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COMPLETE RESPONSE AFTER AVELUMAB MAINTENANCE THERAPY: SUCCESSFUL MANAGEMENT OF METASTATIC UROTHELIAL CARCINOMA

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ABSTRACT

Urothelial carcinoma is one of the most frequently diagnosed cancer types in the world and despite progress in treatment, it remains a lethal disease in the metastatic stage. Because of its high programmed cell death ligand 1 protein expression, it is associated with an increased response to immune checkpoints inhibitors. In the past few years, the gold standard for first-line treatment of metastatic urothelial carcinoma has been platinum-based chemotherapy, and avelumab (PD-1 inhibitor) maintenance therapy for non-progressing tumours. After the remarkable benefit demonstrated in the EV-302 study, the guidelines were recently revised to include enfortumab vedotin plus pembrolizumab as the new standard of care in this setting.

Despite the new recommendations, in some countries, this combination is still pending approval. Furthermore, for patients who are ineligible for enfortumab vedotin plus pembrolizumab, platinum-based chemotherapy followed by avelumab maintenance therapy continues to be a preferred treatment option.

This report presents a woman diagnosed with metastatic urothelial carcinoma with histologically confirmed complete response after cisplatin and gemcitabine chemotherapy and avelumab as maintenance therapy, which has been reported in only a few cases in the literature.

KEYWORDS

Avelumab, metastatic urothelial carcinoma, maintenance therapy, complete response

LEARNING POINTS

- Urothelial carcinoma is associated with high mortality despite significant progresses in treatment.
- In metastatic urothelial carcinoma the first-line treatment was recently changed, with enfortumab vedotin plus pembrolizumab being approved by the US Food and Drug Administration and European Medicines Agency. Until now, platinum-based chemotherapy and avelumab maintenance therapy for non-progressing tumours was the only standard of care for these patients.
- In the literature, few cases have been reported with complete response to avelumab maintenance therapy.

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INTRODUCTION

Urothelial carcinoma (UC) is the 9th most frequently diagnosed cancer worldwide, with an estimated 614,000 new cases and 220,000 deaths in 2022[1]. Men are more likely to develop UC than women, however women commonly present with more advanced disease and have worse survival rates[2]. The treatment of metastatic UC has changed in the past few years with the introduction of immunotherapy with checkpoints inhibitors. Platinum-based chemotherapy has been recommended as standard of care in first-line therapy, and avelumab (a PDL-1 inhibitor) as maintenance therapy for patients who have not progressed following chemotherapy[3,4]. Recently, the guidelines were revised to include enfortumab vedotin (EV) in combination with pembrolizumab (a PD-1 inhibitor) as the new standard of care[5,6].

We report the case of a patient diagnosed with metastatic UC, who was treated with platinum-based chemotherapy and avelumab as maintenance therapy and achieved a complete response.

CASE DESCRIPTION

A 75-year-old Caucasian woman was diagnosed in 2019 with UC of the left renal pelvis. She had no relevant personal or family medical background.

In January 2019, she underwent a left nephrectomy due to suspicious xanthogranulomatous pyelonephritis, with a histological result of high-grade papillary UC of the left renal pelvis (pT3NxR0). The case was discussed in a multidisciplinary team meeting (MTM) and it was decided to implement surveillance.

In June 2020, a computed tomography (CT) scan showed a new nodular lesion with 6 mm (largest diameter) in the upper lobe of the right lung *(Fig. 1)*. The case was again discussed in an MTM, and it was decided to maintain surveillance.

In July 2020, the patient underwent a transurethral resection of bladder tumour (TURBT) for a newly identified polypoid lesions in the bladder, with histological results revealing high-grade papillary UC (pT1). In November 2020, she underwent a second TURBT and two more sessile lesions were resected (the major lesion with 30 mm), which were histologically identified as high-grade UC in situ. The MTM decided to start intravesical Bacillus Calmette-Guérin (BCG) treatment, which she began in December 2020.

In March 2021, she underwent a third TURBT, with the resection of new lesions, that were compatible with low-grade UC (pT1). She was reevaluated with a CT scan that showed progression of the pulmonary nodule (12 mm vs 6 mm; *Fig. 2*). She underwent a pulmonary nodule biopsy, which confirmed UC metastasis.

The case was discussed in an MTM, and it was decided to start systemic palliative chemotherapy with cisplatin (70 mg/m^2) and gemcitabine (1000 mg/m^2), which she began in June 2021. She completed 5 cycles without delays or dose reductions, and she underwent a CT scan in September 2021, which showed a partial response, with a decrease in the pulmonary nodule (10 mm vs 15 mm; *Fig. 3*) and no new bladder wall thickening.

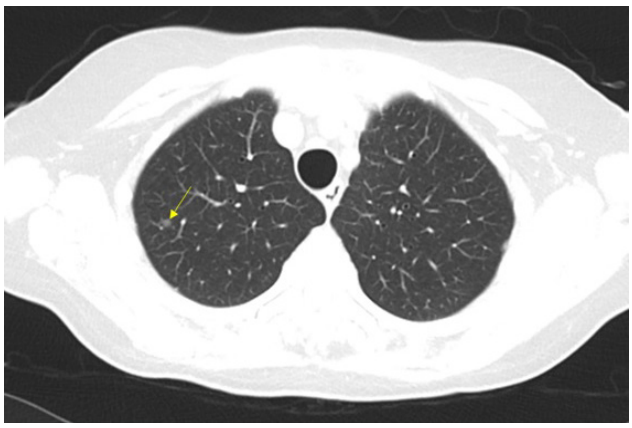

Figure 1. Computed tomography scan showing a new nodular lesion with 6 mm in largest diameter in the upper lobe of the right lung (arrow).

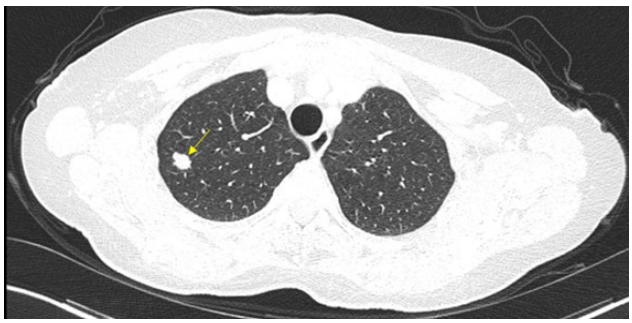

Figure 2. Computed tomography scan with an increase in size of the pulmonary nodule, from 6 mm to 12 mm in largest diameter (arrow).

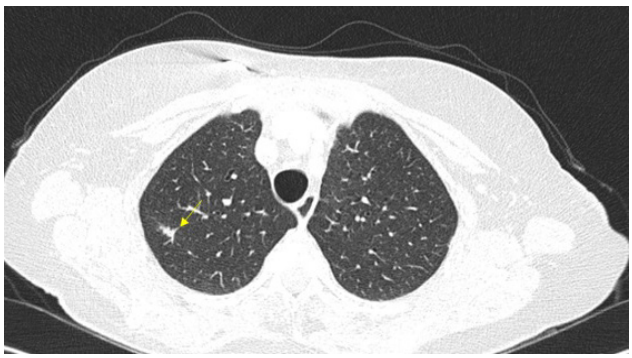

Figure 3. Computed tomography scan exhibiting a decrease in the pulmonary nodule from 15 mm to 10 mm, in largest diameter (arrow).

She completed 6 cycles of chemotherapy in October 2021. The last one with 15% dose reduction of cisplatin due to complaints of grade 2 vomiting, refractory to antiemetic therapy. In November 2021, it was decided to start maintenance treatment with avelumab (800 mg/m^2) every 14 days, which she began in December 2021. After 5 cycles of avelumab, she underwent a CT scan that showed stability of the pulmonary lesion. After 2 years of avelumab maintenance therapy, she had no adverse events, and the pulmonary lesion was stable.

In June 2024, after 54 cycles of immunotherapy, with stable disease, the MTM proposed the patient to perform a metastasectomy. In July 2024, she underwent a wedge

resection of the left superior pulmonary lobe. The histopathology result was fibro-sclerosis with no evidence of malignant cells, and it was decided to suspend avelumab therapy. Since then, she has remained under surveillance with regular imaging tests and no evidence of recurrence of the disease.

DISCUSSION

The treatment of metastatic UC has not evolved since platinum-based chemotherapy was established as the first-line treatment more than 20 years ago. In the past few years this paradigm was changed by the introduction of immunotherapy, with checkpoint inhibitors. This type of cancer is characterized by high PD-L1 protein expression, which is associated with an increased response to immune checkpoints inhibitors[7]. Before October 2023, platinum-based chemotherapy was recommended as the standard of care in first-line treatment, and avelumab was established as maintenance therapy for patients who had not progressed following chemotherapy[3,4].

The phase 3 JAVELIN Bladder 100 trial, published in 2020, led to approval of avelumab as first-line maintenance therapy in patients with advanced UC who had not progressed with platinum-based treatment[8].

In this trial, avelumab was associated with a significantly longer overall survival (OS) when compared with best supportive care (median OS, 21.4 months vs 14.3 months, respectively; HR 0.69 [95% CI: 0.56-0.86]; p=0.001) and the benefit was higher when started immediately after first-line chemotherapy in patients with no progressive disease[8]. Furthermore, the updated results of the JAVELIN Bladder 100 trial after ≥ 2 years of follow-up continued to show prolonged OS with avelumab as maintenance therapy (median OS, 23.8 months in avelumab arm vs 15.0 months in best supportive care arm; HR 0.76 [95% CI: 0.63-0.91]; p=0.0036)[9].

Patients should receive preferably six cycles of chemotherapy before starting avelumab and a radiological evaluation should be performed after four cycles of chemotherapy to provide a baseline measure[10]. Avelumab treatment should be continued until disease progression or unacceptable toxicity, although the interruption could be considered after 2 years in patients with complete response[10].

In phase 3 JAVELIN Bladder 100 trial, the incidence of adverse events (AE) in the avelumab group was higher than control arm[8]. The most frequents AE reported were fatigue (17.7%), pruritus (17.2%) and urinary tract infection (17.2%), with AE of grade 3 occurring in 47% of the patients[8]. Nevertheless, no new safety signals were identified and only 12% discontinued maintenance therapy[8].

Recently, the EV-302/KEYNOTE 39A phase III trial, led to approval of enfortumab vedotin (EV) in combination with pembrolizumab as the new standard of care for first-line treatment in patients who are eligible for combination therapies[6]. In this trial, progression free survival (PFS) was significantly prolonged with EV plus pembrolizumab versus platinum-based chemotherapy, reducing the risk of progression by 55% (median PFS, 12.5 months vs 6.3 months, respectively; HR 0.45 [95% CI: 0.38-0.54]; p<0.00001)[6]. Also, OS was significantly prolonged with EV plus pembrolizumab when compared with chemotherapy, reducing the risk of death by 53% (median OS, 31.5 months vs 16.1 months, respectively; HR 0.47 [95% CI: 0.38-0.58]; p<0.00001)[6]. Furthermore, about 30% of the patients in the control arm received avelumab as maintenance therapy[6].

For patients who are ineligible for EV (such as non-controlled diabetes, grade ≥2 peripheral neuropathy or meaningful pre-existing skin disorders) platinum-based chemotherapy followed by avelumab maintenance therapy remains a reliable treatment option[5].

Despite the approval of EV plus pembrolizumab by the US Food and Drug Administration and European Medicines Agency, in Portugal, like other countries, this combination therapy is still pending approval in first-line treatment for metastatic UC.

In the literature, there are only a few cases of a complete response after avelumab maintenance therapy. In our clinical case a patient with pulmonary histological confirmed metastatic UC, underwent 6 cycles of combined platinum-based chemotherapy (cisplatin and gemcitabine), and maintenance therapy with avelumab for 2.5 years, with an excellent treatment tolerance. After this, the patient underwent a pulmonary metastasectomy in July 2024 with no evidence of malignant cells in the pathology report, so it was decided to suspend immunotherapy, and she maintains surveillance since then. Indeed, in patients undergoing immunotherapy, suspension may be considered after 2 years of stable disease. In this case, we can just talk about “cure” after 5 years of surveillance without maintenance therapy and in the absence of disease recurrence.

Despite the new recommendations in metastatic UC treatment, platinum-based chemotherapy and avelumab maintenance therapy demonstrated notable results and it is one of the preferred treatment options for patients who are ineligible to EV plus pembrolizumab.

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