INPLASY PROTOCOL

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None declared.

Predictive value of pretreatment PD-L1 expression in EGFR-mutant non-small cell lung cancer: a meta-analysis

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Review question / Objective: **To investigate the predictive value of programmed death-ligand 1 (PD-L1) expression in non-small cell lung cancer (NSCLC) patients treated with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs).**
Condition being studied: **At present, several studies have investigated the predictive value of PD-L1 expression in EGFR-mutant NSCLC patients treated with EGFR-TKIs. However, previous studies regarding this topic have yielded conflicting results because of different sample size, antibody clone for immunohistochemistry (IHC), and IHC scoring system applied.**
Information sources: **rom the establishment date of databases to August 30th, 2020, we searched PubMed, Embase, , Cochrane library and China National Knowledge Infrastructure (CNKI) with terms related to "non-small cell lung cancer", "PD-L1", "EGFR-TKIs", and "prognosis". Besides, potentially eligible studies were also manually checked through the reference lists of included studies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 April 2021 and was last updated on 18 April 2021 (registration number INPLASY202140093).

INTRODUCTION

Review question / Objective: **To investigate the predictive value of programmed death-ligand 1 (PD-L1) expression in non-small cell lung cancer (NSCLC) patients treated with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs).**

Rationale: **In the past few years, the immune checkpoint inhibitors (ICIs), which target the programmed death-1 (PD-1)/ programmed death-ligand 1 (PD-L1) axis,**

have led to a long-lasting response in some patients with NSCLC by prompting the exhausted tumor infiltrating lymphocytes. However, a limited effect of PD-1/PD-L1 inhibitors in patients with EGFR-mutant NSCLC was reported by Gainor et al. Moreover, the expression of PD-L1 was generally lower in EGFR-mutated tumors than in EGFR wild-type tumors. This might be the reason for the poor response to immune checkpoint inhibitors in EGFR-mutated tumors. The expression of PD-L1 reveals the immunogenic nature of the tumor microenvironment. Therefore, it is probably related to clinical outcomes of the treatments other than ICIs.

Condition being studied: At present, several studies have investigated the predictive value of PD-L1 expression in EGFR-mutant NSCLC patients treated with EGFR-TKIs. However, previous studies regarding this topic have yielded conflicting results because of different sample size, antibody clone for immunohistochemistry (IHC), and IHC scoring system applied.

METHODS

Search strategy: ((((((((((Non-Small Cell Lung Cancer[Title/Abstract]) OR (Non-Small Cell Lung Carcinoma[Title/Abstract])) OR (NSCLC[Title/Abstract])) OR (Non Small Cell Lung Carcinoma[Title/Abstract])) OR (Non-Small-Cell Lung Carcinoma[Title/Abstract])) OR (Non-small Cell Lung Cancer[Title/Abstract])) OR (Non-Small-Cell Lung Carcinomas[Title/Abstract])) OR (Non-Small-Cell Lung Carcinoma[Title/Abstract])) OR (lung adenocarcinoma[Title/Abstract])) AND ((programmed death-ligand 1[Title/Abstract]) OR (PD-L1[Title/Abstract]))) AND ((((((((tyrosine kinase inhibitor[Title/Abstract]) OR (TKI[Title/Abstract])) OR (osimertinib[Title/Abstract])) OR (dacomitinib[Title/Abstract])) OR (afatinib[Title/Abstract])) OR (erlotinib[Title/Abstract])) OR (gefitinib[Title/Abstract])) OR (icotinib[Title/Abstract]))) AND (("0001/01/01"[Date - Publication] : "2020/08/30"[Date - Publication])).

Participant or population: Patients were diagnosed with advanced NSCLC and treated with EGFR-TKIs alone.

Intervention: PD-L1 expression in the tumors of patients before EGFR-TKI treatment.

Comparator: High versus low expression of PD-L1 in tumors of patients before EGFR-TKI treatment.

Study designs to be included: Prospective or retrospective cohort studies and randomized controlled studies.

Eligibility criteria: The inclusion criteria were as follows: (1) patients were diagnosed with advanced NSCLC and treated with EGFR-TKIs alone; (2) the primary outcomes were progression-free survival (PFS) and/or overall survival (OS); (3) the relationship between PD-L1 expression and PFS/OS was described; (4) necessary survival data including hazard ratio (HR), 95% confidence interval (CI) or Kaplan-Meier survival curve was provided. The exclusion criteria were: (1)a previous history of chemotherapy or radiotherapy; (2) case reports, comments, corresponding letters, reviews, and meeting abstracts; (3) necessary survival data to calculate the HR with 95% CI was not provided.

Information sources: From the establishment date of databases to August 30th, 2020, we searched PubMed, Embase, , Cochrane library and China National Knowledge Infrastructure (CNKI) with terms related to “non-small cell lung cancer”, “PD-L1”, “EGFR-TKIs”, and “prognosis”. Besides, potentially eligible studies were also manually checked through the reference lists of included studies.

Main outcome(s): The primary outcomes were the hazard ratio (HR) and 95% confidence interval (CI).

Additional outcome(s): The following data were recorded: the name of the first author, publication year, origin of the study, study period, sample size, type of cancer, stage

of cancer, detective methods, and grouping methods.

Data management: Excel 2016 & Stata(Version 16.0; Stata Corporation, Texas, US).

Quality assessment / Risk of bias analysis: We performed a sensitivity analysis by removing included studies one-by-one to test whether the results were robust. We applied Egger's test and Begg's test to assess the possibility of publication bias.

Strategy of data synthesis: Stata (version 16.0; Stata Corporation, Texas, US) software was applied to analyze the extracted data. HR with 95% CI was used to assess the significance of PD-L1 expression on OS and PFS of the patients with NSCLC treated with EGFR-TKIs.

Subgroup analysis: Patients can be divided into TPS, Moderate staining and H scores according to the different tumor PD-L1 immunohistochemistry detection scoring systems in different literature. Patients can be divided into groups of greater than 100 patients and less than 100 patients according to the number of patients included in different literature. The patients can be divided into 22C3 antibody, SP263, 28-8, SP142, E1L3N and ab58810 groups according to the different antibodies used for PD-L1 immunohistochemistry of the patients' tumors. The groups can be divided into multi-factor analysis model group and single-factor analysis model group according to the survival data model.

Sensitivity analysis: A sensitivity analysis was conducted by excluding each study from the meta-analysis at each time.

Country(ies) involved: China; Italy; Korea; Japan.

Keywords: Non-small cell lung cancer; Epidermal growth factor receptor; Programmed death-ligand 1; Prognosis.

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