Anti-PD-1 Inhibitor for the Treatment of Esophageal Cancer Refractory or Intolerant to Previous Chemotherapy: A Meta-Analysis of Randomized Controlled Trials

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Research Article

Keywords: Adverse events, Esophageal cancer, Immune checkpoint inhibitor, meta-analysis, chemotherapy, randomized controlled trial

DOI: https://doi.org/10.21203/rs.3.rs-156736/v1

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Abstract

Background

Clinical studies have suggested that PD-1 inhibitor is useful in the management of advanced Esophageal Cancer. However, the efficacy and safety of Anti-PD-1 inhibitor for the treatment of advanced Esophageal Cancer is inconclusive. Thus, we conducted a meta-analysis aiming to comprehensively explore the effectiveness and safety of the therapeutic effects of PD-1 inhibitors on patients with advanced esophageal cancer.

Methods & Materials:

The PubMed (since its inception), Cochrane library (since its inception), EMBASE (since its inception), and ClinicalTrials.gov (since its inception) were searched till 1st December 2020 for the randomized controlled trials (RCTs) that evaluated the effectiveness and safety of PD-1 inhibitors for patients with esophageal cancer. Two investigators independently performed study selection, data extraction and assessment of the methodological quality. RevMan 5.3 was applied statistical analysis.

Results

Three RCTs were included for this meta-analysis, with a total of 1477 patients. Compared with chemotherapy, PD-1 inhibitors had superior objective response rates (Odds ratio (OR) = 14.96, 95% confidence interval (CI): 0.47, 476.97; P = 0.13). PD-1 inhibitors group had better overall survival compared to chemotherapy group (Hazard ratio (HR): 0.80, 95% CI: 0.70, 0.91, P = 0.0007). The progression-free survival (HR: 0.94, 95% CI: 0.71, 1.26, P = 0.69) were similar between the two groups. The grade 3 or more adverse events rate were lower in the PD-1 inhibitors group as compared to those of chemotherapy group (OR: 0.25, 95% CI: 0.13, 0.46, P < 0.0001).

Conclusions

Our study indicated that PD-1 inhibitors are efficacious and safe for the management of EC refractory or intolerant to previous chemotherapy.

1. Introduction

Esophageal cancer (EC) is one of the common cancer and with poor prognosis. It is reported that 572,034 new cases and 508,585 deaths were reported globally[1]. Despite the advanced of treatment technology and surgery, the overall survival of EC is still poor[2].

Immune checkpoint inhibitors (ICI) is widely used for various types of cancer[2]. Pd-1 inhibitors now are gain worldwide attention. Moreover, ICIs are considered as an option for salvage-line chemotherapy for metastatic or recurrent EC patients. Here, we performed a meta-analysis of randomized controlled trials (RCTs) assessing the efficacy and safety of anti-PD-1 inhibitors in the treatment of EC refractory or intolerant to previous chemotherapy.
2. Methods & Materials

2.1 Study registration

The meta-analysis complies with the PRISMA statement[6].

2.2 Criteria for considering studies

2.2.1 Study types

This meta-analysis only included fully published RCTs. Other types of studies (such as animal studies, case reports, retrospective studies, comments) were excluded.

2.2.2 Types of patients

Cancer patients aged ≥18 years old, with histological confirmed of EC refractory or intolerant to previous chemotherapy.

2.2.3 Types of interventions

Treatment intervention: PD-1 inhibitor was given for the management of EC.

Control intervention: chemotherapy.

2.2.4 Outcomes of interest

The primary outcomes included overall survival(OS), progression-free survival(PFS), objective response rate and completed response rate. The secondary outcomes included grade 3 or more adverse events rate.

2.3 Searching methods for Eligibility studies

The following databases were included for searching: PubMed (since its inception), Cochrane library (since its inception), EMBASE (since its inception), and ClinicalTrials.gov (since its inception). The lastest search was December 1st, 2020. The language was restricted to English only. The main search terms included “PD-1”, “Immune checkpoint inhibitors”, and “esophageus cancer”. Furthermore, references of all relevant identified studies were examined for yielding more RCTs.

2.4 Selection of study

The studies from initial search were import into the Note express software. By using this software, duplicated references were excluded. The remaining studies were required a title and abstracts screen by two independent researches (G.L and Z.Z) in accordance to the inclusion criteria. The potential meet inclusion criteria studies retrieved as a full text form will be screen and evaluated by two independent reviewers for the final inclusion. Any disagreement was discussed and resolved by the author group. References of the studies identified for including analysis was evaluated for the potential missing studies.

2.5 Data extraction
Data from the inclusion studies were extracted using a pre-piloted and standardized form. The extracted information included the following: first author of the study, country location, years of publication, sample sizes of each interventions, details of intervention methods, details of patients in each intervention (including ages, sex, body mass index, cancer types, dose and duration of radiation), and outcomes of interest. Adverse events were defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. Data extraction was carried out by two independent reviewers. Any disputes were resolved by discussion by the reviewer group.

2.6 Assessment risk of bias for the inclusion RCTs

Risk of bias were appraised using the Cochrane tools[7] by pair reviewers.

2.7 Measurement of treatment effect

For dichotomous parameters (e.g. response rate and adverse events), the events in each arm was recorded. The analysis was using odds ratio (OR) and its 95% confidence interval (CI). Hazard ratio(HR) and its 95% CI were applied for measuring survival outcomes.

2.8 Publication bias assessment

Publication bias was evaluated using funnel plot of the outcomes of interest. In addition, the Egger’s test and Begg’s test [8] were also used for detection of publication bias.

2.9 Data synthesis

STATA 12.0 and RevMan 5.3 software will be utilized for the data analysis. As we list above, Chi\(^2\) test will be adopt for measuring the heterogeneity. The I\(^2\) values [7] of 25%, 50%, and 75% were considered low, moderate, and high, respectively. Continuous variables were measured using weighted mean difference (MD) with a 95% confidence interval (CI). Dichotomous variables, like the incidence of complications, were analyzed using odds ratios (ORs) with a 95% CI. If I\(^2\)<25%, a fixed-effects models will be adopted for evaluation. Otherwise, a random-effects model was utilized. Subgroup analysis was performed to validate the reliable of the results and to find out the potential source of heterogeneity. Sensitivity analysis was carried out without trials of great risk of bias.

3. Results

In total, there were 973 studies identified from the initial search. After carefully title and abstract screening, 29 studies were left for full text screening. In accordance to the inclusion criteria, only three studies[9–11] were included for this analysis. The study selection chart is presented in Fig. 1. The general information regarding studies were listed in Table 1. Risk of bias assessment is presented in Fig. 2.
Table 1
The basic information of included studies for meta-analysis

| Study     | year | Study Design | group                     | cases | Treatment                                                                                      | Median followed-up (M) | Median OS  | Median PFS |
|-----------|------|--------------|---------------------------|-------|----------------------------------------------------------------------------------------------|------------------------|------------|------------|
| Attraction-3 | 2019 | Phase III    | PD-1 inhibitor chemotherapy | 210   | Nivolumab 240mg every 2 weeks, paclitaxel at 100 mg/m² once per week for 6 weeks followed by 1 week of and docetaxel at 75 mg/m² every 3 weeks | 10.5 M 8.0M           | 10.9M 8.4M | 1.7M 3.4M  |
| ESCORT    | 2016 | Phase III    | PD-1 inhibitor chemotherapy | 228   | Camrelizumab 240mg every 2 weeks, Docetaxel (75 mg/m², each 3-week cycle) or irinotecan (180 mg/m², every 2 weeks) | 8.3M 6.2M             | 8.3M 6.2M | 1.9M 1.9M  |
| Keynote-181 | 2017 | Phase III    | PD-1 inhibitor chemotherapy | 314   | Pembrolizumab 200 mg every 3 weeks, paclitaxel 80–100 mg/m² on days 1, 8, and 15 of each 28-day cycle, docetaxel 75 mg/m² on day 1 of each 21-day cycle, or irinotecan 180 mg/m² on day 1 of each 14-day cycle | 7.1 M 6.9M           | 9.3M 6.7M | 2.6M 3.0M  |

3.1 Overall survival

All of the three studies[9–11] reported of survival outcomes. Pooling analysis using a random-effect model indicated that treatment with pd1 inhibitors has a better OS (HR: 0.80, 95% CI: 0.70, 0.91; P = 0.0007), the heterogeneity was low ($I^2 = 22\%$, $P = 0.28$) as outlined in Fig. 3.
3.2 Progression-free survival

Three studies mentioned of PFS[9–11]. The combination data indicated that the two groups had similar PFS (HR:0.94, 95%CI:0.71,1.26,P = 0.69), the analysis was with high heterogeneity ($I^2 = 85\%$, $P = 0.001$) (Fig. 4), and the analysis was using a random-effect model.

3.3 Objective response rate

All three trials reported of objective response rate (ORR)[9–11]. The combination data indicated the two groups had similar objective response rate (OR:1.87, 95%CI:0.82,4.25,$P = 0.13$) (Fig. 5), a random-effected model was applied because of high heterogeneity.

3.4 completed response rate

Two RCTs[10, 11] mentioned of completed response rate. Pooling data indicated the two groups had a similar rate of completed response (OR:0.63, 95%CI:0.10,3.76), a fixed-effect model was used due to no significant heterogeneity among studies. ($I^2 = 0$, $P = 0.69$) (Fig. 6).

3.5 The grade 3 or more adverse events

All of the three studies[9–11] reported of adverse events (AE). In terms of more than grade 3 events, Pd-1 groups had a lower rate of adverse events compared to that of chemotherapy group (OR:0.25, 95%:0.13,0.46,$P < 0.0001$), the analysis was used a random-effected model due to high heterogeneity ($I^2 = 85\%$, $P = 0.001$) (Fig. 7).

3.6 Subgroup analysis

In terms of OS, we performed a subgroup analysis and meta-regression based on the ECOG status, sex, age, and TPS score, and the results were not affected as outlined in Table 2.
### Table 2
Subgroup and meta-regression assessing overall survival in patients with esophageal cancer between PD-1 inhibitors and chemotherapy

| Items                  | No. of studies | Pooled HR and its 95%CI | Z value | P value | Heterogeneity | Meta-regression P value |
|------------------------|----------------|--------------------------|---------|---------|---------------|-------------------------|
|                        |                |                          |         |         | I²(%)         |                         |
| ECOG                   |                |                           |         |         |               | 0.660                   |
| 0                      | 3              | 1.42(1.12,1.79)          | 2.95    | 0.003   | 64            | 0.007                   |
| 1                      | 3              | 1.19(1.01,1.40)          | 2.07    | 0.04    | 0             | 0.50                    |
| age                    |                |                          |         |         |               | 0.655                   |
| ≥ 65                   | 3              | 1.33(1.04,1.70)          | 2.30    | 0.02    | 74            | 0.004                   |
| < 65                   | 3              | 1.23(1.03,1.47)          | 2.28    | 0.02    | 2             | 0.40                    |
| sex                    |                |                          |         |         |               | 0.597                   |
| male                   | 3              | 1.28(1.01,1.63)          | 2.02    | 0.04    | 51            | 0.07                    |
| female                 | 3              | 1.32(1.09,1.61)          | 2.83    | 0.005   | 36            | 0.18                    |
| PD-L1 CPS score        |                |                          |         |         |               | 0.286                   |
| ≥10                    | 3              | 1.33(1.09,1.61)          | 2.84    | 0.004   | 45            | 0.10                    |
| < 10                   | 3              | 1.27(0.95,1.68)          | 1.63    | 0.10    | 46            | 0.12                    |

HR, hazard ratio; CI: confidence interval;

### 3.7 Publication bias
Publication bias was evaluated using funnel plot of adverse events. The studies were outlined in the 95% CI and indicated no obvious publication bias (Fig. 8). Because the limited studies, Egger’s test and Begg’s test were not performed.

### 4. Discussion
EC is a lethal disease, it is the 7th in incidence and 6th in mortality worldwide[12]. Treatment guidelines for the second-line or later-line of the treatment of EC is not well established. Recently, three randomized controlled trials have published their efficacy results regarding the use of PD-1 inhibitor in the management of EC. Therefore, we undertook a systemic review and meta-analyze the results of these studies. Our studies indicated that compared to chemotherapy, the application of PD-1 inhibitor had a better OS (HR:0.80, 95% CI:0.70,0.91, P = 0.0007) and
lower grade 3 or more adverse events (OR: 0.25, 95% CI: 0.13, 0.46, P < 0.0001) in the second-line treatment of EC. The two groups had no significant difference in PFS, objective response rate, and completed response rate.

The application of PD-1/PD-L1 inhibitors in the treatment of a variety cancers had been widely reported[12]. The level of PD-L1 expression, and/or tumor mutation burden (TMB) in tumor cells can be a prognostic factor for determining the efficiency of PD-1/PD-L1 inhibitors. According to published reports, the proportion PD-L1 expression in EC was ranged from (14.5 to 82.8%) [2]. The application of PD-1/PD-L1 inhibitors in EC patients were reported in several trials[9–11, 13, 14].

Our analysis indicated the application of PD-1 inhibitors can prolong the OS as compared to chemotherapy in EC patients. As reported in KEYNOTE-181 trial[9], In the intentions treatment (ITT) population, the application of Pembrolizumab in the treatment of EC did not gain survival benefit in terms of median OS. However, in patients with PD-L1 CPS score more than 10, the used of Pembrolizumab had survival benefit compared with chemotherapy (median OS: 9.3 and 6.7 months). Moreover, in the ESCORT trial[10], the application of camrelizumab resulted in better overall survival in the second-line treatment of EC. Our analysis also indicated in subgroup analysis the results were not affected, as according to ECOG status, sex, age, and TPS score. And the meta-regression analysis indicated the results was stable. In the attraction-3 trial[11], The median OS was 10.9 months and 8.4 months in the Nivomab group and chemotherapy group, respectively. In the Keynote-028 trial[14], the application of Pembrolizumab as a late-time treatment for EC achieved a median OS of 7 month. In the attraction-1 trial, sixty-five patients with metastatic oesophageal squamous cell carcinoma (ESCC) received of Nivolumab and the median OS was 1.51 month[13].

In terms of PFS, as reported in Keynote-181 trial[9], In patients with PD-L1 CPS more than 10, median PFS was longer in the Pembrolizumab group compared with that of in the chemotherapy group. In the ESCORT trial, median PFS was both 1.9 months in Camrelizumab group or in chemotherapy group.

In the attraction-3 trial, The PFS was not significant difference between Nivolumab group and chemotherapy group.

In terms of ORR, as mentioned in attraction-3 trial, The ORR rate was 19% in the Nivolumab group and 22% in the chemotherapy group. As reported in the ESCORT trial, the ORR was 20.2% in the Camrelizumab group and 6.4% in the chemotherapy group. In the Keynote-181 trial[9], the ORR was 13.1% in the in the Pembrolizumab group and 6.7% in the chemotherapy group.

In terms of treatment AE, as reported in the attraction-3 trial, serious treatment-related adverse events (Grade 3 or higher) rate was 16% in the Nivolumab group and 23% in the chemotherapy group. Grade 3 or higher treatment-related AEs was 18% in the Pembrolizumab group and 40.9% in the chemotherapy group as reported in the Keynote-181 trial[9]. And in the ESCORT trial, the serious treatment-related adverse events was 19% in the Camrelizumab group and 39% in the chemotherapy group. In published studies, the grade 3 or higher AE was ranged from 10.3% to 14.3%[9]. The most common any-grade treatment related adverse events were fatigue.

Limitations in this meta-analysis should be taken into account. First, the numbers of study included is limited and only three trials were included. Second, the included patients were from different parts of the world.
including Japan, China and USA, some heterogeneity may exist.

In conclusion, our study indicated treatment EC refractory or intolerant to previous chemotherapy with PD-1 inhibitors resulted a better OS. The grade 3 or more adverse events rate were lower in the PD-1 group. Due to the limited studies, More well designed RCTs are required to explore the treatment effect of PD-1 inhibitor for second-line treatment of EC refractory or intolerant to previous chemotherapy.

**Abbreviations**

RCT: randomised controlled trials;
OR: Odds ratio;
CI: confidence interval;
HR: Hazard ratio;
EC: Esophageal cancer;
ICI: Immune checkpoint inhibitors;
OS: overall survival;
PFS: progression-free survival;
TMB: tumor mutation burden.

**Declarations**

**Disclosure**

**Availability of data**

All data generated or analysed during this study are included in this published article.

**Ethics approval**

The study did not need ethics approval.

**Acknowledgements**

None.

**Authors’ contributions**

GXL, TZ, and ZHZ performed the study search, study selection, data extraction and analysis. MSY, XML, and MK performed data analysis. All authors approved the final manuscript.

**Consent to Publication**
Conflicts of interest statement

No conflict of interest was declared.

Founding data

Shenzhen Natural Science Foundation (No.JCYJ20170307095828424), Research Project of Shenzhen Health and Family Planning System (No.SZBC2017024), the Project for Youth of Shenzhen people's Hospital (No.SYKYPY2019029) were founding for this study.

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