Letter to the Editor

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Pseudoprogression or unexpected favorable response to third-line therapy: a challenging metastatic bladder cancer case

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Introduction

Bladder cancer is the first most common urologic malignancy in adults and it is highly lethal in the metastatic setting.[1] The incidence rate is approximately 3 times higher in men than in women. The most well-established risk factor for urothelial carcinogenesis is cigarette smoking.[2] Approximately 10% to 20% of patients with invasive urothelial cancers present with metastatic disease at diagnosis and another 20% to 70% will subsequently develop it after definitive treatment of the invasive primary tumor, depending on the stage and lymph node status.[3] The most frequent sites of metastization are the pelvic region, bone, lymph nodes, and lung. The presence of bone or liver metastasis and poor performance status (PS) are predictive of poor response and survival. Platin-containing combination chemotherapy is the standard approach for the initial treatment of patients with metastatic urothelial malignancy.[4] In second-line single agent paclitaxel and docetaxel are commonly used worldwide and in Europe,[5,6] and vinflunine has been approved on the basis of an overall survival (OS) advantage of 2 months over best supportive care.[7] Nowadays, immune checkpoint inhibitors offers an additional option for patients progressing after their initial systemic therapy or when the patients are not eligible for platinum.

Tumors respond differently to immunotherapies compared with chemotherapeutic drugs, raising questions about the assessment of changes in tumor burden—a mainstay of evaluation of cancer therapeutics that provides key information about objective response and disease progression.[8] A consensus guideline—iRECIST—was developed by the Response Evaluation Criteria in Solid Tumors (RECIST) working group for the use of modified RECIST in cancer immunotherapy trial.[8] The existing literature describes pseudoprogression as an increase in the size of lesions or the visualization of new lesions, followed by a response, which might be durable.[9] Although well described, differentiating transient pseudoprogression from true progression, potentially requiring an alteration in therapy, can be challenging. Although early discontinuation of an effective drug is not desirable, continued long-term treatment with a noneffective drug past true progression might delay the initiation of potentially effective salvage therapy. The authors present a case of a 58-year-old patient diagnosed with metastatic bladder cancer with a deep and durable unexpected favorable response to third-line treatment.

Case report

In February of 2016, a 58-year-old smoker of 10 cigarettes/day, a man with Eastern Cooperative Oncology Group. Eastern Cooperative Oncology Group (ECOG) 0 was admitted in the emergency with macroscopic hematuria. The etiologic investigation carried out identified malignant cells in the urinary cytology with characteristics of urothelial carcinoma (UC). The patient underwent transurethral resection with diagnosis of extensive bladder neoplasia, which involved the right posterior, lateral wall and cervix of the bladder. In January 2017 the patient underwent radical cystectomy with ileo-obturator lymphadenectomy. As a postoperative period complication, the patient presented dehiscence of the operative wound. Histological examination showed UC of the bladder compatible with the pT4N0 stage (Fig. 1A). No adjuvant chemotherapy regimen was performed because it was out of time in the context of postoperative complications. In June 2017, a computed tomography showed pulmonary lesions. The patient completed the study with FDG PET (Positron-emission tomography with use of fluorodeoxyglucose), which showed 1 hepatic lesion, 1 bone lesion in L1, and 2 lung lesions (SUV max of 14). The patient started palliative chemotherapy with carboplatin and gemcitabine regimen due to decreased renal function (1000 mg/m^2 of gemcitabine IV on days 1 and 8, followed by carboplatin Area Under The Curve (AUC) 5 days 1 every 3 weeks). After the first cycle, he was hospitalized for grade 4 febrile neutropenia (FN—version 5.0 CTCAE). After dose reduction by 20%, optimization of supportive medication and omission of D8 in chemotherapy regimen, the patient had new hematological toxicity requiring new hospitalization due to a new FN. After this complication, it was decided to change systemic therapy for pembrolizumab. Our patient in the histological sample revealed a combined positive score (CPS) >10 as we can see in Figure 1B. Before second-line treatment, the revaluation PET showed partial response of the first-line regimen with persistent lung disease.

The patient started pembrolizumab (200 mg IV every 3 weeks) in December 2017, without intercurrences. After 12 weeks, reevaluation with PET revealed new lesions in liver, lung, and lymph nodes. Tumor progression was assumed and therapeutic regimen was changed for paclitaxel (80 mg/m^2), in April 2018.

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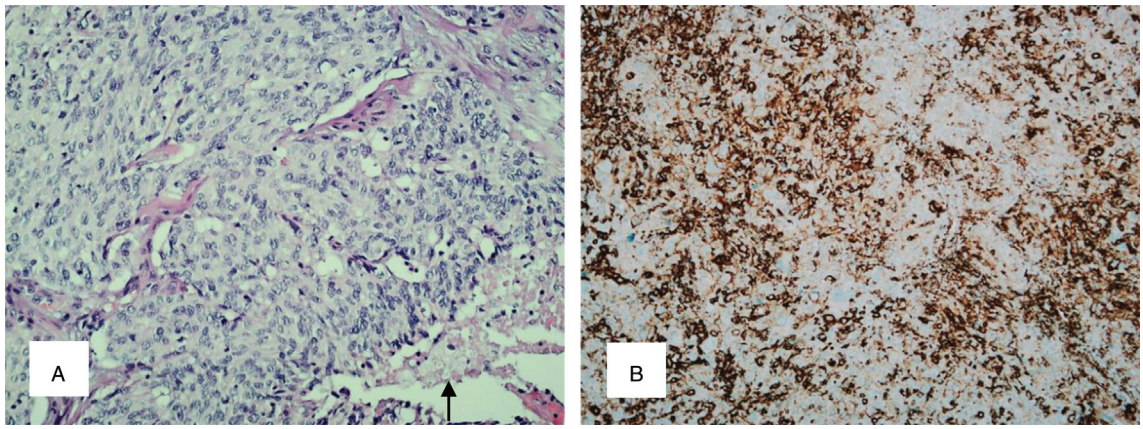

Figure 1. Invasive urothelial carcinoma of the bladder. A, High-grade lesion with large irregular nests and clusters of tumor cells with overt cytological atypia and necrotic areas (arrow) (H&E, 200×). B, PD-L1 expression (22C3 antibody) in tumor cells and tumor-associated inflammatory cells. combined positive score (CPS) >10 (200×).

After 10 cycles of paclitaxel, the imaging study showed stable disease. PET after the 25th cycle showed only adenophatic focus in the right acetabulum with complete response in the lung and liver. The patient is currently without treatment-associated toxicity and with ECOG 0. Current survival is 20 months and Progression-free survival (PFS) is 11 months.

Discussion

UC of the bladder is categorized into 3 main disease states based on clinical staging: nonmuscle invasive bladder cancer, muscle invasive bladder cancer, and metastatic UC. At the time of diagnosis, most patients present with nonmuscle invasive bladder cancer, which has a 50% to 70% rate of superficial recurrence and a 10% to 30% rate of progression to muscle invasive bladder cancer.[2]

Cisplatin-based chemotherapy remains the standard of treatment in patients with metastatic UC. The overall response rates (ORRs) are 60% to 70% with cisplatin-based chemotherapy and are associated with an OS of 14 to 15 months and a 5-year survival of 13% to 15%.[3] In the modern era, the 2 most commonly used regimens are gemcitabine plus cisplatin or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC; also referred to as high-dose intensity MVAC or accelerated MVAC). More than 50% of patients are ineligible ("unfit") for cisplatin because of poor PS, impaired renal function or comorbidity that forbids high volume hydration. The European Organization for the Research and Treatment of Cancer led the first trial, which evaluated the optimal first-line metastatic regimen for cisplatin-ineligible patients by comparing gemcitabine and carboplatin (GCa) to the older regimen of methotrexate, carboplatin, and vinblastine. In that study, cisplatin-ineligible criteria were an estimated glomerular filtration rate between 30 and 60 mL/min and/or a performance score of 2. Both the ORR and toxicity profile favored GCa, establishing GCa as the preferred regimen in cisplatin-ineligible patients.[10] Cisplatin-ineligible patients have a median OS of 8 to 9 months with first-line carboplatin-based combination chemotherapy. In this case, the patient started with carboplatin and gemcitabine because of impaired renal function (clearance <60 mL/min). In the European Organization for the Research and Treatment of Cancer trial,[10] 20% of the patients had grade 4 FN. In this case, patient had an FN after the first and second cycle of treatment with unacceptable hematological toxicity, even after dose reduction and filgrastim support.

After nearly 3 decades of limited advances in the treatment and systemic management of urothelial cancer, recent advances in immunotherapy are now available. Antibodies targeting negative regulation of immune cells, known as immune checkpoint inhibitors, have dramatically impacted the therapeutic landscape for numerous cancers. In bladder cancer, 5 immunotherapies targeting the PD-1 pathway were approved between 2015 and 2016 after a period of decades without any new drug approvals.[11] Pembrolizumab, a PD-1 inhibitor was approved in the second-line setting based on phase III KEYNOTE 045. Although the chemotherapy arm of the trial had a longer median PFS (3.3 vs 2.1 months) compared with pembrolizumab, the median OS was superior with pembrolizumab compared with chemotherapy at 10.3 versus 7.4 months for ($P < .01$). For PD-L1 CPS score ≥10%, there was a median OS advantage with pembrolizumab (8.0 vs 5.2 months, $P = .005$). For patients with PD-L1 CPS score <10%, there was numerically greater OS with pembrolizumab, but it did not reach statistical significance. The time to deterioration was significantly longer in those treats with pembrolizumab compared with chemotherapy and a serious treatment-related adverse events were significantly less frequent too.

Pembrolizumab received first-line accelerated approval for cisplatin-ineligible locally advanced or metastatic UC based on the results of the phase II KEYNOTE-052 study. Among 370 patients, ORR was 29%, with 7% of patients achieving CR at a median follow up of 9.5 months. PD-L1 CPS of ≥10% had a higher ORR of 51%. Median duration of response was not reached, with 82% of responders maintaining their response for ≥6 months.

In our case, patient initiated pembrolizumab because he had inacceptable toxicity to platinum. After 12 weeks, the PET became worse with new lesions in liver, lung, and lymph nodes. The doubt settled on the possibility of clinical progression versus pseudoprogression associated with immunotherapy. Although early discontinuation of an effective drug is not desirable, continued long-term treatment with a noneffective drug past true progression might delay the initiation of potentially effective salvage therapy. The definition of imaging criteria for evaluation

of response to different therapies is essential. Immunotherapy generates a response that is not yet fully understood. iRECIST requires the confirmation of progression to rule out or confirm pseudoprogression. Although this recommendation is in keeping with that of RECIST 1.1 to continue treatment and repeat imaging in the case of a mixed response or equivocal findings, if pseudoprogression is common, patients might be exposed to a higher risk (of continuing ineffective therapy or increasing exposure to radiation) or cost (for the potentially ineffective therapy or the costs of imaging). In this case, patient had visceral metastasis that could rapidly evolve to liver insufficiency and the medical team did not desire to lose the therapeutic window opportunity. Because of that, it was assumed tumor progression, and therapeutic regimen was changed for paclitaxel.

After first line, reported response rates with single agents in the larger series have generally been 20% or less.[12] The experience with single agent paclitaxel following the failure of a platinum-based regimen is limited and based upon small retrospective reports. A retrospective study evaluated 42 patients with metastatic urothelial bladder carcinoma treated with first-line cisplatin-based combination regimens and second-line paclitaxel monotherapy.[13] The median duration of this regimen was 3 months, and the median number of paclitaxel administrations was 7. During the observation period, no patient exhibited complete response, whereas 4, 15, and 21 patients met the criteria for partial response, stable disease, and progression disease, respectively. Therefore, the ORR and disease control rate were 9.5% and 45.2%, respectively. The median PFS of second-line chemotherapy was 3 months and the median OS following the start of second-line therapy was 6.4 months. In this case, after 10 cycles of paclitaxel, the imaging study shows stable disease. PET after the 25th cycle showed only adenopathic focus in the right acetabulum with complete response in the lung and liver. The patient is currently without treatment-associated toxicity and with ECOG 0. This is a great response and there is no case described in the literature with such a long-term survival. The patient remains asymptomatic and has no toxicity associated with this drug.

At this time, with the optimal response obtained in this therapeutic line, the authors are in doubt whether this will be in the context of a profound, delayed, and lasting response related to immunotherapy or a rare favorable response to weekly paclitaxel. Overall, given the rarity of pseudoprogressions, classical RECIST remains a reasonable and rational method for assessing the response to immunotherapy. Continued treatment beyond progression should be proposed only in carefully selected patients whose clinical conditions are stable and without serious toxicities and when they are not in risk of visceral crisis. It is imperative to develop definitive criteria for the evaluation of responses in immunotherapy, as well as the inclusion of these criteria in clinical trials, to identify biomarkers predictive of efficacy to immunotherapy, aiming to assist the clinician in the therapeutic decisions to obtain the best results for our patients.

At present, the medical team has additional questions: when paclitaxel should hold and, after progression, what should be the best drug to be reintroduced.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67:7–30.

[2] Burger M, Catto JWF, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013;63:234–241.

[3] Von der Maase H, Sengelov L, Roberts JT, et al. Long-Term Survival Results of a Randomized Trial Comparing Gemcitabine Plus Cisplatin, With Methotrexate, Vinblastine, Doxorubicin, Plus Cisplatin in Patients With Bladder Cancer. J Clin Oncol. 2005;23:4602–4608.

[4] Loehrer PJ, Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol. 1992;10:1066–1073.

[5] Oing C, Rink M, Oechsle K, Seidel C, Von Amsberg G, Bokemeyer C. Second line chemotherapy for advanced and metastatic urothelial carcinoma: vinflunine and beyond: a comprehensive review of the current literature. J Urol. 2016;195:254–263.

[6] Raggi D, Miceli R, Sonpavde G, et al. Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: a systematic review and meta-analysis. Ann Oncol. 2016;27:49–61.

[7] Bellmunt J, Théodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol. 2009;27:4454–4461.

[8] Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18:e143–e152.

[9] Soria F, Beleni AI, D'Andrea D, et al. Pseudoprogression and hyperprogression during immune checkpoint inhibitor therapy for urothelial and kidney cancer. World J Urol. 2018;36:1703–1709.

[10] De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol. 2012;30:191–199.

[11] Farina MS, Lundgren KT, Bellmunt J. Immunotherapy in urothelial cancer: recent results and future perspectives. Drugs. 2017;77:1077–1089.

[12] Murio JE, Margarit C, Baselga J. Feasibility trial of methotrexate-paclitaxel as a second line therapy in advanced urothelial cancer. 2002;20:673–685.

[13] Sideris S, Aoun F, Zanaty M, et al. Efficacy of weekly paclitaxel treatment as a single agent chemotherapy following first-line cisplatin treatment in urothelial bladder cancer. Mol Clin Oncol. 2016;4:1063–1067.