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Case report

Neoadjuvant chemotherapy with paclitaxel/carboplatin/bevacizumab in advanced vulvar cancer: Time to rethink standard of care?

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ABSTRACT

Vulvar cancer remains a rare entity and treatment options for advanced disease are limited. This case report highlights the excellent response of two patients with FIGO Stage IV vulvar cancer treated with neoadjuvant paclitaxel/carboplatin/bevacizumab chemotherapy. While definitive conclusions are impossible, neoadjuvant chemotherapy may ultimately prove to be a better initial treatment option for locally advanced disease in terms of quality of life and response compared to the traditional chemoradiation regimens.

1. Introduction

Vulvar cancer is amongst the rarest of gynecological cancers with an estimated 6120 new cases and 1350 estimated deaths annually (Siegel et al., 2020). Current treatment strategies for vulvar cancer typically include combinations of chemotherapy, radiation and resection. However, due to the low prevalence of the disease, especially advanced disease, performing prospective and randomized clinical studies is challenging, and thus standard of care treatments are often extrapolated from smaller studies or from other disease sites, like cervical cancer, and rely on category 2, lower level evidence (Reade et al., 2014; Gray, 2010). Current National Comprehensive Cancer Network (NCCN) treatment recommendations for locally advanced vulvar cancer are chemoradiation with or without groin node dissection (National Comprehensive Cancer Network, 2020). More recent studies have examined the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), as adjunctive therapy in many gyencological cancers; although this has mainly been studied in patients with cervical cancer (Tewari et al., 2017; Suzuki et al., 2019). The objective of the current case report was to describe the recent successful treatment of two advanced vulvar cancer patients with neoadjuvant chemotherapy with paclitaxel/carboplatin/bevacizumab and to review the current clinical recommendations for treatment of locally advanced vulvar cancer as well as the rationale for potential adoption of neoadjuvant treatment as another option.

2. Case 1

A 67 year old female with a past medical history of diverticulitis, hypertension, hyperlipidemia and hypothyroidism presented with perineal pain, a vulvar mass and inability to sit down due to pain. Physical exam revealed an 11 cm × 6 cm ulcerative and exophytic vulvar mass that replaced the entire perineum with vaginal extension. It encompassed the entire peri-anal region and extended laterally almost to the thigh (Fig. 1A). Biopsy was consistent with poorly differentiated invasive squamous cell carcinoma. The original treatment plan was for chemoradiation; however, computed tomography (CT) confirmed multiple solid and cavitary pulmonary nodules ranging in size from 3 to 14 mm (Fig. 2A), multiple enlarged and pathologic appearing left inguinal lymph nodes (up to 15 mm), and one external iliac node measuring up to 16 mm. These findings confirmed the diagnosis of FIGO Stage IVB vulvar cancer and neoadjuvant chemotherapy with paclitaxel, carboplatin and bevacizumab was initiated. After cycle 2, she already had a marked local response (Fig. 1B) and was off all narcotic pain medications. At the completion of cycle 6, genitourinary exam revealed essentially a complete response (Fig. 1C). In addition, CT revealed interval resolution of all the pulmonary metastatic nodules (Fig. 2B) and a normalization of the prior enlarged left inguinal lymph node, from 16 to 8 mm. Given her excellent response to therapy with paclitaxel, carboplatin and bevacizumab, she has continued maintenance bevacizumab for a total of 8 cycles with no evidence of recurrence.

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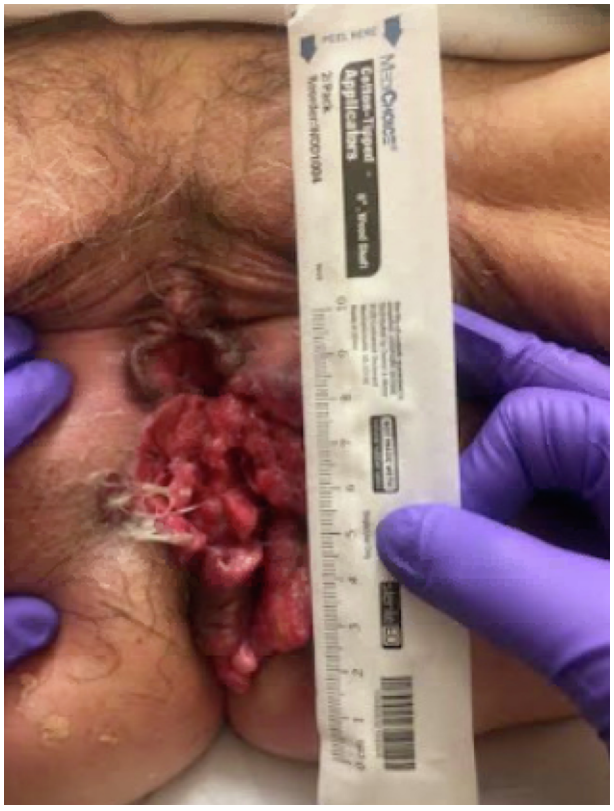

Fig. 1A. Case 1: Large exophytic vulvar lesion on initial presentation.

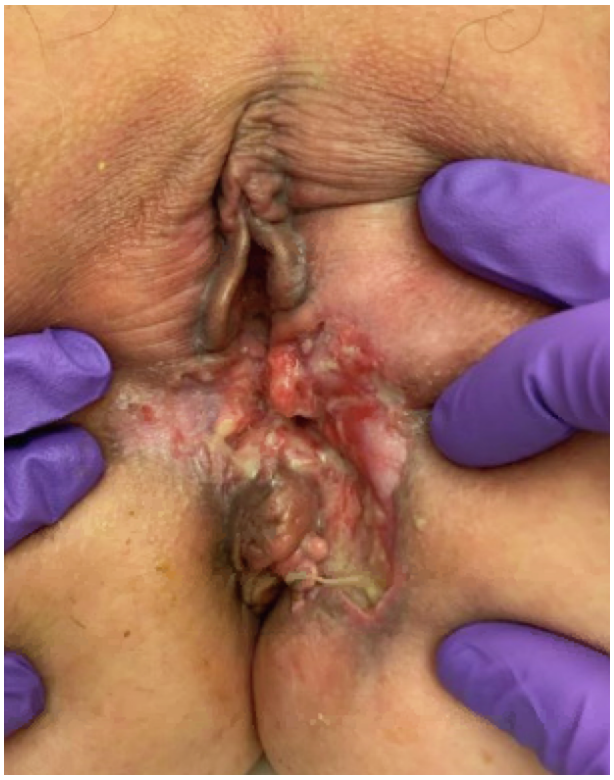

Fig. 1B. Same lesion following two cycles of neoadjuvant chemotherapy.

3. Case 2

A 54 year old female with a past medical history of tobacco and alcohol use presented with a vulvar mass, pain and infection. She was unable to sit down at all and was found to have a large necrotic vulvar mass that replaced the bilateral labia and mons which had eroded the skin (Fig. 3A). Biopsy confirmed a moderately differentiated invasive squamous cell carcinoma. CT revealed an 8.3 cm × 5.8 cm × 5 cm vulvar mass with adjacent right inguinal metastatic lymphadenopathy. Given her massive disease volume and her diagnosis of FIGO Stage IVA vulvar cancer, neoadjuvant chemotherapy was initiated with paclitaxel, carboplatin and bevacizumab. Similar to the first case, she was able to come off all narcotics by the end of cycle two with a marked decrease in size of the vulvar mass and sloughing off of all the exophytic tumors (Fig. 3B). She is continuing on treatment.

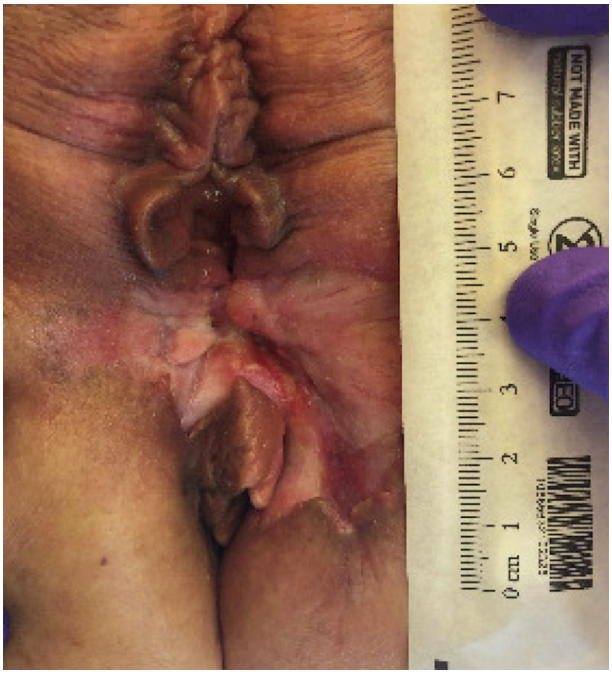

Fig. 1C. At the completion of six cycles.

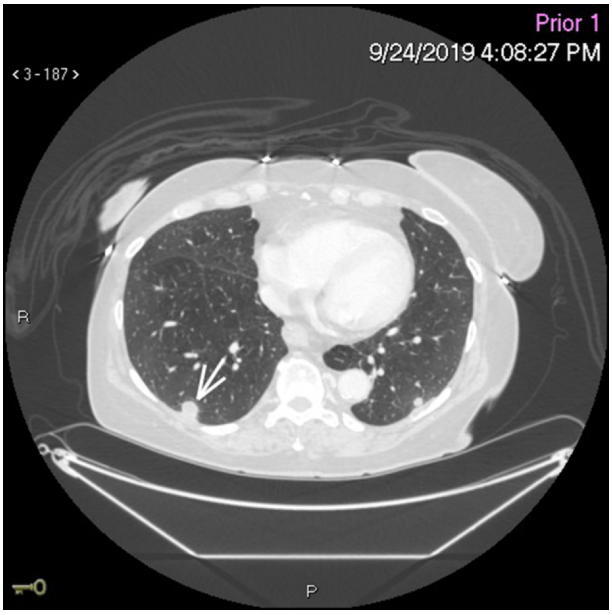

Fig. 2A. Axial image from CT chest from the patient in case 1 on initial presentation demonstrating the largest pulmonary nodule measuring 14 mm diameter in the right lower lobe.

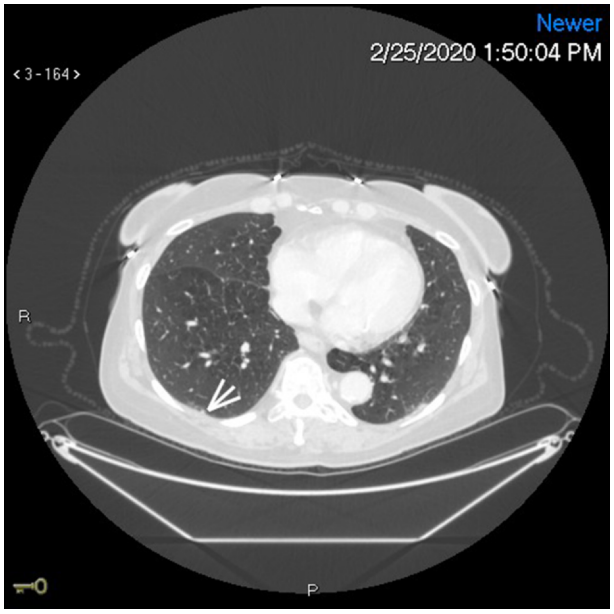

Fig. 2B. Axial image from CT chest following six cycles of paclitaxel/carboplatin/bevacizumab, demonstrating near complete interval resolution of the same right lower lobe nodule.

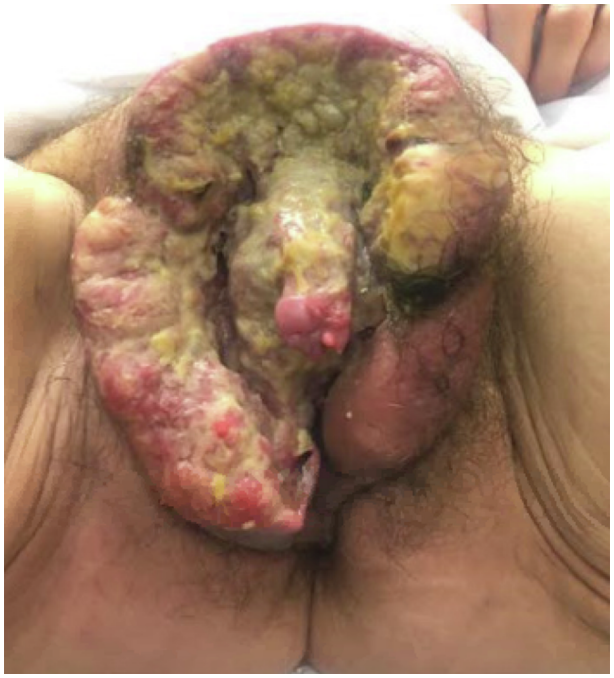

Fig. 3A. Case 2: Initial presentation with necrotic vulvar lesion encompassing the labia, mons, clitoris and perineum.

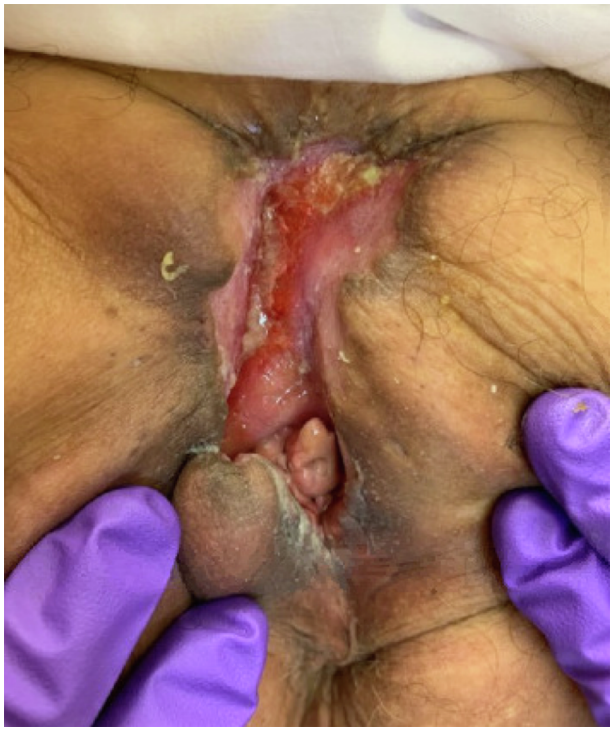

Fig. 3B. Following two cycles of neoadjuvant chemotherapy.

4. Discussion

Current treatment options for locally advanced and unresectable vulvar cancer typically include combinations of chemotherapy and external beam radiation therapy with or without nodal dissection (National Comprehensive Cancer Network, 2020). For metastatic disease beyond the pelvis, the 2020 National Comprehensive Cancer Network (NCCN) guidelines recommend external beam radiation therapy for locoregional control and/or systemic therapy for metastatic disease beyond the pelvis or best supportive care (National Comprehensive Cancer Network, 2020). Our case report lends support to further investigation of neoadjuvant chemotherapy with paclitaxel, carboplatin and bevacizumb as an initial treatment regimen in terms of excellent response rate and improvement in quality of life.

Given the low incidence of advanced vulvar cancer, it is difficult to perform prospective and randomized clinical trials to demonstrate clear superiority and clinical efficacy of one regimen over another (Reade et al., 2014). Therefore, treatment regimens for advanced vulvar cancer have historically been extrapolated from treatment regimens studied for advanced cervical cancer given the similarities between cervical and vulvar tumors (Gray, 2010). Common current treatment regimens include cisplatin based chemoradiation regimens with or without fluorouracil or combinations of systemic chemotherapy with cisplatin or carboplatin with most frequently paclitaxel therapy (Reade et al., 2014).

Many systemic therapies have been studied with limited success in improving overall survival in advanced vulvar carcinoma in recent decades (Ramanah et al., 2012). Prior studies have historically revealed a relatively poor response to chemotherapy alone suggesting an element of chemoresistance in vulvar carcinoma (Reade et al., 2014; Thigpen et al., 1986). One prior phase II study examined the efficacy of cisplatin in the treatment of vulvar carcinoma, which revealed a 0% response rate (Thigpen et al., 1986). However, a subsequent phase II study revealed that the addition of radiation to cisplatin therapy, demonstrated a complete clinical response rate of approximately 64% (Moore et al., 2012). Given the inferred resistance to primary chemotherapy, treatment regimens for vulvar cancer commonly rely on a combination of both systemic chemotherapy and radiation therapy (Reade et al., 2014; Moore et al., 2012).

Current research has shifted to explore alternative treatment regimens including targeted therapy and immunotherapy (Reade et al., 2014). More recent studies have investigated the response of epidermal growth factor receptor (EGFR) blockade with erlotinib, an EGFR inhibitor, in gynecological cancers. A recent phase II trial examined the efficacy of erlotinib in the treatment of vulvar carcinoma but demonstrated only a 27.5% partial response rate (Horowitz et al., 2012). Additionally, further studies have started to examine the role of immunotherapy and immune modulatory pathways in gynecological

cancers, including vulvar carcinoma (Shields and Gordinier, 2019). Recent research has attempted to explore targeted expression of immunomodulators such as PD-1 and PDL-1 but current data are limited and show limited efficacy. For example, a recent phase II trial examined the response of patients with cervical, vaginal and vulvar cancer with treatment with nivolumab, a PDL-1 inhibitor with a 20.8% objective response rate but only 5 of the 24 treated patients had vaginal or vulvar cancer (Naumann et al., 2019).

Multiple studies have examined the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), in treatment regimens in gynecological cancers and confirmed improved outcomes in women with cervical cancer (Tewari et al., 2017; Suzuki et al., 2019). The molecular basis for treatment with bevacizumab in vulvar cancer is supported by the fact that angiogenesis and VEGF have previously been found to play an important role in the progression of vulvar carcinoma (MacLean et al., 2000) and multiple studies have demonstrated good response with the addition of bevacizumab to traditional chemotherapy in the treatment of cervical cancer (Tewari et al., 2017; Suzuki et al., 2019). For example, GOG 240, a recent randomized phase III trial, demonstrated improved overall survival rates in patients with advanced or recurrent cervical cancer who were treated with combination chemotherapy (cisplatin and paclitaxel or topotecan and paclitaxel) with bevacizumab compared to those treated with chemotherapy alone (Tewari et al., 2017). Additionally, a recent phase II trial showed a median overall survival rate of 88% with treatment with paclitaxel/carboplatin/bevacizumab in patients with advanced or recurrent cervical cancer (50% achieved complete response and 38% achieved partial response) (Suzuki et al., 2019). Our case report and the biologic plausibility for extrapolating cervical cancer treatment to vulvar cancer lends support to potential use of bevacizumab in advanced vulvar cancers.

Radiation to the pelvis is commonly used in many gynecological cancers, including locally advanced vulvar cancers, as a mainstay of treatment to attain local disease control, both as a component of primary therapy or as initial therapy to decrease the tumor size and allow a smaller and less morbid surgical resection. Pelvic radiation, however, is associated with significant toxicity and morbidity. Some of the immediate effects of radiation to the pelvis include radiation enteritis, cystitis and cutaneous desquamation, while long term effects of radiation to the pelvis include fistulas, strictures, radiation necrosis, scarring and severe pain (Viswanathan et al., 2014). Alternative treatment regimens such as neoadjuvant chemotherapy with paclitaxel/carboplatin/bevacizumab could potentially shrink the tumors and offer not only improved response but also decreased morbidity and improved quality of life by allowing more limited subsequent surgical resection or radiation fields.

This case report adds to a growing body of literature demonstrating the success of patients with advanced vulvar cancer treated with systemic therapy with paclitaxel, carboplatin, bevacizumab. As demonstrated by the figures, both patients had significant reduction in the size of both their primary tumor and sites of metastases. While higher level research is needed to fully understand bevacizumab safety profile and efficacy, preliminary evidence suggests that clinicians could consider the addition of bevacizumab and targeting of angiogenesis in treatment regimens for advanced vulvar cancer. Future directions could also include combination targeted agents with bevacizumab and potentially immunotherapy as well to afford women with this difficult disease access to improved responses and quality of life.

Written consent was obtained from both patients to allow use of their clinical information and images for this case report.

Author contribution statement

Dr. Modesitt was responsible for ideas, coordination and editing. Dr. Klavans performed the chart review, literature review and writing. Dr. Erickson provided the images.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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