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Case Report

Cemiplimab for Cisplatin Resistant Metastatic Penile Cancer

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Keywords
Penile cancer · Checkpoint inhibitor · Cemiplimab · Immunotherapy

Abstract
We report on a 75-year old man who presented with metastatic, squamous-cell carcinoma (SCC) of the penis whose disease had progressed after radiotherapy (RT) and cisplatin-based chemotherapy (CT). A strong PD-L1 expression as well as a CDKN2A mutation was documented, and he was given cemiplimab every 3 weeks at time of disease progression. Complete response (CR) was demonstrated after 10 cycles, and no toxicity was reported. However, this treatment was stopped after 13 cycles when the patient developed moderate severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pneumonitis which required a 2-week hospitalization for oxygen support. Six months later, he remains in CR. To our knowledge, this is the first demonstration of a CR with cemiplimab in a metastatic penile SCC patient previously treated with CT and RT for relapse. Furthermore, the patient remains disease-free despite cemiplimab was withdrawn due to SARS-CoV-2 pneumonitis.

Introduction

Relapsed locally advanced or metastatic penile cancer is a rare disease and systemic treatment is cisplatin-based chemotherapy (CT). Despite salvage treatments, prognosis is very poor and median overall survival (OS) is about 7 months [1]. More recently checkpoint inhibitors (CPIs) have been shown to improve OS in a wide range of diseases. Of interest to us is the OS benefit demonstrated with nivolumab and pembrolizumab in metastatic head and neck squamous-cell carcinoma (SCC) patients either before or after cisplatin [2, 3]. Indeed head and neck SCC and penile cancer share similarities: both are SCCs, a fraction of which is

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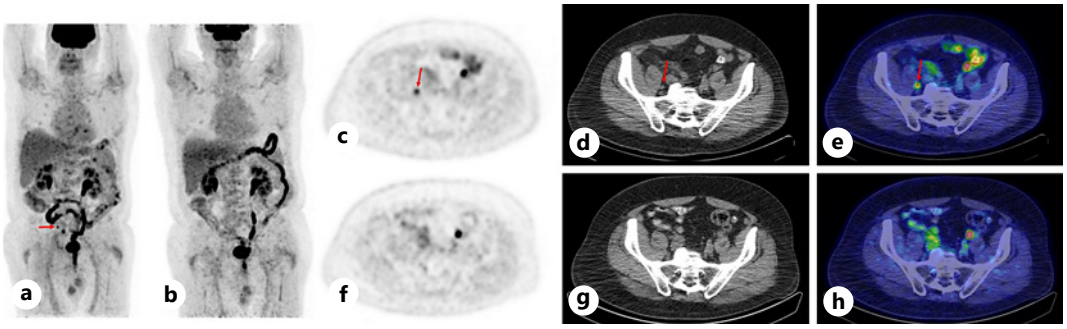

Fig. 1. The FDG PET/CT performed 4 months after salvage chemotherapy (TPF) and RT showed one FDG-avid right iliac lymph node pointed out with the red arrows (maximum intensity projection PET images (**a**); PET (**c**); CT (**d**); fused PET/CT (**e**)). The FDG PET/CT performed after 10 cycles of cemiplimab showed CR of the lymph node and no new lesion (maximum intensity projection PET images (**b**); PET (**f**); CT (**g**); fused PET/CT (**h**)). Gray and colour scales of all PET images range from 0 to 5 SUV. RT, radiotherapy; CT, chemotherapy; CR, complete response; FDG PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography.

HPV induced, both are curable with surgery or radiotherapy (RT), and both are cisplatin- and taxane-sensitive. Similarly, cemiplimab, another PD-1 inhibitor, has been recently FDA and EMA approved to treat metastatic or non-resectable cutaneous SCC based on phase 2 data showing a 44% overall response rate (ORR) including 13% complete response (CR) [4]. Far less is known about the effect of CPI in advanced penile cancer.

Case Report

We report on a 75-year old man who was diagnosed with cT3 N0 M0, penile SCC. He underwent glans penis resection and sentinel nodes analyses which revealed a 3-cm, p16 negative, moderately differentiated keratinizing SCC infiltrating both corpus spongiosum and corpus cavernosum. Resection was complete with negative inguinal sentinel nodes, the staging being pT3 pN0(sn) R0.

Three months later, local relapse was diagnosed with palpable right inguinal nodes and no distant metastasis identified. Total penectomy with radical right inguinal lymphadenectomy was performed. Extensive bilateral corpus cavernosum tumour infiltration was seen with lympho-vascular invasion and infiltration of 2 out of 10 inguinal lymph nodes with extra nodal extension, rpT3 N3. Strong (>95%) programmed cell death protein 1 ligand (PD-L1) expression was documented with Ventana PD-L1 (SP142) assay. Next-generation sequencing revealed a cyclin-dependent kinase N2A (CDKN2A) mutation, c.238C>T; p.(Arg80Ter); exon 2.

Eight weeks later, a 38 mm right ischiopubic relapse was identified using magnetic resonance imaging and [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT).

The lesion was not resectable and 4 cycles of salvage CT combining cisplatin, fluorouracil, and docetaxel (TPF) were delivered with a CR after 3 cycles. RT consolidation on the site of relapse (25 × 2.2 Gy), the right pelvic and inguinal lymph nodes areas (25 × 1.8 Gy) was delivered using intensity modulated RT.

Four months later, FDG-avid right iliac lymph node was detected using FDG PET/CT (pointed out with the red arrows in Fig. 1) and was confirmed by magnetic resonance imaging 2 months later. Serum lactate dehydrogenase (LDH) was in the normal range.

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Therefore a treatment with cemiplimab, a programmed cell death protein 1 (PD-1) inhibitor given intra-venously at a dose of 350 mg q3w was started. FDG PET/CT showed a partial response after 5 cycles, and CR was subsequently demonstrated after 10 cycles (shown in Fig. 1). No toxicity was observed. Treatment was withdrawn after 13 cycles due to moderate severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pneumonitis which required a 2-week hospitalization for oxygen support. Six months later, he remains in CR.

Discussion

Adjuvant CT is recommended for patients with pN2-N3 tumours after complete lymphadenectomy [5]. This strategy could not be implemented in our patient due to lymphocele, and, in the meantime, a non-resectable regional relapse was documented. The use of TPF regimen for metastatic penile cancer has been first tested in a British single-arm phase 2 trial after initial encouraging case reports [6]. Our patient was given 4 cycles of TPF and a radiological CR was documented after 3 cycles. Due to the high likelihood of relapse with reported median progression-free survival ranging from 3 to 7 months [1, 6], consolidation RT was delivered in the present case. This approach did not prevent metastatic iliac lymph node relapse from occurring shortly, 4 months after the end of RT. Such an early relapse after cisplatin- and taxane-based CT did not suggest any durable benefit with a similar strategy.

Overall PD-L1 expression in penile SCC was 40% in the largest series reported [7]. Although the expression of PD-L1 by cancer cells has been variably associated with response to anti-PD-1/PD-L1, the high PD-L1 expression in our patient supported the use of a CPI, none of which being approved for penile cancer. Despite CPI including anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and anti PD-1/PD L-1 being available, data in penile cancer remains extraordinarily scarce. CDKN2A alterations were reported in 40% of the 20 penile cancer patients who underwent a comprehensive genomic profiling and was therefore the most common clinically relevant alteration with TP53 alterations being the most common overall [8].

The first report of a response, albeit partial, to the anti PD-1 nivolumab, in a multi-treated patient with a CDKN2A altered penile cancer brought hope in this poor-prognosis situation [9]. Other encouraging reports with pembrolizumab were later released including 1 patient with high tumour-mutational burden (TMB) but with unknown PD-L1 status who experienced a long-lasting 38-month CR [10].

In a recent retrospective series of 46 patients with advanced cutaneous SCC treated with either nivolumab, pembrolizumab or cemiplimab, the authors reported a CR for the only patient with penile cancer and an ORR of 58.7% with 15% achieving CR [11]. The drug given to that penile cancer patient was not reported. However, they highlighted the poor influence of elevated serum LDH at treatment initiation on ORR, disease-control rate, progression-free survival, and OS. The normal LDH serum level in our patient may have contributed to his favourable outcome together with the strong PD-L1 expression despite unknown TMB.

Combination of anti-CTLA4 and anti-PD-1, notably ipilimumab and nivolumab, has led to an impressive response in a patient with metastatic penile SCC whose cancer was refractory to the paclitaxel, ifosfamide, cisplatin regimen and showed a high PD-L1 expression, high TMB, high microsatellite instability, and alterations in DNA mismatch repair genes [12]. Although increased toxicity may be expected with dual inhibition this was not reported and the limited data from the literature are consistent with a favourable toxicity profile for penile cancer patients treated with single-agent CPI [10]. Consistent with this, our patient did not experience toxicity neither clinical nor biological.

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To our knowledge, this is the first demonstration of a CR with cemiplimab in a metastatic penile cancer patient previously treated with CT and RT for relapse. Furthermore, cemiplimab was discontinued when the patient developed hypoxemic SARS-CoV-2 pneumonitis requiring hospitalization. After recovery, cemiplimab was not resumed and the patient remains in CR suggesting that CPI might be safely put on hold in patients with documented CR providing careful surveillance is maintained. This report has limitations: it is a single patient story, and the follow-up is short. However, it illustrates how a patient with a rare advanced disease can be managed with promising immune treatment in the global SARS-CoV-2 pandemia.

Statements of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

Brieuc Sautois has served in a consulting or advisory role for Clovis Oncology, Astellas, Janssen, and Sanofi and received financial support for travel and/or accommodation from Janssen. The other authors have nothing to declare.

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Authors Contributions

Conception and design: Brieuc Sautois, Chloé Denis, and Pierre Frères. Provision of study materials or patients: Brieuc Sautois and Nadia Withofs. Collection and assembly of data: all authors. Data analysis and interpretation: all authors. Manuscript writing: Chloé Denis, Brieuc Sautois, and Nadia Withofs. Final approval of the manuscript: all authors. Accountable for all aspects of the work: all authors.

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