

Long lasting complete response with immunotherapy in a metastatic bladder carcinoma: a case report

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Abstract

At diagnosis, approximately 25% of urothelial carcinoma are invasive and only 15% of stage IV are alive at 5-years. We report a case of a 69-year-old woman with oligometastatic bladder cancer, treated with Atezolizumab in first-line, achieving a complete response after 4 cycles. Presently, the patient has an overall survival and progression free survival of 26 months with an improvement in her quality of life. Therefore, immunotherapy seems to be a promising treatment in advanced urothelial carcinoma. The previously performed radiotherapy, in association with a good performance status and oligometastatic disease, might have contributed to this admirable outcome.

Keywords: complete response, immunotherapy, metastatic bladder carcinoma

To the Editor,

We present a case of a 69-years-old patient diagnosed with stage IV bladder cancer, who had a long lasting complete response (CR) after atezolizumab treatment. Currently, her overall survival (OS) and progression free survival (PFS) are 26 months. Additionally, a brief review of the main treatment options in the metastatic setting, of the prognosis factors and of the identified predictive biomarkers of response was done.

Introduction

Bladder cancer is the most common cancer of urinary system.¹ Cigarette smoking is the most recognized risk factor; likewise patients who had upper urothelial carcinoma (UC) are at increased risk of developing bladder carcinoma.^{2,3}

Approximately 25% of newly detected cancers are invasive with 5% being metastatic disease.² In stage IV only 15% of patients outlive 5 years with the standard treatment of a cisplatin-based combination chemotherapy. As many patients are ineligible for this regimen, immunotherapy becomes an option in this setting.^{4,5}

Case

A 69-years-old woman with chronic kidney disease (CKD) stage 3b, in follow-up of an UC of the renal pelvis (treated with radical

left nephroureterectomy), without family history of cancer, was diagnosed with a solid lesion in the anterior bladder wall in December 2016. Histology of transurethral resection revealed a muscle invasive high grade UC of the bladder. Computed tomography (CT) was negative for distant metastasis. The patient underwent radical cystectomy with ileo-obturator lymphadenectomy and no chemotherapy regimen was performed due to renal impairment. Histology revealed a pT3bN0R0 stage disease.

In November 2017, the patient was admitted to the emergency department with constipation and tenesmus. Thoracoabdominal-pelvic (TAP) CT scan showed a nodular structure, in relation with sigmoid colon, on the left side of the pelvis with 32 × 43 mm (Fig. 1). Sigmoidoscopy revealed extrinsic compression at 20 cm from the anal margin. The multidisciplinary team considered the pelvic lesion unresectable and the patient ineligible for platinum-based chemotherapy, so it was then proposed radiotherapy for pain control and a prosthesis placement. The patient underwent radiotherapy, 56 Gy in 28 fractions, until March 2018. In January 2018, the prosthesis was expelled and a derivative colostomy was performed. Re-evaluation TAP-CT showed a stable pelvic lesion (50 × 31 mm). Treatment with atezolizumab (1200 mg every 3 weeks) was proposed and started in April 2018. After 12 weeks, a re-evaluation CT revealed complete resolution of the pelvic mass (Fig. 1). After 8 cycles, renal function deteriorated slightly (clearance 28 mL/min, without proteinuria deterioration) and once patient maintained CR, it was decided to discontinue treatment. Last image evaluation, in June 2020, showed no evidence of disease. The patient is currently asymptomatic with an Eastern Cooperative Oncology Group performance status (ECOG) of 1. Current OS and PFS are 26 months.

Discussion

Cisplatin combination regimens have been the standard first-line treatment for metastatic UC for at least 30 years.⁶ These treatments substantially improved patient outcomes with an overall response rate (ORR) of ~50%, achieving an OS of 14 to 15 months and a 5-year survival of 13% to 15%. Cisplatin/gemcitabine is preferred over methotrexate/vinblastine/doxorubicin/cisplatin due to a better safety profile.⁴ Regarding that 50% of patients are considered unfit for cisplatin, due to an ECOG ≥ 2,

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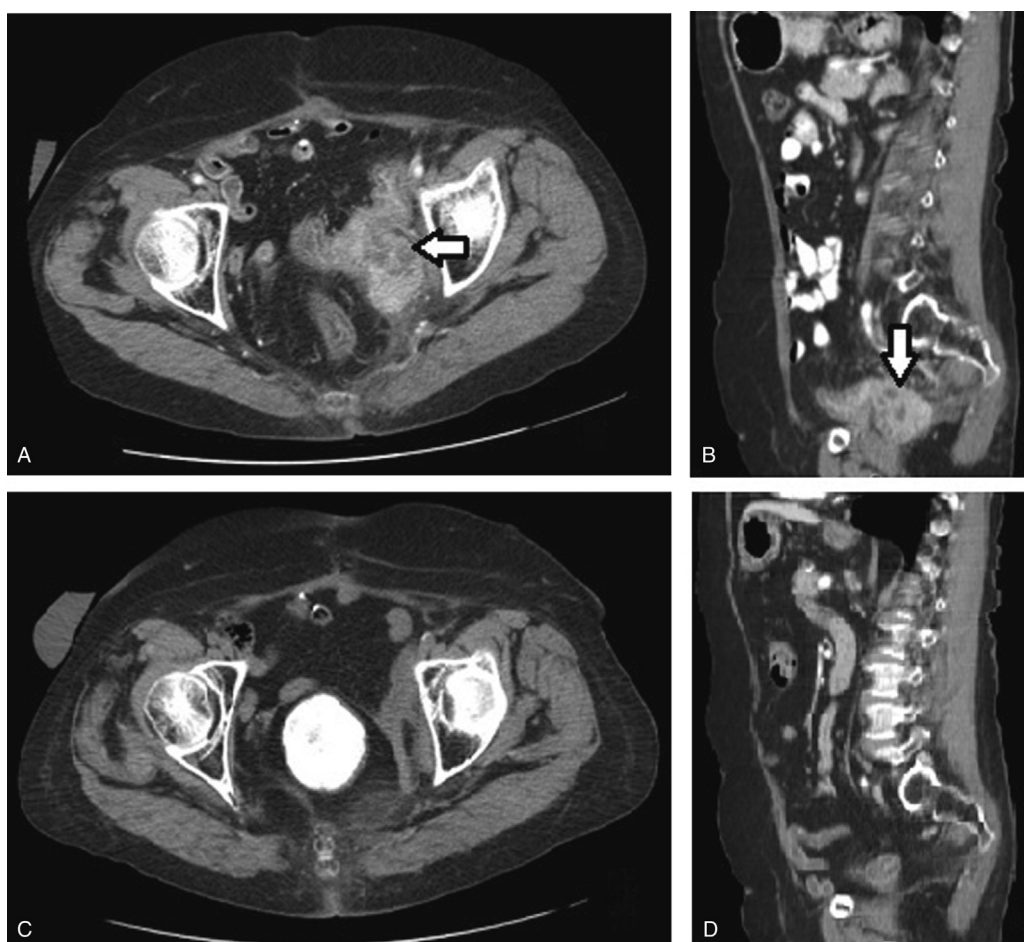


Figure 1. Thoracoabdominopelvic computed tomography. (A) Transverse and (B) Sagittal plan of the nodular structure (arrow) on the left side of the pelvic cup with 32 × 43mm, in relation with the sigmoid colon. (C, D) Transverse and sagittal plan, respectively, showing resolution of pelvic lesion.

a clearance <60 mL/min or comorbidity that forbids high-volume hydration,⁶ for these patients the treatment of choice is carboplatin-based chemotherapy, providing a lower OS of 8 to 9 months.⁶ In this case, impaired renal function led the patient to be considered unfit for cisplatin.

In recent years, the paradigm of cancer treatment has changed with the advent of immune checkpoint inhibitors (ICI). Since 2016, 5 immunotherapies targeting the PDL-1/PD-1 pathway were approved in UC.⁵ Atezolizumab, a monoclonal antibody against PDL-1, was approved in the front-line setting, based on IMvigor210.^{5,7} Recent results of IMvigor130, a 3-arm trial, are in accordance to IMvigor210. In the atezolizumab arm the ORR was 23%, with 6% achieving a CR, the median duration of response was not estimable. With a median follow-up of 12 months, the OS was 15.7 months in the atezolizumab arm and 13.7 months in the platinum-based chemotherapy. When PDL-1 expression was $\geq 5\%$ the OS was not yet achieved.⁸ In patients with tumor PDL-1 expression <5% the preliminary results pointed to a harmful effect of atezolizumab monotherapy, which led to a restriction in the prior approval to use atezolizumab only in tumors with PDL-1 expression $\geq 5\%$. However, in the final analysis, survival curves favoured platinum-based chemotherapy earlier but atezolizumab later.⁸

In this case, immunotherapy seemed to be the best therapeutic option, providing an improvement to OS with a safety toxicity profile. In IMvigor210 adverse events have occurred in 16% of

the patients, and no decline in glomerular filtration rate was observed.⁷ In this case the patient did not experience any treatment-related toxicities, the slight deterioration in renal function (increase of 0.2 mg/dL in serum creatinine) with stable mircoalbuminuria was not attributed to atezolizumab treatment. Our patient had an excellent response to atezolizumab, achieving CR after 4 cycles, sustained 1.5 years after treatment discontinuation. To our knowledge there are no case reports of a CR maintained for so long. The oligometastatic disease with no visceral metastases and the good performance status might have contributed to this outcome.⁴ Furthermore, our patient underwent radiotherapy prior to atezolizumab—could this have contributed to this outcome? Some studies pointed to a synergy between these treatments: RT promotes antitumor response and increase tumor antigen release, and ICI augment local and systemic immunity, and potentially reduce the risks for metastatic recurrences. Nevertheless, additional studies are required to define optimal radiation dose and timing respecting ICI.⁹

Ongoing efforts are being made to identify biomarkers to predict ICI response, to provide a better selection of patients. PDL-1 expression is the most frequently explored, and despite some correlation in most studies, it is not universally predictive, so others predictors are being suggested, as high tumor mutational burden and molecular subtypes of UC.^{5,7,8}

The patient had experienced an improvement in quality of life, and currently is asymptomatic and without evidence of disease.

Finally, the medical team has raised some questions: what should be the time to discontinue immunotherapy in a responder patient and, after progression, whether or not should atezolizumab be reintroduced.

With the recent results of IMvigor130 and JAVELIN bladder 100, chemotherapy associated or followed by maintenance immunotherapy, may become the new standard of care in front-line. Now we need evidence for treatments options after first-line immunotherapy.

Assistance with the study

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Conflicts of interest

The authors declare no conflicts of interest.

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