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Immune-checkpoint inhibitors in previously treated patients with advanced or metastatic urothelial carcinoma: A systematic review and meta-analysis

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ABSTRACT

Immunotherapy represents a new hope for patients with advanced urothelial carcinoma (UC). However, to date, only one of two randomized studies showed a clear survival advantage with these treatments.

Aimed to investigate the role of immune-checkpoint inhibitors in patients with platinum progressed metastatic UC we performed a systematic review and meta-analysis of clinical trials to evaluate the efficacy and activity, in terms of Overall Survival (OS) and Objective Response Rate (ORR).

Immune checkpoint inhibitors have showed to improve OS compared to chemotherapy in unselected patients (HR 0.80, 95% CI 0.69–0.93, p = 0.003), while the difference was not significant in patients selected for PD-L1 expression (HR 0.72, 95% CI 0.48–1.09, p = 0.12). Pooled probability of response was 0.18 (95% CI 0.16–0.20) in unselected patients and 0.27 (95% CI 0.25–0.32) in PD-L1 selected patients.

Immunotherapy results in a significant survival advantage in PD-L1 unselected patients suggesting that PD-L1 expression may not be a reliable marker in previously platinum treated patients.

1. Introduction

Urothelial cancer of the bladder, renal pelvis, ureter and other urinary organs is the ninth most common malignancy worldwide. Advanced stages of the disease including locally advanced or metastatic tumours still remain associated to poor prognosis with an estimate 5-years survival of only 5–30% making management of this tumour a priority and an open challenge for clinicians and researchers (Torre et al., 2015; Siegel et al., 2018).

Platinum-based regimens represent the standard treatment choice as first-line regimen, allowing a median overall survival (OS) of about 14 months (von der Maase et al., 2005; De Santis et al., 2012; Galsky et al., 2012). Unfortunately, a not negligible percentage of patients is unfit to receive standard cisplatin or carboplatin chemotherapy due to poor performance status and/or high number of comorbidities, and this leads to a further worsening of prognosis. Moreover, patients progressed during or after first-line have very few treatment options, represented mainly from platinum based regimens (for patients progressed more than 12 months after first-line) or single agent chemotherapy (docetaxel, paclitaxel or vinflunine). Of note, more than observed in other solid tumours, only a minority of patients progressed after first-line still remain fit for a subsequent treatments. Furthermore, none of the above listed agents have shown a statistically significant and clinically relevant benefit in OS in this setting (Locke et al., 2016; Raggi et al., 2016). Also Vinflunine failed to show an OS benefit over best supportive care in the intention to treat population (Locke et al., 2016; Raggi et al., 2016; Bellmunt et al., 2009, 2013).

Recently, a new class of drugs : the immune-checkpoint inhibitors, have been tested in advanced settings of urothelial carcinoma with very interesting results. These agents are able to bind receptors or ligands of specific pathways; whose inhibition leads to a restored anti-tumour immune activity. Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4), Programmed Death Receptor 1 (PD-1) and Programmed Death Receptor Ligand-1 (PD-L1) are the main targets of these drugs.

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Very recently, two large randomized phase III trials tested the anti-PD-1 monoclonal antibody pembrolizumab and the anti-PD-L1 monoclonal antibody atezolizumab as second-line treatment in patients progressed during or after platinum-based therapy, providing conflicting results: namely, the former produced a positive result (Bellmunt et al., 2017), while the trial testing the latter drug was formally negative (Powles et al., 2018). Both these agents have been approved by FDA in platinum resistant patients with more clinical benefit achievable in patients showing higher PD-L1 expression.

Despite these conflicting outcomes, immunotherapy represents a new promising approach for the management of patients with urothelial carcinoma. Within this scenario, we carried out a systematic review and literature-based meta-analysis, with the aim of evaluating the activity and the efficacy of immune checkpoint inhibitors in this setting, as well as of evaluating if the different results obtained are only apparently conflicting, and could be actually explained by several reasons, including the poor ability in selecting patients on the basis of PD-L1 expression.

2. Methods

2.1. Trial identification criteria

All clinical trials (phase I, phase II, phase III), published between 01 January 2014 and 28 February 2018, testing an immune checkpoint inhibitor as single-agent. Keywords used for searching on Pubmed/Medline, Cochrane library were: Urothelial carcinoma OR Urothelial cancer OR transitional cell carcinoma AND/OR: ''PD-1 inhibitor'', ''PD-L1 inhibitor'', ''CTLA-4 inhibitor'', ''Atezolizumab'', ''Avelumab'', ''Durvalumab'', ''Ipilimumab'', ''Nivolumab'', ''Pembrolizumab'', ''Tremelimumab''. Papers published in peer-reviewed journals, in English language, were considered. Furthermore, proceedings of the main International meetings (American Society of Clinical Oncology, European Society of Medical Oncology, American Association for Cancer Research annual meetings), were searched from 2014 onwards for relevant abstracts. When more than one report was available describing results of the same trial, the most recent information (corresponding to a longer follow-up and/or a higher number of patients) was considered in the analysis (Fig. 1).

2.2. Aims of the meta-analysis

Aims of the meta-analysis were:

(i) To evaluate the efficacy of single-agent immune-checkpoint inhibitors vs. single-agent chemotherapy in platinum resistant patients with advanced urothelial carcinoma in terms of overall survival (OS) and objective response rate (ORR). For this aim, randomized trials comparing an immune-checkpoint inhibitor vs. chemotherapy in the specified setting were eligible.
(ii) To describe the activity of single-agent immune-checkpoint inhibitors in patients with advanced urothelial cancer, in terms of ORR. For this aim, both the experimental arm of randomized trials and single-arm trials were eligible. Two analysis were planned: the first, in all patients, and the second, in the subgroup of patients previously treated with platinum-based chemotherapy.
(iii) To explore the predictive value of patients' selection according to PD-L1 expression for the activity and efficacy of immune-checkpoint inhibitors. For this aim, all the analyses were repeated in the subgroup of patients included, within each trial, in the highest category of PD-L1 expression.

2.3. Data extraction for meta-analysis

The following data were extracted for each publication: (a) first author and year of publication; (b) type of experimental drug and number of patients assigned to experimental treatment with immune checkpoint inhibitor; (c) for randomized trials only: type of control drug and number of patients assigned to control treatment; (d) for randomized trials only: overall survival outcome expressed as hazard ratio (and 95% confidence interval) for patients assigned to experimental treatment vs. patients assigned to control treatment, in intention-to-treat population and in the subgroup of cases selected for high PD-L1 expression; (e) for randomized trials only: objective response expressed as odds ratio (and 95% confidence interval) for patients assigned to experimental treatment vs. patients assigned to control treatment, in intention-to-treat population and in the highest category of PD-L1 expression; (f) for all trials: objective response expressed as proportion of responses observed in patients receiving experimental treatment, in all patients and in the highest category of PD-L1 expression. All data were reviewed and separately computed by two investigators.

2.4. Data synthesis

Primary endpoints of the meta-analysis were OS and ORR.

For aim (i), meta-analysis of randomized trials was performed using the Review Manager (RevMan 5.3) software. Summary measure was hazard ratio (HR) with 95% confidence interval (CI) for OS and odds ratio (OR), with 95% CI, for ORR. A random-effects model was applied. Statistical heterogeneity between studies was examined using the $\square^2$ test and the I^2 statistic.

For aim (ii), including the description of ORR in both randomized and non-randomized trials, the observed proportion and the 95% confidence interval (without continuity correction) was calculated for each study and for the overall case series (Julious, 1998).

3. Results

3.1. Systematic review of literature

3.1.1. CTLA-4 inhibitors

Ipilimumab is a fully human monoclonal antibody directed against CTLA-4 which is able to induce tumour regression and improved survival in murine bladder cancer model (Mangsbo et al., 2010). To date, only a phase II trial in which ipilimumab was administered in combination to chemotherapy (cisplatin and gemcitabine) evaluated this immune-checkpoint inhibitor in urothelial carcinoma. (Galsky et al., 2017).

Unfortunately, despite the study was designed as single-arm and there was no control arm, the addition of ipilimumab failed to show a significant clinical outcome improvement as compared to what expected with chemotherapy alone. Nonetheless, several trials are currently exploring the combination between CTLA-4 and PD-1/PD-L1 inhibitors (CheckMate 901, STRONG, NCT01928394) and so the possible role of this drug in urothelial carcinoma will be better defined in the near future.

3.1.2. Atezolizumab

Atezolizumab is a humanized IgG1κ engineered monoclonal antibody targeting PD-L1. In a first phase Ib study, carried out on 95 patients progressed to at least two lines of therapy, atezolizumab showed a safety profile as well as an interesting objective response rate (ORR, 26%), with a median duration of response of 22.1 months and a median overall survival (OS) of 10.1 months (3-year OS rate of 27%) (Petrylak et al., 2018). Of interest, patients' outcomes were evaluated according to PD-L1 expression, detected with Ventana SP142 immunohistochemistry assay. Response to treatment occurred in 40% and 11% of patients with PD-L1 expression of at least 5% and less than 5%, respectively. Furthermore, patients with higher PD-L1 expression showed longer OS as compared to patients with lower expression (median OS 14.6 vs. 7.6 months). Based on these promising results,