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Original Article

PD-1/PD-L1 Immune Checkpoint Inhibitors after Platinum-based Chemotherapy in Metastatic or Locally Advanced Urothelial Bladder Carcinoma: A Systematic Review and Meta-analysis

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ABSTRACT

Objective: This study aimed to assess the effect of anti-programmed cell death-1/programmed cell death-ligand-1 (PD-1/PD-L1) agents compared with second-line therapy in patients with metastatic or locally advanced urothelial bladder carcinoma following previous platinum-containing chemotherapy.

Material and Methods: We systematically searched three electronic databases. The protocol of the study was registered in Prospero (CRD42019142494). Using the Grading of Recommendations Assessment, Development, and Evaluation approach, the certainty of evidence (CoE) was estimated.

Results: The search results initially found 8168 publications. For qualitative synthesis, two publications were included. Pooled results indicated that patients treated with anti-PD-1/PD-L1 agents had significantly prolonged overall survival (hazard ratio (HR) 0.80; 95% confidence interval (CI) 0.7-0.9; I2 21.0%; moderate CoE). According to positive PD-L1 expression, PD-1/PD-L1 inhibitors had significantly more survival than chemotherapy (HR 0.75; 95% CI 0.5-0.9, I2 57.0%, low CoE). Furthermore, there was no significant difference in adverse events (AE) between the anti-PD-1/PD-L1 agents and second-line chemotherapy (risk ratio 0.68; 95% CI 0.3-1.4; I2 97.0%, low CoE).

Conclusion: The present meta-analysis and systematic review provide strong evidence that anti-PD-1/PD-L1 agents

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could improve overall survival and have similar results in AEs compared with second-line chemotherapy. Further studies will confirm the power of immunotherapy for the treatment of metastatic or locally advanced urothelial bladder carcinoma.

Keywords: advanced urothelial carcinoma; metastatic urothelial carcinoma; PD-1/PD-L1 inhibitors

INTRODUCTION

Urothelial bladder carcinoma (UBC) is the most common cancer of the urinary system. In the United Kingdom, this malignancy is the 7th most common cancer and cause of death. The age-standardized rate in 2012 was 16.8 per 100,000 in men and 5.6 per 100,000 in women.[1-3]

Nearly 25.0% of patients with UBC have muscle-invasive disease or metastases. The standard of care for patients with metastatic or locally advanced UBCs is systemic platinum-based chemotherapy. Unfortunately, patients often have progression or recurrence of urothelial bladder cancer following a first-line platinum-containing regimen for metastatic or locally advanced disease. The 5-year survival probabilities were 13.0-15.3%, while the median survival time was 8.2-12.5 months the median progression-free survival was 7.7-8.3 months. platinum-based chemotherapy has a significant drawback, as it leads to intolerable side effects in many patients.[4,5]

Current cancer immunotherapy involves blocking the programmed cell death-1 (PD-1) receptor, and its ligand (PD-L1) immune checkpoints have been mentioned in several cancers. The United States Food and Drug Administration (USFDA) has approved these immunotherapy agents for treatment in head and neck squamous cell cancer, melanoma, triple-negative breast cancer, non-small-cell lung cancer, and UBC.[6]

Because metastatic or locally advanced UBC has poor outcomes and prognosis, anti-PD-1/PD-L1 agents have emerged as a novel immunotherapy option. Rosenberg et al. performed a phase II trial of atezolizumab in patients with metastatic or locally advanced UBC following treatment with platinum-based chemotherapy and reported that response rates were 26.0% in 5.0% or higher of PD-L1-positive immune cells.[7] Furthermore Powles et al. conducted a phase I/II open-label study in patients with metastatic or locally advanced UBC following treatment with platinum-based chemotherapy and found a response rate of 27.6% in positive PD-L1 expression (>25.0% of PD-L1-positive immune cells). In comparison, negative PD-L1 expression (<25.0% of PD-L1-positive immune cells) had a response rate of 5.1%.[8]

For adverse events (AE), grade 3-4 AEs of various PD-1/PD-L1 inhibitors have been reported in 6.8-21.8% of cases[9-12], while grade 3-4 AEs of platinum-based chemotherapy ranged between 0.8-19.0% of cases.[13] Furthermore treatment-related AEs that led to the death of durvalumab were reported in 1.0% from autoimmune hepatitis and pneumonitis.[8]

Anti-PD-1/PD-L1 agents have emerged as a novel immunotherapy option. However, a lack of evidence of systematic review and meta-analysis of the updated phase III clinical trials have been carried out in the literature review. We systematically examined the effect of anti-PD-1/PD-L1 agents with the aim of assessing and comparing them with second-line therapy in patients with metastatic or locally advanced UBC following previous platinum-containing chemotherapy.

MATERIAL AND METHODS

Literature search

This study (Prospero code: CRD42019142494) was conducted following the Preferred Reporting Items for

Systematic Reviews and Meta-analyses (PRISMA) reporting guideline recommendations.[14] We searched the PubMed and Cochrane Central Register of Controlled Trials databases from January 2000 to June 2019, and Embase from January 2000 to September 2019.

The following search terms were used: "Bladder tumor" OR "Bladder cancer" OR "metastatic bladder cancer" OR "Urinary Bladder Neoplasms" OR "metastatic urothelial carcinoma" AND "Programmed cell death ligand 1" OR "Programmed cell death" OR "PD-L1" OR "PD-1" OR "Immunotherapy" OR "immune checkpoint inhibitor" OR "Avelumab" "Durvalumab" OR "Nivolumab" OR "Atezolizumab" OR "Pembrolizumab". The publications were limited to human research published in English. Two investigators independently assessed the titles and abstracts retrieved by the search strategy for potential eligibility. Any disagreements were resolved through discussion until a consensus was reached.

Selection criteria and abstract screening

The search publications were imported into the web-based application Rayyan, while duplicates were deleted.[15]

The inclusion criteria for the articles were (I) phase III randomized clinical trial (RCT) studies which evaluated PD-1/PD-L1 inhibitors as immunotherapy for metastatic or locally advanced UBC; (II) participants must have previously received treatment with at least one platinum-based chemotherapy before enrollment in the RCT; (III) publications with or without mentioned PD-L1 expression levels; (IV) available results including at least one of overall survival (OS) and/or drug-related AE rate. Case reports, letters, review articles, and editorials were excluded.

Full-text screening and data extraction

Two authors (TT and TB) independently read the full-text for screening. Two authors independently performed the data extraction. Any disagreements were discussed and resolved by consensus. The following information was retrieved: author, publication year, number of patients, type of cancer, intervention, the intervention dose, number of AEs, and median survival time.

Assessment of risk of bias in included studies

Two reviewers independently evaluated the risk of bias and quality assessment based on consensus. Using the Cochrane risk of bias tool, we evaluated the risk of bias as follows; (I) random sequence generation; (II) allocation concealment; (III) blinding of participants and personnel; (IV) blinding of outcome assessment; (V) incomplete outcome data; (VI) selective reporting; and (VII) other sources of bias.[16]

Statistical analysis

Based on Tierney et al., the difference between the numbers of observed and expected events (O-E) and the variance (V) was calculated when studies reported a hazard ratio (HR) of 95% confidence intervals (CI). Generating the O-E and V from Kaplan-Meier curves was performed when HRs were unavailable.[17]

Risk ratios (RRs) and 95% (CIs) were used to assess the associa-tions between AEs and anti-PD-1/PD-L1 agents. The heterogeneity among studies was determined using the I^2 statistic; values more than 50.0% indicate substantial heterogeneity. A random effects model was created for pooling the RRs if considerable heterogeneity existed. If not, a fixed-effects model was used. Subgroup analysis was performed for estimating the source(s) of heterogeneity. Sensitivity analysis was performed to evaluate the effects of single studies on the overall estimate by ignoring one study at a time. In addition, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to measure the certainty of a body of evidence according to each outcome with GREADpro.[18-20] P-values of less than 0.050 were considered significant with two-sided test statistics.

Survival rates on the graphical illustration of the Kaplan–Meier curves were extracted by Plot Digitizer Version 2.6.8. The pooled HRs, RR, with 95% CI were calculated by Review Manager 5.3 software (Cochrane Collaborative, Oxford, UK).

RESULTS

Literature search

The initial search yielded a total of 8,168 publications, as shown in Figure 1. Inclusion and exclusion criteria were applied to titles and abstracts for 6,892 articles after the removal of 1,276 duplicate publications. Six thousand seven hundred eighty-seven studies were removed after screening the titles and abstracts. In detail, studies were excluded by abstract and title screening due to not-relevant population (n = 6,751), non-randomized trial (n = 33), not-relevant intervention such as comparison between chemotherapy and concurrent chemoradiotherapy (n = 3).

Fulltext analysis was then performed on 105 studies, following which two studies were continued for qualitative synthesis while 103 studies were excluded due to non-randomized trial (n = 54), not interested population such as patients with advanced prostate cancer, non-small cell lung cancer, or cervical cancer (n = 30), not interested intervention (n = 4), not interested outcome (n = 4), no data available (n = 10), or duplication (n = 1). Therefore, the authors evaluated the quality of the two papers and included them in the quantitative synthesis. The summarized characteristics of the two studies are presented in Table 1.

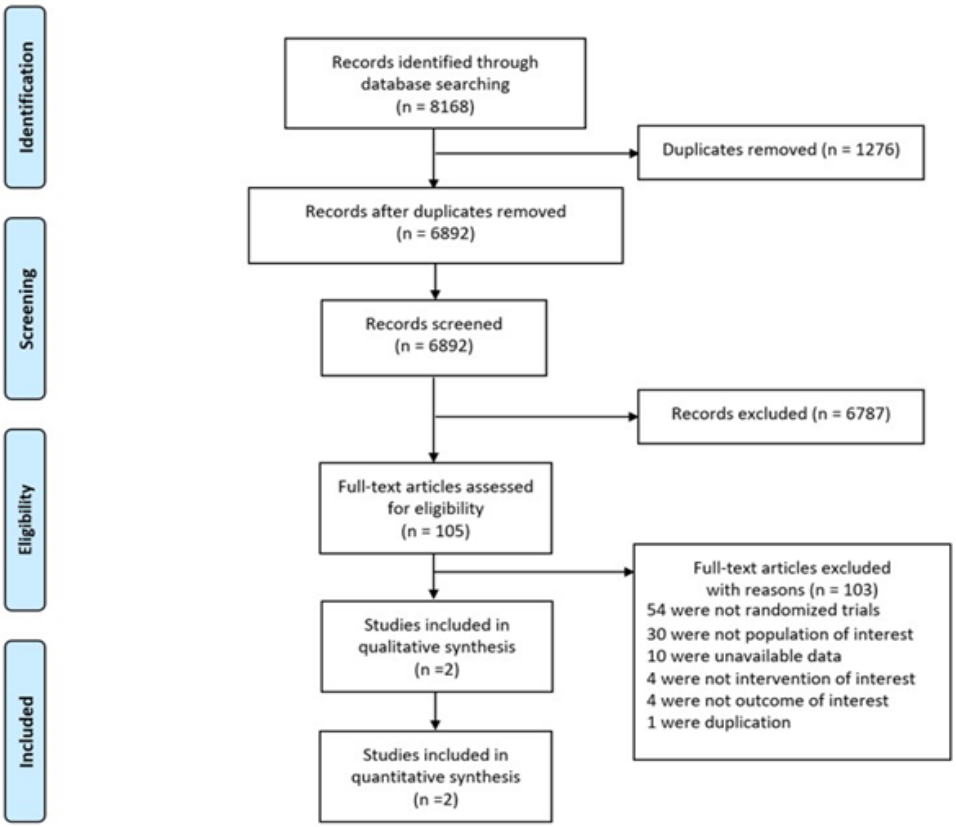

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram

Table 1 Study characteristics and cohort demographics

Study	Year	Design	Number of patients	Median age (years)	Median time folow-up (months)	Response rate	Median survival time (months)
Bellmunt et al.	2017	RCT, 120 sites	270 (Pembrolizumab group) and 272 (Chemotherapy group)	67 (Pembrolizumab group) and 65 (Chemotherapy group)	14.1 (95% CI 9.9–22.1)	21.1% (Pembrolizumab group), 11.4% (Chemotherapy group)	10.3 (95% CI 8.0–11.8, Pembrolizumab group) and 7.4 (95% CI 6.1– 8.3, Chemotherapy group)
Powles et al.	2018	RCT, 217 sites	467 (Atezolizumab group) and 464 (chemotherapy group)	67 (Atezolizumab group) and 67 (Chemotherapy group)	17.3 (95% CI 0.0–24.5)	63.0% (Atezolizumab group), 21.0% (Chemotherapy group)	8.6 (95% CI 7.8–9.6, Atezolizumab group) and 8.0 (95% CI 7.2–8.6)

RCT = randomized clinical trial

Meta-analysis

Two studies with a total of 1,473 patients focused on the relationship between PD-1/PD-L1 inhibitors and overall survival, as shown in Figure 2A. When compared to CMT, patients with immunotherapy had significantly prolonged OS (HR 0.80; 95% CI: 0.7–0.9). No substantial heterogeneity was observed with the I^2 test of 21.0%. Bullment et al. reported that 334 deaths occurred in the intention-to-treat population. However, events were not divided by treatments. Therefore, the number of events in this paper was not reported in the results.

According to positive PD-L1 expression, PD-1/PD-L1 inhibitors had significantly more survival advantages than chemotherapy (HR 0.75; 95% CI 0.5–0.9). However, the I^2 test was 57.0%, indicating visible heterogeneity, as shown in Figure 2B.

For AE outcomes, AE events of grade 3 or higher were extracted from the supplemental materials, from 1,383 patients. In detail, 34.1% (234/685) of grade 3 or higher AEs was observed in PD-1/PD-L1 inhibitors, while the chemotherapy group found grade 3 or higher AEs in 51.2% (358/698) of patients. There was no difference between the PD1/PD-L1 inhibitor and chemotherapy groups in AEs (RR 0.68; 95% CI 0.3–1.4; I^2 97.0%), as shown in Figure 2C.

Bias and quality assessment

The radiologic evaluations of response treatment were blinded in Bellmunt et al.[21]; both patients and investigators were blinded to the PD-L1 expression status in Powles et al.[22] However, both RCTs were open-label studies where treatment assignments were not blinded. Performance and detection bias were considered in the included studies, as shown in Figure 3. Moreover, both RCTs were unclear about the risk of bias in allocation concealment. Because there were less than eight papers included, the funnel plots were not performed to assess publication bias.

The certainties of evidence (CoE) estimate for overall pooled HR, pooled HR of positive PD-L1 expression, and RR of AEs were considered to be moderate, moderate, and low, respectively, as per the GRADE criteria because of serious risks of bias and heterogeneity, as shown in Table 2.

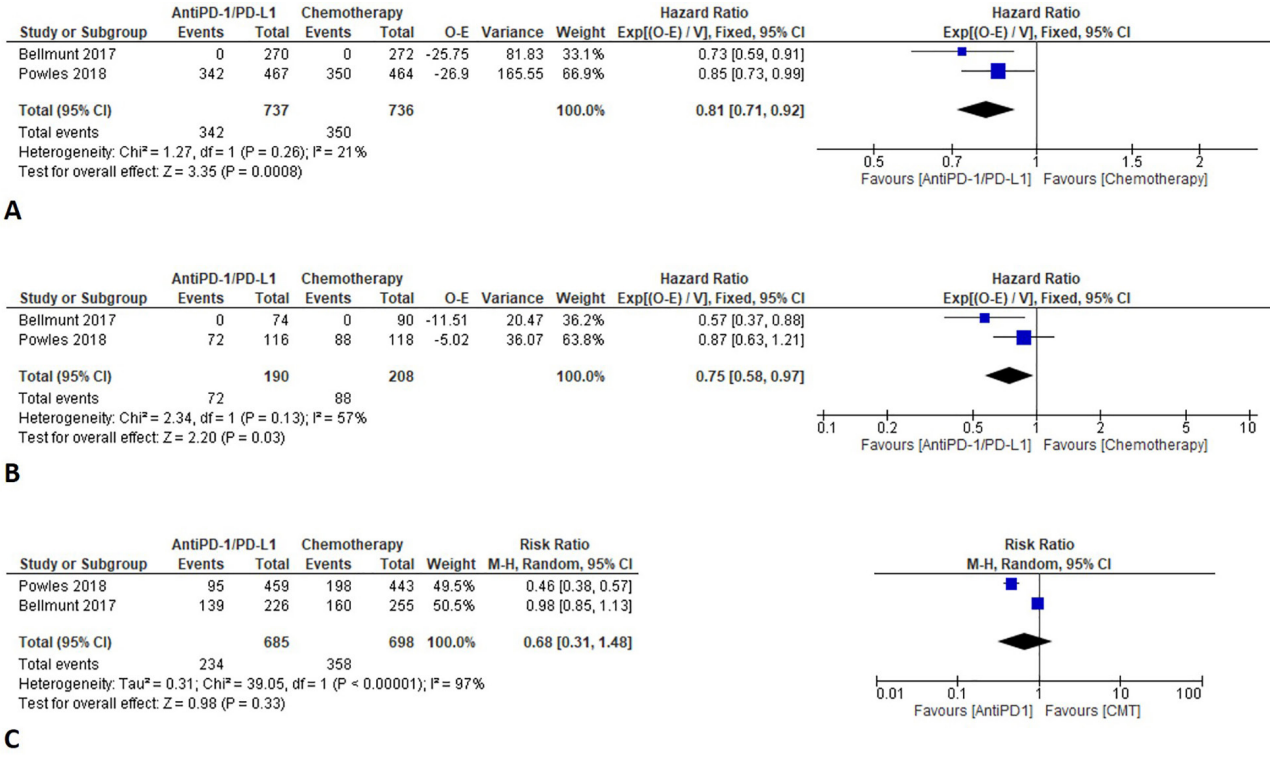

Figure 2 Forest plot of publications according to (A) overall survival, (B) overall survival in positive PD-L1 expression, and (C) adverse events

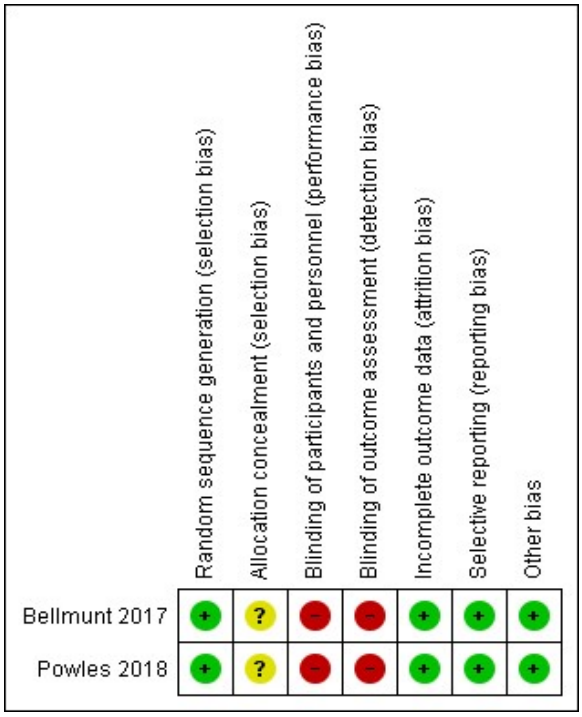

Figure 3 Assessment of risk of bias for each randomized clinical trial

Table 2 Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment of the level of evidence contributing to each outcome

Outcome	Pooled statistics* (95% CI)	Certainty					
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of the evidence
Overall survival of 2 RCTs	HR 0.8 (0.7 to 0.9)	serious*	not serious	not serious	not serious	none	+++o Moderate
Overall survival of positive PD-L1 expression of 2 RCTs	HR 0.8 (0.6 to 1.0)	serious*	serious†	not serious	not serious	none	++oo Low
Adverse event of 2 RCTs	RR 0.7 (0.3 to 1.5)	serious*	serious†	not serious	not serious	none	++oo Low

*Both RCTs did not blind †Substantial heterogeneity was observed

RCTs = randomized clinical trials; HR = hazard ratio PD-L1 = programmed cell death-ligand-1

DISCUSSION

Metastatic or locally advanced UBCs are unfavorable outcomes. Treatment options for these patients have been limited. Although platinum-based chemotherapy is the first-line treatment, the results have not been satisfactory.[23] In terms of immunotherapy, PD-1/PD-L1 inhibitors have been studied as a new treatment option. As a result, pooled data analysis demonstrated the survival benefit of PD-1/PD-L1 inhibitors over chemotherapy for overall survival. However, the CoE of this outcome was moderate because both included RCTs were open-label studies. Also, progressive-free survival outcomes were was not analyzed in the pre-sent study because the data were not complete for comparison.

PD-L1 expression has become an indicator for predicting response treatment. After conducting a systematic review and metaanalysis, Fan et al. reported that positive PD-L1 expression had a higher objective response rate than the negative group.[23] From subgroup analysis based on PD-L1 expression, PD-1/PD-L1 inhibitors still had significant survival benefits over chemotherapy according to positive PD-L1 expression. Recently, Rizzo et al. performed a systematic review and meta-analysis to evaluate PD-L1 expression as a predictive biomarker. The pooled results from three RCTs found that metastatic urothelial bladder carcinoma patients with PD-L1-positive had a significant survival benefit from immune checkpoint inhibitors.[24]

There is currently no consensus cutoff value of positive PD-L1 expression in UBC, Visible heterogeneity was observed because the cutoff values of positive PD-L1 expression varied between both included RCTs. The study of Bellmunt et al. used 10.0% or higher cutoff[21], while Powell et al. used 5.0% or higher.[22] In regard to other cancers, a positive levelof PD-L1 expression in of non-small-cell lung cancer study usually used 50.0% or higher PD-L1 expression.[25-28] The CoE of this outcom was low due to inconsistency and unblinded trials.

For immune-mediated AEs, Plimack et al. studied pembrolizumab in patients with metastatic or locally advanced UBC and found that the most common treatment-related adverse events were fatigue in 18.0% of the patients and peripheral edema in 12.0%, while 9.0% of the participants had patients who experienced serious AEs.[9] Rosenberg et al. reported on AEs of atezolizumab and found grade 3-4 AEs in 5.0% of the cases, though

no treatment-related deaths occurred.[7] From the RCTs included in this study, Bellmunt found grade 3 or higher AEs in 52.3% of the pembrolizumab group, with grade 3 or higher AEs in the chemotherapy group occurred in 62.7% of the patients, with treatment-related deaths in the pembrolizumab and chemotherapy groups of 3.9% and 3.1%, respectively.[21] From the Powles study, grade 3 or higher AEs in the atezolizumab and chemotherapy groups occurred in 20.6% and 44.9% of the patients, respectively.[22] As a result of the pooled events, there was no difference between anti-PD-1/PD-L1 agents and chemotherapy in grade 3 or higher AEs from phase III RCTs. However, the substantial heterogeneity can be explained by noting the various anti-PD-1/PD-L1 agents used and the open-label methodology of both included RCTs that caused a low CoE.

From the pooled results, PD-1/PD-L1 inhibitors tended to confer a survival benefit in locally advanced UBCs. Therefore, the efficacy or effectiveness of these immunotherapies should be examined in real-world situations such as clinical outcome research, observational studies, or phase IV clinical trials. Health economic studies would also be useful to examine the cost-effectiveness immunotherapy compared to chemotherapy, as novel treatments are usually more expensive than conventional treatments. Studying the immunotherapy from a health economics aspect will provide helpful information for seting up treatment strategies for use of the novel therapy in resource-limited settings.[29]

The major limitation of the present study should be acknowledged, namely that the number of included studies was small. Higher numbers are required to bolster the results. Several phase III RCTs are currently being conducted, i.e. NCT02500121, NCT02632409, and NCT 2807636. Updated meta-analyses should be conducted when these trials have finished.

CONCLUSION

The present meta-analysis and systematic review provide strong evidence that anti-PD-1/PD-L1 agents could improve OS and have similar results in AEs compared with second-line chemotherapy.

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