Atezolizumab Plus Chemotherapy Vs Chemotherapy Alone for Non-small Cell Lung Cancer: A Meta-analysis of Different PD-L1-expression Levels

Zhang Hong
hengshui people hospital
Zhong Xiaoyu
Hengshui people hospital
Liu Zhaowei
hengshui people hospital
Miao Feifei
hengshui people hospital
Zhang Changgeng (zcg909@yeah.net)
Hengshui People's Hospital, Hebei Province

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Abstract

Background Atezolizumab was effective and well tolerated in pretreated non-small-cell lung cancer (NSCLC). This meta-analysis assessed that the efficacy and safety of atezolizumab plus chemotherapy combination, compared to chemotherapy alone.

Methods This meta-analysis included double-blind randomized controlled trials (RCTs) comparing atezolizumab plus chemotherapy combination with chemotherapy alone for NSCLC. The subgroups were the high expression of PD-L1（PD-L1-high）, the low expression of PD-L1 （PD-L1-low） and the negative expression of PD-L1 (PD-L1-negative). The hazard ratios (HRs) and odds ratios (ORs) with 95% confidence interval (CI) were calculated. The outcome parameters were overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and adverse events Grade 3-5（AEs G3-5）.

Results A total of 6 articles were included in this meta-analysis. The results indicated that atezolizumab plus chemotherapy combination had better efficacy than chemotherapy alone for PFS (HR=0.64, 95% CI=0.60 to 0.70,*P*<0.001), PFS（PD-L1-high）(HR=0.41, 95% CI=0.34 to 0.51,*P*<0.001), PFS（PD-L1-low） (HR=0.63,95% CI 0.55 to 0.72,*P*<0.001) and PFS（PD-L1-negative）(HR=0.71, 95% CI=0.61 to 0.83,*P*<0.001). There were statistically significant improvements in terms of OS (HR = 0.79, 95% CI = 0.73 to 0.86,*P*<0.001) 、OS (PD-L1-high) (HR = 0.65, 95% CI = 0.48 to 0.88,*P*<0.01) and OS (PD-L1-negative) (HR = 0.84, 95% CI = 0.72 to 0.98,*P*<0.05). Significant benefits were observed in ORR (OR=1.81,95% CI=1.58 to 2.08, *P*<0.001), ORR（PD-L1-high）(OR=2.24,95% CI=1.24 to 4.06,*P*<0.01), ORR（PD-L1-low）(OR=1.51,95% CI=1.03 to 2.21,*P*<0.05) and ORR（PD-L1-negative）(OR=1.54,95% CI=1.05 to 2.27,*P*<0.05). Meanwhile, atezolizumab was well tolerated and the incidence of AEs G3-5 (OR = 1.32, 95% CI = 1.06 to 1.64,*P*=0.01).

Conclusion The atezolizumab plus chemotherapy combination had excellent efficacy and great safety than chemotherapy alone for NSCLC. Furthermore, these benefits had nothing to do with the state of PD-L1 expression.

Introduction

Lung cancer has the highest morbidity and mortality rate in the world. It is the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths)[1]. According to histopathological classification, lung cancer can be divided into small cell lung cancer and non-small cell lung cancer（NSCLC）. NSCLC is a common type of lung cancer, accounting for about 85%. The outcomes for patients diagnosed with advanced NSCLC are poor despite recent advances in treatment. The advent of immune checkpoint inhibitor (ICI) has represented one of the most important innovations in the treatment of lung cancer over the last decades[2].

Atezolizumab is an engineered, humanised monoclonal anti-PD-L1 antibody that inhibits binding of PD-L1 to PD-1 and CD80, thus restoring anticancer immunity[3]. Some clinical researches have investigated the efficacy and safety of atezolizumab in patients with previously treated advanced or metastatic

NSCLC[4-6]. A phase study of atezolizumab has shown durable anti-tumour responses in NSCLC patients and has shown an association of PD-L1 expression on tumour cells and tumour-infiltrating immune[7]. A phase POPLAR study of atezolizumab has shown improved overall survival (OS) compared with docetaxel in patients with previously treated NSCLC[8]. A phase OAK study of atezolizumab has shown a clinically relevant improvement of OS versus docetaxel in previously treated NSCLC, regardless of PD-L1 expression or histology, with a favourable safety profile[9]. On the basis of these data, atezolizumab was approved by FDA for the treatment of NSCLC patients.

Many studies have proved that atezolizumab were effective and safe, but there was uncertain effectiveness against different PD-L1 expression states of NSCLC. Therefore, this meta-analysis is the first comprehensive analysis of the efficacy and safety of atezolizumab plus chemotherapy combinations, compared to chemotherapy alone. So as to provide further reliable basis for clinical application.

Materials And Methods

3.1 Information sources

The following electronic databases were searched: PubMed, Web of Science, Cochrane Library and EMBASE. The articles were searched from 1st January 2013 to 1st June 2020 for studies published in English. We also manually searched the abstracts on our subject accepted by the AACR, ASCO, ESMO, WLCC and ELCC congresses. The keywords were as follows: “immune checkpoint inhibitor”, “immunotherapy”, “chemotherapy”, “PD1 or PD-L1”, “atezolizumab”, “lung cancer”, “non-small cell lung cancer”, “NSCLC”. In addition, the references of these articles were also screened to find other relevant articles. An appropriate search strategy was shown in Fig.1.

3.2 Study selection and data extraction

This study included randomized clinical trials (RCT), non-randomized clinical trials (non-RCT) and observational studies that evaluated adult cancer patients who underwent treatment atezolizumab associated with chemotherapy. The studies were analyzed for inclusion and exclusion criteria in two phases. Phase 1 (reading of titles and abstracts) excluded studies that compared between atezolizumab and docetaxel. Phase 2 (reading of the full texts) excluded studies that provided invalid data.

The data were extracted independently by two researchers, discrepancies were resolved by discussion with a third researcher. The following information was collected: study design, baseline patient characteristics, interventions, national clinical trial number, PD-L1-expression level. The effective parameters were overall survival (OS), progression-free survival (PFS) and objective response rate (ORR). The safety parameters was adverse events Grade 3-5AEs G3-5. The methodological quality of included studies was assessed by one independent reviewer. Any disagreements were discussed with the third researcher.

3.4 Statistical analysis

This meta-analyses was performed using Revman version 5.3. We used hazard ratios (HRs) and 95% confidence interval (CI) as measure to assess the association for PFS and OS. We calculated the logarithm of HRs (logHRs) and its standard error for each RCT included in this analysis. For the other parameters, we performed meta-analysis to calculate odds ratios (ORs) and 95% CI using the *Mantel-Haenszel* statistical method. A random effect model was used to calculate the data. Heterogeneity was calculated using the I^2 statistic. A value greater than 50% was considered to indicate substantial heterogeneity between the studies. Sensitivity analysis was performed by excluding low-quality studies. All tests were 2-tailed, and $P < 0.05$ was considered statistically significant.

Results

4.1 Selection and characteristics of studies

The electronic search identified 318 references and the manual search of congress abstracts added 1 more. Finally, 6 articles contained 2032 patients with atezolizumab plus chemotherapy combinations, 1778 patients with chemotherapy alone were included. The randomized phase III IMpower130[5],IMpower131[10],IMpower132[11] and IMpower150[6] studies were included in this study. All included studies scored tumour cells expressing PD-L1 as a percentage of total tumour cells (TC) and tumour-infiltrating immune cells (IC) expressing PD-L1 as a percentage of tumour area. The high expression of PD-L1（PD-L1-high）was as follows: TC3≥50% or IC3≥10%. The low expression of PD-L1（PD-L1-low）was as follows: TC1/2 or IC1/2 (PD-L1 expression on≥1% of TC or IC and <50% of TC and <10% of IC). The negative expression of PD-L1 (PD-L1-negative) was as follows: TC and IC<1%. The process of study selection was described in Fig.1. The detailed characteristics of each study were represented in Table 1.

Table 1 The detailed characteristics of each study in this meta-analysis

Author	Year	NCT	Drugs	Age (years)	Male N(%)	effective parameters	safety parameters
Horn [12]	2018		atezolizumab plus chemotherapy chemotherapy	64 (28-90) 64 (26-87)	129 (64.2%) 132 (65.3%)	OS,PFS ORR	AEs G3–5
Socinski [13]	2018		atezolizumab plus chemotherapy chemotherapy	63(31-89) 63(31-90)	240 (60.0%) 239 (60.0%)	OS,PFS ORR	AEs G3–5
Papadimitrakopoulou [11]	2018	NCT02657434	atezolizumab plus chemotherapy chemotherapy	64 (31-85) 63(33-83)	192 (65.8%) 192 (67.1%)	OS,PFS ORR	AEs G3–5
Reck [6]	2019	NCT02366143	atezolizumab plus chemotherapy chemotherapy	63(31-89) 63(31-90)	240 (60.0%) 239 (60.0%)	OS,PFS ORR	AEs G3–5
West [5]	2019	NCT02367781	atezolizumab plus chemotherapy chemotherapy	64 (18-86) 65 (38-85)	266 (59.0%) 134 (59.0%)	OS,PFS ORR	AEs G3–5
Jotte [10]	2020	NCT02367794	atezolizumab plus chemotherapy chemotherapy	65 (23-83) 65 (38-86)	280 (81.6%) 277 (81.5%)	OS,PFS ORR	AEs G3–5

4.2 Risk of bias in individual studies

The Cochrane risk-of-bias criteria was used to assess the risk of bias by two researchers. It was consisted of 7 items. It included: □ random sequence generation; □ allocation concealment;□ blinding of participants and personnel; □ blinding of outcome assessment; □ incomplete outcome data; □ selective reporting; □ other bias. Overall, the risk of bias for most of the studies was judged to be low (Fig.2). For each quality item, it was graded as low risk, high risk, or unclear risk. In this meta-analysis, there was moderate heterogeneity between the included studies (0% < I^2 < 47%), hence the random-effects model was performed.

4.3 Results of effective parameters

The meta-analysis of the six studies with survival data showed a signifcant PFS benefit for the atezolizumab plus chemotherapy combination, compared to chemotherapy alone (HR=0.64, 95% CI=0.60 to 0.70,*P*<0.001). The significant differences were also found in PFS□PD-L1-high□, PFS□PD-L1-low□ and PFS□PD-L1-negative□subgroups, for chemotherapy combinations with atezolizumab (HR=0.41, 95% CI=0.34 to 0.51,*P*<0.001; HR=0.63,95% CI 0.55 to 0.72,*P*<0.001; HR=0.71, 95% CI=0.61 to 0.83,*P*<0.001) (Fig.3).

As shown in Fig.4, atezolizumab maintained a significant OS benefit excepted in the OS□PD-L1-low□ subgroup. There were significant differences in OS (HR = 0.79, 95% CI = 0.73 to 0.86,*P*<0.001) □OS (PD-L1-high) (HR = 0.65, 95% CI = 0.48 to 0.88,*P*<0.01) and OS (PD-L1-negative) (HR = 0.84, 95% CI = 0.72 to 0.98,*P*<0.05) between atezolizumab plus chemotherapy and chemotherapy.

The ORR for combination atezolizumab–chemotherapy was statistically superior to that of chemotherapy alone in this meta-analysis (OR=1.81,95% CI=1.58 to 2.08, *P*<0.001). The benefits were obtained regardless of the PD-L1expression status. Signifcant benefits were observed in ORR□PD-L1-

high（OR=2.24,95% CI=1.24 to 4.06,*P*<0.01), ORR（PD-L1-low（OR=1.51,95% CI=1.03 to 2.21,*P*<0.05) and ORR（PD-L1-negative（OR=1.54,95% CI=1.05 to 2.27,*P*<0.05) (Fig. 5).

4.4 Results of safety outcomes

As shown in Fig.6, atezolizumab plus chemotherapy combination was well tolerated and the incidence of AEs G3-5 (OR = 1.32, 95% CI = 1.06 to 1.64,*P*=0.01) compared with chemotherapy alone.

Discussion

Recently, PD-1/PD-L1 inhibitors have demonstrated their efficacy as first-line treatment for NSCLC[14-15]. Especially, the results of several preclinical studies showed the benefits of the atezolizumab in combination with chemotherapy drugs. However, there was uncertain effectiveness against different PD-L1 expression states for NSCLC. To further validate the role and safety of atezolizumab in patients with NSCLC, a meta-analysis was performed in this paper.

This meta-analysis demonstrated comparable PFS, OS and ORR effective of atezolizumab plus chemotherapy combination, compared to chemotherapy alone. The subgroups of patients with high and negative PD-L1-expressing NSCLC have significant positive benefits for the atezolizumab plus chemotherapy combination on the PFS, OS and ORR compared with chemotherapy alone. There were significant positive benefits for the atezolizumab plus chemotherapy combination on the PFS and ORR compared with chemotherapy alone in the subgroup of patients with low PD-L1-expressing NSCLC. However, there were no significant improvements in terms of OS between atezolizumab plus chemotherapy combination and chemotherapy alone in the subgroup of patients with low PD-L1-expressing NSCLC. The results of other recently published meta-analyses were in agreement with our study[16-17], even though they did not specifically address the subgroups of patients with high,low or negative PD-L1-expressing NSCLC. The data suggested that the observed clinical benefits were not driven by PD-L1 expression states.

This study shown that atezolizumab plus chemotherapy combination was well tolerated and the incidence of AEs G3-5 compared with chemotherapy alone. This suggested that atezolizumab plus chemotherapy combination has an advantage in safety over chemotherapy alone in the treatment of NSCLC. However, the sample size of current researches on atezolizumab were small.

In this meta-analysis, sensitivity analyses that excluded low-quality trials and studies. This study had some limitations. Some data were not available, and they were not individual patient data. The atezolizumab plus chemotherapy combination, compared to chemotherapy alone, as first-line treatment of patients with high and negative PD-L1-expressing NSCLC significantly prolonged OS, PFS and ORR. However, the optimal combinations in terms of efficacy and safety needed to be discussed later.

Declarations

Conflicts of interest

All authors declare no conflicts of interest.

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