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Case Report

RRx-001 Priming of PD-1 Inhibition in the Treatment of Small Cell Carcinoma of the Vagina: A Rare Gynecological Tumor

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Keywords

Small cell carcinoma · Vagina · Tumor-associated macrophage stimulation · Immunotherapy · Chemotherapy · Pseudoprogression · RRx-001

Abstract

Small cell carcinoma of the vagina is rare, so rare in fact that the total number reported in English-language journals is less than 30. Due to this extremely low incidence, no specific treatment guidelines have been established, and most of what is clinically known is derived from a handful of single case reports. However, as befitting its highly aggressive histologic features, which are reminiscent of small cell lung cancer (SCLC), first-line treatment is modeled after SCLC. Herein is reported the case of a 51-year-old African-American patient with metastatic biopsy-proven small cell carcinoma of the vagina that progressed through multi-

ple therapies: first-line cisplatin and etoposide (making it platinum-resistant) and radiotherapy, followed by the tumor macrophage-stimulating agent RRx-001 in a clinical trial called QUADRUPLE THREAT, which per protocol preceded a mandated rechallenge with cisplatin and etoposide. RECIST v.1.1 tumor progression on both RRx-001 and cisplatin/etoposide was accompanied by central necrosis in several of the enlarged lymph nodes and hepatic metastases, which may have been evidence of pseudoprogression, accounting for her ongoing longer-than-expected survival, since the necrotic tissue may have primed the activity of the PD-1 inhibitor. The lack of response to RRx-001 is hypothesized to have correlated with sparse tumor macrophage infiltration, seen on pre- and post-treatment biopsies, since the mechanism of action of RRx-001 relates to stimulation of tumor-associated macrophages.

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Introduction

Primary malignant epithelial tumors of the vagina are divided into three types: adenocarcinoma, squamous cell carcinoma, and small cell carcinoma [1]. Small cell carcinomas, which account for 1–2% of gynecological malignancies, occur with decreasing frequency in the cervix, endometrium, ovary, vagina, and vulva [2]. Accordingly, in the vagina, it is extremely rare [3] – less than 30 cases have previously been reported in English-language journals [4] – which makes it a unicorn, since, in medical parlance, horses are commonplace diagnoses, zebras are rare diagnoses, and unicorns are even rarer ones. Like its pulmonary counterpart, which it is nevertheless distinct from, small cell carcinoma of the vagina is extremely aggressive; despite high initial response rates to cisplatin/etoposide, the prognosis is poor given the nearly inevitable development of recurrent, progressive, chemoresistant disease; by analogy with recurrent resistant small cell lung cancer (SCLC), survival is <6 months.

RRx-001 is a tumor-associated macrophage (TAM)-stimulating agent that may be associated with transiently increased tumor volumes or pseudoprogression [5], which probably corresponds with the reduced cellularity, central necrosis, and extensive immune infiltrates present in patient tumor biopsies. In a phase II clinical trial, called QUADRUPLE THREAT (NCT02489903), which treats patients with SCLC, non-SCLC, high-grade neuroendocrine tumors, and resistant/refractory ovarian tumors, RRx-001 is dosed parenterally every week until progression, at which point first-line platinum doublets are reintroduced. To date, responses to RRx-001 and/or sequentially reintroduced platinum doublets have correlated with the presence of TAMs. The following report presents the case of a 51-year-old African-American female with platinum-resistant small cell carcinoma of the vagina that, despite progression on RRx-001 and reintroduced platinum doublets, exceeded survival expectations.

Case Presentation

This 51-year-old African-American patient was diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage III vaginal small cell carcinoma positive for the neuroendocrine markers, synaptophysin, CD56, and chromogranin A in May 2015. Initial treatment consisted of a multimodality regimen of 5 cycles of cisplatin, etoposide, and paclitaxel with concurrent locoregional radiotherapy (XRT) until September 9, 2015. Ap-

proximately 3 months later on December 15, 2015, metastatic disease in the lungs and the liver was detected, which meets the definition of platinum-resistant disease. On January 8, 2016, our patient began treatment with RRx-001. Her clinical course both before and during treatment with RRx-001 was complicated by the paraneoplastic syndrome of inappropriate antidiuretic hormone (SIADH), common in SCLC, which led to several hospitalizations for hyponatremia.

At 6 weeks, having progressed according to RECIST v.1.1 despite the appearance of centrally hypodense tumor necrosis on CT (Fig. 1), the patient was rechallenged per protocol with cisplatin and etoposide on March 1, 2016. On March 31, having been rescanned during another hospitalization for recurrent symptomatic hyponatremia secondary to SIADH, progressive disease was determined on the basis of a new pleural effusion and enlargement of tumor metastases and lymph nodes in the lung and liver. However, the CT scan not only redemonstrated the presence of lesions with a hypodense core surrounded by a hyperdense periphery but also showed multiple centrally necrotic appearing cervical and supraclavicular lymph nodes, which may suggest pseudoprogression, associated with a favorable prognosis and prolonged survival. She started nivolumab 3 mg/kg every other week with initial evidence of a partial response (Fig. 1), attributed to the priming effect of RRx-001, since necrotic tumor cells may provide a source of tumor antigen, before passing away. Her overall survival was 7.5 months. The lack of response to RRx-001, as a TAM-stimulating agent, is thought to correlate with the absence of tumor-infiltrating macrophages, which was seen on pre- and post-treatment biopsies.

Discussion

Small cell carcinoma accounts for 2% of female genital tract malignancies and an even smaller percentage arise in the vagina [6]. While this unicorn-like rarity is itself worthy of a report, the current case is additionally, to the best of our knowledge, the first instance of pseudoprogression ever described in small carcinoma of the genital tract. Loosely defined as a transient, self-resolving increase in tumor volume due to cytotoxic edema, necrosis, and/or immune infiltration, pseudoprogression has been described most often in the setting of glioblastoma treatment [7] with radiotherapy and temozolomide, imatinib treatment for gastrointestinal stromal tumors [8], and checkpoint inhibition with PD-1 or CTLA-4 [9].

In addition to central necrosis and the formation of cavitation that can also occur as a result of rapid tumor growth, pseudoprogression with RRx-001 is usually associated with dramatic symptomatic improvement, which differentiates it from true tumor progression, where patients are almost always clinically worse [10] and not better.

The survival of small cell carcinoma patients is typically less than 6 months. By that metric, this patient with resistant SCLC and extensive disease burden, who lived for 7.5 months, exceeded historical expectations, which possibly may be attributed to the activity of RRx-001.

Statement of Ethics

The research behind this case report complies with the guidelines for human studies. Any subjects have given their informed consent in the study and the study protocol has been approved by the relevant institute's institutional review board (IRB), also known as an independent ethics committee (IEC), ethical review board (ERB), or research ethics board (REB).

Disclosure Statement

The authors declare that the research and clinical trials associated with drug RRx-001 have been funded by EpicentRx, Inc. Authors B.O., S.J., and S.C. are employees of EpicentRx, Inc. The authors have no other competing interests to declare.

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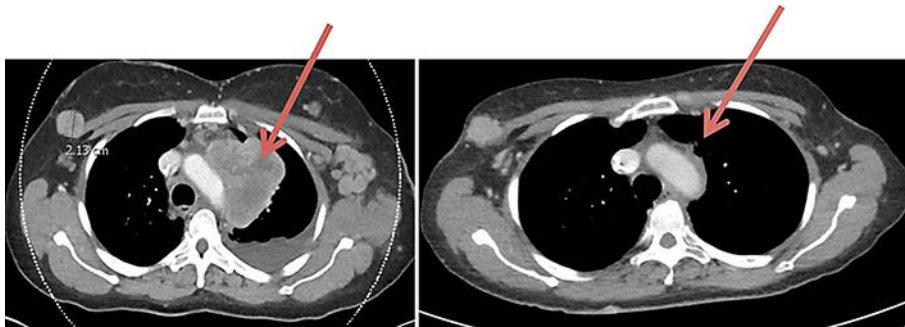


Fig. 1. Axial contrast-enhanced CT image on the left shows a huge left para-aortic mass (red arrow) with irregular hypodense areas of necrosis on March 30, 2016, following re-treatment with platinum doublets after RRx-001. Due to radiologic progression, the platinum doublets were stopped and nivolumab was started. On June 3, 2016, the patient was rescanned, which demonstrated that the para-aortic mass disappeared completely (red arrow).