CTLA-4 pathway inhibitors had similar median PFS (HR=0.77, 95% CI: 0.54 to 1.09, \( P = 0.14\), Table 2). The symmetric funnel plots suggested the non-existence of publication bias.

**Table 2.** Network meta-analysis of PFS, OS, ORR, and 3/4 AE for PD-1 compared with CTLA-4 pathway inhibitors

<table>
<thead>
<tr>
<th>Variable</th>
<th>PD-1 pathway inhibitors</th>
<th>CTLA-4 pathway inhibitors</th>
<th>Pooled HR/OR</th>
<th>95% CI</th>
<th>( P )-value</th>
<th>Association</th>
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<tr>
<td></td>
<td>No. of events/deaths</td>
<td>Total No. of patients</td>
<td>No. of</td>
<td>Total No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>events/deaths</td>
<td>of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>1069*</td>
<td>1262</td>
<td>114</td>
<td>138</td>
<td>0.766</td>
<td>0.536-1.093</td>
</tr>
<tr>
<td>OS</td>
<td>787*</td>
<td>1262</td>
<td>102</td>
<td>138</td>
<td>0.620</td>
<td>0.458-0.839</td>
</tr>
<tr>
<td>ORR</td>
<td>233</td>
<td>1262</td>
<td>39</td>
<td>182</td>
<td>0.756</td>
<td>0.336-1.702</td>
</tr>
<tr>
<td>3/4 AE</td>
<td>111</td>
<td>903</td>
<td>85</td>
<td>182</td>
<td>0.033</td>
<td>0.003-0.443</td>
</tr>
</tbody>
</table>

*acquired from Kaplan-Meier curves.

**Figure 2.** Meta-analysis of effect in median PFS.

**Figure 3.** Meta-analysis of effect in median OS.

*Overall survival*

Four studies [20-23] evaluated the median OS of patients underwent PD-1 pathway inhibitor treatment, and only one [12] assessed the median OS of patients underwent CTLA-4 path-
way inhibitor treatment. According to the traditional meta-analysis, when compared with controls, the PD-1 pathway inhibitors had longer median OS among patients with NSCLC (HR=0.67, 95% CI: 0.61 to 0.75, \(P<0.01\), Figure 3), however, the CTLA-4 pathway inhibitors had the similar median OS among patients with NSCLC (HR=1.08, 95% CI: 0.81 to 1.43, \(P=0.62\), Figure 3). Furthermore, according to the network meta-analysis, the PD-1 pathway inhibitors had significantly longer median OS among patients with NSCLC than CTLA-4 pathway inhibitors (HR=0.62, 95% CI: 0.46 to 0.84, \(P<0.01\), Table 2). Publication bias did not exist.

**Overall response rate**

Four studies [20-23] evaluated the overall response rate of patients underwent PD-1 pathway inhibitor treatment, and two [11, 12]
assessed the overall response rate of patients underwent CTLA-4 pathway inhibitor treatment. According to the traditional meta-analysis, both PD-1 (OR=1.86, 95% CI: 1.44 to 2.40, \( \text{P}<0.01 \), Figure 4) and CTLA-4 (OR=2.46, 95% CI: 1.14 to 5.32, \( \text{P}=0.02 \), Figure 4) pathway inhibitors had a significantly higher ORR than controls. However, according to network meta-analysis, the PD-1 and CTLA-4 pathway inhibitors had similar ORR (OR=0.76, 95% CI: 0.34 to 1.70, \( \text{P}=0.50 \), Table 2). Publication bias did not exist.

**Adverse effect**

Four studies [20-23] evaluated the adverse events of patients underwent PD-1 pathway inhibitor treatment, and two [11, 12] assessed the adverse events of patients underwent CTLA-4 pathway inhibitor treatment. According to the traditional meta-analysis, compared with controls, the PD-1 pathway inhibitors had significantly lower incidence of grade 3 or 4 adverse events among patients with NSCLC (OR=0.15, 95% CI: 0.07 to 0.32, \( \text{P}<0.01 \), Figure 5), however, the CTLA-4 pathway inhibitors had a similar incidence of grade 3 or 4 adverse events (OR=4.50, 95% CI: 0.38 to 53.33, \( \text{P}=0.23 \), Figure 5). Furthermore, according to the network meta-analysis, the PD-1 pathway inhibitors had significantly lower incidence of grade 3 or 4 adverse events among patients with NSCLC than CTLA-4 pathway inhibitors (OR=0.03, 95% CI: 0.01 to 0.44, \( \text{P}<0.01 \), Table 2). Publication bias did not exist.

**Discussion**

This meta-analysis aimed to summarize and compare the therapeutic effects and associated adverse events of PD-1 and CTLA-4 pathway inhibitors in the treatment of NSCLC by systematic evaluation of six clinical phase II/III randomized controlled trials. We demonstrates that patients use of PD-1 pathway inhibitors have the advantages in the OS, tumor response and grade 3 or 4 AE when compared with traditional chemotherapy; however, patients use of CTLA-4 pathway inhibitors only have a significant advantage on tumor response when compared with traditional therapy. In addition, our network meta-analysis further revealed that patients use of PD-1 pathway inhibitors have more advantages in OS and 3 or 4 AE than patients use of CTLA-4 pathway inhibitors.

Although the treatment options for NSCLC are increasing year by year, the improvement of patients’ survival is still negligible, except among patients with EGFR, ALK, BRAF or KRAS mutations [27]. Docetaxel is considered to be the standard agent for the second or later lines to treat the patients with NSCLC, but the overall efficiency and safety are far from satisfactory [28]. During recent years, scholars are considering immune checkpoint inhibitors including the CTLA-4 and PD-1 pathway inhibitors to treat NSCLC [29]. In various clinical trials of CTLA-4 and PD-1 pathway inhibitors, the later agents may have gained more remarkable attentions due to their impressive efficacy and safety in the clinical trials [30], yet the direct or indirect evidences were still absence. To our knowledge, the present study provides the first evidence regarding the efficacy and safety of PD-1 versus CTLA-4 pathway inhibitors.

In our traditional meta-analyses, the therapeutic effects of PD-1 pathway inhibitors for NSCLC are mainly reflected in terms of prolonged OS, increased ORR, and decreased grade 3/4 AE, which are mainly consistent with the results of previously clinical phase II/III randomized controlled trials [20-23]. In the same time, the heterogeneities also exists in this meta-analysis. It is known, PD-L1 is regarded as the logical biomarker on which to guide molecular selection for NSCLC receiving agents of PD-1/PD-L1 inhibitors that because the individuals with high PD-L1 expression have higher sensitivity to these agents [31]. Hence, we inferred that the heterogeneity may result from the different proportions of patients with high PD-L1 expression during the including studies. In addition, we should note that the meta-analytic results of CTLA-4 pathway inhibitors are consistent with the outcomes of the study by Lynch et al. [12]. This is because the weight of this study was 64.8% to 100% in the meta-analysis.

In clinical practice, the balance between therapeutic effect and associated adverse events should be carefully evaluated before final selection. In our meta-analyses, due to the impressive efficacy and safety of PD-1 pathway inhibitors, this agents rather than CTLA-4 pathway inhibitors could prioritize to use for the treatment of NSCLC. The major limitation of this study is the small number of studies involved and the inconsideration of PD-L1 expression.
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Therefore, more studies with stratified analysis of PD-L1 expression and large sample size or update data are required to further identify the clinical values of PD-1 pathway inhibitors in the treatment of NSCLC.

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Disclosure of conflict of interest

None.

Authors’ contribution

Author HZ and XH designed the study. HZ wrote the protocol and the first draft of the manuscript. Author HZ, YY managed the literature searches. Author HZ and BZ finished the data extraction. Author YY and SH undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

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