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Anti-Tumour Treatment

Immune checkpoint inhibitors for metastatic bladder cancer

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ABSTRACT

Chemotherapy has represented the standard therapy for unresectable or metastatic urothelial carcinoma for more than 20 years. The growing knowledge of the interaction between tumour and immune system has led to the advent of new classes of drugs, the immune-checkpoints inhibitors, which are intended to change the current scenario.

To date, immunotherapy is able to improve the overall responses and survival. Moreover, thanks to its safety profile immune-checkpoint inhibitors could be proposed also to patients unfit for standard chemotherapy.

No doubts that these agents have started a revolution expected for years, but despite this encouraging results it appears clear that not all subjects respond to these agents and requiring the development of reliable predictive response factors able to isolate patients who can more benefit from these treatments as well as new strategies aimed to improve immunotherapy clinical outcome.

In this review we describe the active or ongoing clinical trials involving Programmed Death Ligand 1 (PD-L1), Programmed Death receptor 1 (PD-1) and Cytotoxic-T Lymphocyte Antigen 4 (CTLA 4) inhibitors in urothelial carcinoma focusing our attention on the developing new immune-agents and combination strategies with immune-checkpoint inhibitors.

Introduction

Urothelial cancer of the bladder, renal pelvis, ureter and other urinary organs is the most common malignancy involving the urinary system and the ninth most common malignancy worldwide, with about 430,000 new cases diagnosed in 2012 [1].

In metastatic or unresectable disease, Cisplatin combination regimens have represented the standard First line therapy for patients with good performance status while patients unfit to Cisplatin were generally treated with Carboplatin regimens or platinum-free combinations containing taxanes and gemcitabine with an Overall Survival (OS) benefit achieved of 14 months [2–5].

After progression to first line several drugs have been tested without significant improvement in mOS except for Vinfluine, which showed an OS benefit only in eligible patients population compared to best supportive care in a phase III trial [6,7].

From more than 20 years no active treatments have shown to improve clinical outcome of patients with UC compared to chemotherapy. This until the demonstration that bladder cancer, like melanoma and non small cell lung cancer, is a tumour with a high somatic mutation frequencies and a high antigenic expression resulting in an optimal target for immune-checkpoint inhibitors [8].

PD-1 and PD-L1 are members of the Ig superfamily expressed on hematopoietic and non-hematopoietic cells (PD-L1) as well as on T Cell surface (PD-1). PD-L1/PD-1 interaction leads to "T-Cell exhaustion" that consisted of impaired cytotoxic activity and decreased effector cytokine production resulting in immune-response inhibition.

Atezolizumab (MPDL3280A) is an engineered, humanized monoclonal IgG1 antibody, with a high affinity for PD-L1 acting as inhibitor of the interaction between PD-L1 and PD1/B7.1. It was the

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First immune agents who showed clinical activity in UC [9]. On the wave of the positive results obtained in phase I trial, a following phase II trial (IMvigor 210 trial, NCT02108652) with two different cohorts was performed (cohort 1, patients with metastatic urothelial cancers ineligible for platinum based chemotherapy for First line treatment; cohort 2, patients who progressed during or following platinum-based treatment). Regarding, Cohort 2 (n = 310), patients who received Atezolizumab showed an Objective Response Rate (ORR) of 15% and a 12-month OS of 37% in the overall population with a median duration of response not reached after a medium of 17.5 months of follow-up [10].

Results of Cohort 1 (n = 119) showed an ORR of 23% in the whole cohort with a median duration of response not reached at 14.4 months of follow-up and a median OS of 14.8 months (95% CI 10.1 months to not reached) [11].

On the basis of the favourable results of the cohort 2, Atezolizumab has been approved by FDA for the treatment of patients with locally advanced or metastatic UC who have progressed during or following platinum-based chemotherapy or whose disease has worsened within 12 months neoadjuvant or adjuvant platinum-based chemotherapy.

Despite these remarkable results, more recently Powees et al. recently presented preliminary results of IMvigor211. This was a randomized phase III trial of Atezolizumab compared to chemotherapy (docetaxel, paclitaxel and vinflunine) in patients progressed to platinum based therapy. Surprisingly Atezolizumab failed to show an improvement in Overall Survival in overall population (8.6 vs 8.0 months for Atezolizumab and chemotherapy respectively, HR 0.85) and in patients with high PD-L1 expression (11.6 vs 10.6 months, HR 0.87) [12].

Pembrolizumab (MK-3475) is a humanized monoclonal IgG4 antibody against PD-1, which showed to be a safety and active treatment in a phase I basket trial involving also patients with UC [13]. Thanks to the positive results obtained in this study Pembrolizumab has been compared to standard second line chemotherapy in a large phase III clinical trial (Keynote 045) [14]. In this study 542 patients with locally advanced or metastatic predominantly transitional UC, progressed to First line platinum regimens or with recurrence disease within 12 months after adjuvant or neoadjuvant platinum containing therapy, were randomized (1:1) to receive Pembrolizumab 200 mg every 3 weeks (Q3W) or chemotherapy (paclitaxel 175 mg/m^2 Q3W or docetaxel 75 mg Q3W or Vinfluine 320 mg/m^2 Q3W). Results of this study showed a better OS for patients treated with Pembrolizumab in overall population (mOS 10.3 vs 7.4 months HR 0.73, 95% CI, 0.59–0.91, p = .002) and in patients with high PD-L1 expression (mOS 8.0 vs 5.2 months HR 0.57, 95% CI, 0.37–0.88, p = .0048). No differences in terms of PFS have been found between the two arms. ORR as assessed on the intention to treat population) was significantly better in Pembrolizumab arm (21.1% vs 11.4%) with a duration of response not reached (1.6–15.6 + months).

Partial results of the still ongoing phase II KEYNOTE 052 trial seems to confirm this positive results also when Pembrolizumab is adopted as First line therapy in platinum unfit patients with UC [15].

Nivolumab (MDX 1106) is a fully human IgG4 monoclonal antibody against PD-1 that has been approved for treatment of advanced melanoma, Hodgkin lymphoma, non-small cell lung cancer, head and neck cancer, and renal cell cancer. In UC it showed to be an active and safety treatment in phase I and II studies [16,17]. As observed with Nivolumab also the PD-L1 inhibitors Avelumab (MSB0010718C) and Durvalumab (MEDI4736) showed promising activity in phase I/II clinical trials in patients with UC suggesting the development of further clinical trials exploring these agents in different setting of UC [18–21]. The CTLA-4 receptor also known as CD156 is a member of the immunoglobulin superfamily and a transmembrane receptor expressed exclusively on T cells. The activation of CTLA-4 happened through interaction with CD80 and CD86 on antigen presenting cells and leads to a down-regulation of T helper lymphocyte and enhanced regulatory T cell immunosuppressive activity resulting in immune response inhibitor signal [22].

Ipilimumab is a CTLA-4 inhibitor that showed in a small clinical trial to be a safety preoperative treatment in patients with bladder UC [23].

On the basis of the positive outcome obtained it seems clear that the treatment paradigm of UC is about to change. The demonstration that immunotherapy could led to long term responses in different setting of UC and the safety profile showed in different clinical trials have move the development of several studies exploring these agents. This has led to in a complex scenario that will profoundly change the management of the disease. In the next paragraphs we will describe the ongoing and active clinical trials exploring these agents in different setting of the disease. In Table 1 and table are summarized the phase III and phase I, I/II, II descripted in this manuscript (see Table 2).

PD-1 and PD-L1 inhibitors

On the wave of the positive outcome obtained previously descripted clinical trials PD-1 inhibitors: Pembrolizumab and Nivolumab as well as the PD-L1 inhibitors: Atezolizumab, Avelumab and Durvalumab are being tested individually in different clinical trials and in different stages of the disease.

Regarding preoperative setting Pembrolizumab is being tested in a phase II trial enrolling 90 patients with muscle invasive bladder UC (T2-T4 N0) with residual disease after transurethral resection (NCT02736266). Patients enrolled will receive 3 cycles of Pembrolizumab (200 mg Q3W) before planned cystectomy with primary endpoint: pathological complete response rate. Another phase II trial is currently exploring the role of Atezolizumab as preoperative treatment in patients with T2-T4a urothelial bladder cancer (NCT02662309). Of note primary endpoints of this studies are the pathological complete response rate (pCRR, defined as $\geq$20% reduction in residual disease of the bladder based on histological evaluation of the resected bladder specimen collected during cystectomy post-treatment) and the dynamic changes in T cell subpopulations (CD8 and/or CD3) measured in tumour samples collected pre- and post-treatment.

Immune-checkpoint inhibitors are also under investigation in early stage of the disease. Indeed, a phase II trial (NCT02625961) will test Pembrolizumab in 260 patients with high risk non muscle invasive bladder cancer (high risk Ta, T1, carcinoma in situ) refractory to Bacillus Calmette-Guerin (BCG) therapy with primary endpoints: Disease Free Survival (DFS) and pCRR. Furthermore, another phase II trial is currently exploring the role of Atezolizumab in patients with high-grade urothelial bladder cancer refractory to BCG (NCT02844816).

Pembrolizumab and Avelumab are being tested as maintenance therapy after platinum-containing first line therapy. The phase III trial JAVELIN Bladder 100 study (NCT02603432) is currently ongoing to compare maintenance treatment with Avelumab plus best supportive care (BSC) versus BSC alone in metastatic UC patients who have not progressed during or following First-line systemic therapy. Primary endpoint is OS and approximately 668 patients are planned to be enrolled. This study will be completed in July 2019. The phase II trial (NCT02500121) is currently testing Pembrolizumab as maintenance therapy after standard First line chemotherapy in patients with locally advanced or metastatic UC. This study has 6-months PFS as primary endpoint and planned an enrolment of 200 patients with stable disease (SD), complete response (CR) or partial response (PR) after platinum-based first-line that will be randomized to receive Pembrolizumab or placebo.