



What we Really (don't) Know about Immunotherapy: A Clinical Case of Urothelial Carcinoma

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Abbreviations: AE: Adverse Event; Anti-PD-L1: Antibody Against Programmed Death-Ligand 1; BT: Bladder Tumour; CHT: Chemotherapy; CT: Computed Tomography; DFS: Disease-Free Survival; EC: Emergency Department; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GFR: Glomerular Filtration Rate; ICI: Immune Checkpoint Inhibitor; MDT: Multidisciplinary Team; NA: Neoadjuvant; ORR: Objective Rate Response; OS: Overall Survival; PD-1: Programmed Death-1; PD-L1: Programmed Death-Ligand 1; RC: Radical Cystectomy; TUR: Transurethral Resection; UC: Urothelial Carcinoma; US: Ultrasonography; WHO: World Health Organization

Introduction

More than 115000 patients are estimated to die in 2020 from bladder tumour (BT) [1]. Platinum-based chemotherapy (CHT) has been the standard of care in patients with locally advanced or metastatic urothelial carcinoma (UC) with an overall survival (OS) of 9–15 months [2–4]. However, there is no global standard for patients who progress after platinum therapy and the median OS is approximately 7–9 months [5–6]. Several new agents, such as

immune checkpoint inhibitors (ICIs), including programmed death-ligand 1 (PD-L1) and programmed death-1 (PD-1), are addressing this high unmet need [7–10]. This clinical case describes an UC categorized as PD-L1 negative, with an exceptional response to first-line therapy atezolizumab (anti-PD-L1 drug).

Clinical Case

A 64-year-old man, ECOG 0, tourism worker, non-smoker and without other comorbidities besides arterial hypertension, was admitted to the emergency department (ED) in April 2013, complaining of intermittent macroscopic hematuria during the past week, without other symptoms. Physical examination was unremarkable, with unchanged analytical studies. Pelvic US revealed thickening of the bladder wall. Patient was referred to Urology. CT scan confirmed a focal thickening on bladder wall. Cystoscopic examination was performed and pathological diagnosis, made by biopsy obtained during transurethral resection (TUR) of the BT, identified a low-grade papillary UC (pTa). Multidisciplinary team (MDT) purposed it to surveillance. Nine-months later the patient returned to ED because of macroscopic hematuria with an onset of 2-months, associated with severe asthenia. Analytical study revealed Hb 5.6g/dL; CT scan showed a lesion on the right bladder wall, approximately 7.1cm long and

2.2cm thick, without visceral or ganglionic metastasis (Figure 1). At that time, another cystoscopic examination plus biopsy by TUR was performed and pathological diagnosis revealed a non-papillary UC widely invasive of the chorion and detrusor muscle (T3) (Figure 2). MDT decided for neoadjuvant (NA) CHT followed by radical cystectomy (RC). Patient fulfilled 4 cycles, q3w, of cisplatin (70mg/m², d1) plus gemcitabine (1000mg/m², d1, d8), between July and September 2014, with no record of relevant adverse events (AE). CT scan demonstrate a partial imaging response (Figure 3). RC, with bilateral ileo-obturator lymphadenectomy and cutaneous ureteroileostomy, was performed; pathological examination revealed a high-grade non-papillary UC with parietal invasion and without regional ganglionic metastases (pT2bG3N0). MDT decided for surveillance. After 3.5 years, the patient was asymptomatic, but a follow-up CT scan showed ganglionic progression, by means of an increase of right common

iliac adenopathies dimension, and a left uretero-hydronephrosis up to the implantation zone in the ileum. MAG3 renogram scan demonstrated left kidney with 7% function, corresponding to a complete functional exclusion. MDT decided for first-line systemic palliative treatment. At May 2018, patient glomerular filtration rate (GFR) was of 50.1mL/min/1.73m² and, because that, patient was cisplatin-ineligible. Therefore, atezolizumab was started (1200mg IV, q3w). In January 2019, PD-L1 expression was evaluated, using Dako 22C3 immunohistochemistry assay, and a Combined Positive Score of 8 was obtained, corresponding to a negative categorization. The only reported AE was a subclinical hypothyroidism, treated with levothyroxine and monitored in collaboration with Endocrinology. Patient have now completed 39 cycles of atezolizumab and no signs of clinical or imaging relapse were observed (Figure 4).



Figure 1: Axial arterial phase CT scan shows hypervascular focal wall thickening along right lateral bladder wall, with perivesical fat stranding, without lymphadenopathies.

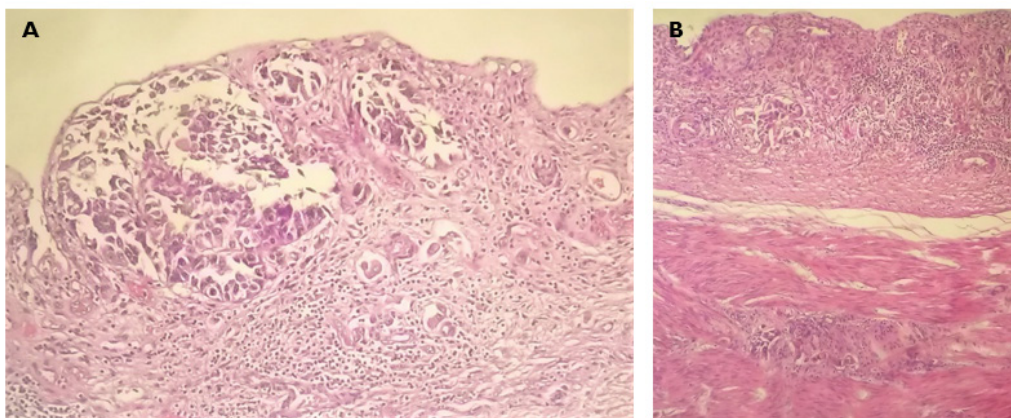


Figure 2: A - Poorly differentiated urothelial carcinoma of the bladder. Mucosa invasion (HE 40x). B - Poorly differentiated urothelial carcinoma of the bladder wall with proper muscle layer invasion (HE 30x).



Figure 3: Axial venous phase CT scan shows partial reduction of the wall thickening, though persistence of perivesical fat density, vaguely nodular in appearance.

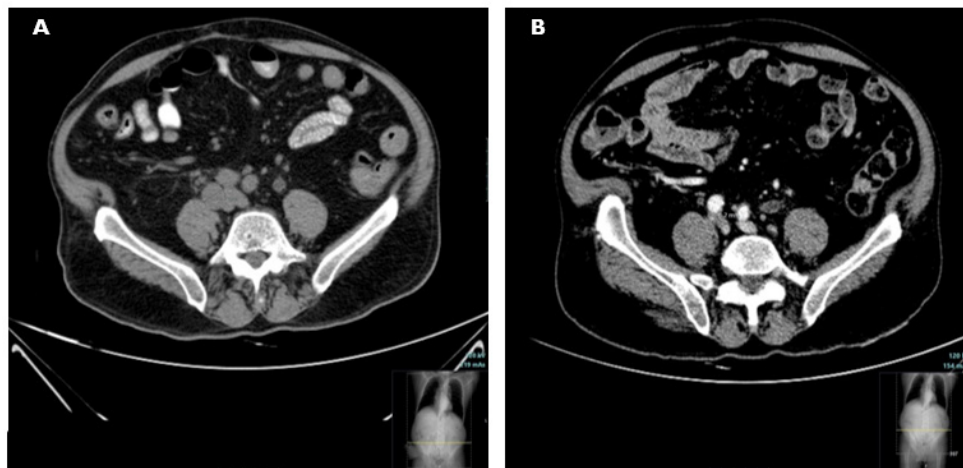


Figure 4: Axial non-contrast (A) and late arterial phase CT scan (B) shows right common iliac lymphadenopathy in February 2018, and its shrinkage after immunotherapy, in May 2020.

Discussion

From the clinical information presented, and despite the absence of risk factors such as smoking, we can state that gender, age and clinical presentation are in favor of UC [11]. Pathological diagnosis was made according to the WHO classification from a biopsy obtained during TUR of the BT. Throughout the course of disease and based upon biopsy's pathological findings, attending to histology, grade and depth of invasion, the UC was treated according to current guidelines: 1) surveillance is indicated to low-grade non-invasive papillary UC; and, 2) for fit patients, RC with extended lymphadenectomy is usually considered to be the standard treatment of muscle-invasive BT. The use of cisplatin-based NA CHT is associated to a 5% absolute increase in 5-year OS and a 9% absolute increase in 5-year disease-free survival (DFS) compared with RC alone [12]. A good response to NA CHT plus RC was observed and for more than three years there was no evidence of clinical and/or imaging relapse. During the follow-up a ganglionic progression occurred. At that time, patient presented ECOG 0, no hearing loss and/or no neuropathy, and GFR <60ml/min [5]. Because GFR, patient was cisplatin-ineligible and atezolizumab was started. The immunohistochemistry assay used to quantify the tumor cell PD-L1 expression was the Dako 22C3 assay; despite the approval immunohistochemistry assay for atezolizumab is the Ventana SP142 assay, some literature reports a concordance among the four commercially available and validated programmed cell death ligand-1 assays [13]. By May 2018, despite of PD-L1 status, ICIs such atezolizumab and pembrolizumab, were first-line treatment options for locally advanced or metastatic UC that has progressed during or after platinum-based CHT; that has progressed within 12 months of NA or adjuvant platinum-based

CHT; who are cisplatin-ineligible and whose tumors express PD-L1; or, in patients who are not eligible for any platinum-based CHT regardless of PD-L1 expression [14,15], and treatment should continue until disease progression [9]. Nowadays, for cisplatin-ineligible patients, the ICIs may be considered for therapy based on PD-L1 testing results. Data from the two-cohort, multicenter, phase 2 IMvigor-210 trial evaluated atezolizumab in patients with metastatic disease, showing a significantly improved objective rate response (ORR) compared to historical controls (15% vs. 10%; $p=0.0058$); and, an analysis of post-progression outcomes showed that those patients who continued atezolizumab had longer post-progression OS (8.6 months) compared to those who received a different treatment (6.8 months) and those who received no further treatment (1.2 months) [9]. As a consequence, by the end of 2018, atezolizumab prescribing information was amended to restrict first-use to patients who either 1) are not eligible for cisplatin-based CHT and whose tumors express PD-L1; or 2) are not eligible for any platinum-containing CHT regardless of the level of tumour PD-L1 expression [16]. Results from a phase 3 trial, that showed a longer median OS for patients treated with pembrolizumab compared to CHT (10.3 months vs. 7.4 months; $p=0.002$), have led the NCCN Panel to assign pembrolizumab a category 1 recommendation as a second-line therapy [17]. From the above, and currently, the recommended treatment for the patient presented in this clinical case, would be CHT with gemcitabine plus carboplatin instead of immunotherapy, with a significant increase in the likelihood of developing adverse events, as well as increased odds of death from an AE and poor quality of life when compared to immunotherapy [18].

Conclusion

Cancer immunotherapies are changing the treatment landscape and the outlook for patients with urothelial carcinoma. To our knowledge, this clinical case supports the clinical benefit of atezolizumab in urothelial cancer treatment. Important future challenges include identifying the patients most likely to benefit from atezolizumab, despite PD-L1 perceived unworthy status for immunotherapy, determining optimal treatment durations and sequencing, and developing urothelial carcinoma treatment algorithms across all lines of therapy.

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