Novel Insights from Clinical Practice

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Brief Report on 3-Weekly Paclitaxel Carboplatin Efficacy in Locally Advanced or Metastatic Squamous Vulvar Cancer

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Established Facts

- Neo-adjuvant chemotherapy has proven to be effective in cervical cancer patients.
- Currently, chemoradiation is the only alternative treatment strategy for patients with locally advanced vulvar cancer, causing high morbidity.

Novel Insights

- Treatment with neo-adjuvant chemotherapy is probably effective for patients with locally advanced vulvar cancer as shown in 2 of the presented cases.
- This case report can be the start of a multicenter trial to further explore the role of neo-adjuvant chemotherapy in vulvar cancer patients.

Keywords
Advanced vulvar cancer · Neoadjuvant chemotherapy · Treatment · Chemoradiation

Abstract
In this brief report, we present our experience with 3-weekly paclitaxel-carboplatin chemotherapy for patients with vulvar cancer. Two patients with locally advanced disease had an impressive response allowing standard vulvar can-

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cer surgery. One patient with metastatic disease had local stable disease though it was progressive in the lymph nodes. The available literature is sparse and retrospective. Based on promising results, however, a prospective multicenter study is mandatory in order to obtain full data in a larger series of patients in order to learn the benefits of neo-adjuvant paclitaxel-carboplatin and compare the results with chemoradiation.

Introduction

Vulvar cancer is a rare gynecological malignancy that constitutes about 3% of all gynecological cancers with an incidence of 2–3 per 100,000 women per year [1, 2]. During the last decades, treatment of vulvar cancer has evolved from a radical procedure into a more conservative and individualized multidisciplinary approach. Current standard care of treatment is surgical and consists of radical local excision and sentinel node procedure of the groins or bilateral inguinal lymph node dissection depending on tumor characteristics [1, 2]. This less radical approach has led to a major decrease in treatment-associated morbidity without compromising prognosis [2, 3]. Despite the high need, little progress has been made in the development of new treatment modalities for advanced stage or recurrent vulvar cancer. Extensive surgery is sometimes not possible or associated with high morbidity rates, especially if the tumor extends to nearby anatomic structures, including the urethra, vagina, bladder, perineum or anus, such as wound infection and sexual, micturition and defecation dysfunction [3]. In addition, musculo-cutaneous transposition flaps may be necessary to close large defects on the vulva and perineum. Furthermore, surgery is not always possible for patients with large primary tumors [2].

Treatment with neo-adjuvant chemotherapy for advanced vulvar cancer has been suggested as a possible effective alternative. This treatment strategy has shown excellent results in the treatment of advanced cervical cancer. Several studies have demonstrated that neo-adjuvant chemotherapy followed by surgery improves overall survival compared to treatment with radiotherapy [4]. However, a recently presented trial (ESMO 2017) on 633 patients with advanced cervical cancer demonstrated an improved disease-free survival for patients treated with chemoradiation compared to patients who received neoadjuvant chemotherapy followed by surgery (76.7 vs. 69.3%, $p = 0.038$). The best treatment strategy for vulvar cancer still needs to be established.

This study reports on the outcome of 2 patients with locally advanced stage vulvar cancer and 1 patient with metastatic disease who were treated with neo-adjuvant 3-weekly paclitaxel-carboplatin.

Methods

Inclusion criteria were biopsy-proven vulvar cancer, a large vulvar tumor considered inoperable or operable leaving a large defect, measurable disease, and a good performance status (0–1) with adequate kidney and liver function enabling safe administration of chemotherapy. All patients had given their informed consent for treatment with neo-adjuvant chemotherapy.

Response and operability was assessed by clinical examination. Where possible, and with the consent of the patients, pictures before and after chemotherapy were taken. Lesions on CT or MRI were evaluated using the Response Criteria in Solid Tumors version 1.1 [5].

Immunohistochemical staining for p53 and p16 was performed according to local protocol.

Case Reports

Patient 1

A 70-year-old patient presented at the university hospital in Leuven with a new diagnosis of vulvar cancer in December 2013. Her medical history was extensive. She underwent treatment with radiotherapy for stage IVa cervical cancer in January 2006. In 2008, she was treated for stage T2N1M0 breast cancer. In December 2013, she presented with poorly differentiated vulvar squamous cell carcinoma. Immunohistochemistry was positive for P16 and negative for p53. The vulvar lesion originated from the right labium major, measured 7 × 5 cm and extended into the rectal mucosa. Although distant metastasis was absent, she had bilateral inguinal lymph node metastases, which were confirmed by fine needle aspiration cytology (FIGO stage IVA). Due to the large tumor volume of the primary tumor and the need for extensive surgery, it was decided to start treatment with neoadjuvant chemotherapy with 4 cycles of taxol (175 mg/m^2)-carboplatin (5 × AUC). Serum SCC dropped from 7.3 to 2.3 μg/L. This treatment strategy was chosen hoping for size reduction of the vulvar tumor and consequently requires only less extensive surgery. Furthermore, radiotherapy was not added to the chemotherapy in order to maintain adjuvant radiotherapy as a treatment option. CT showed partial remission of the inguinal lymph node metastases (Fig. 1a, b). Macroscopically, a partial remission (nearly complete) was reported (Fig. 1c, d).

After 4 cycles of chemotherapy, less extensive surgery turned out to be possible (Fig. 1) and a radical vulvectomy and bilateral inguinofemoral lymphadenectomy saving the clitoris, urethra, and anus was performed. Microscopic examination revealed extensive multifocal high grade vulvar intraepithelial neoplasia (basaloid

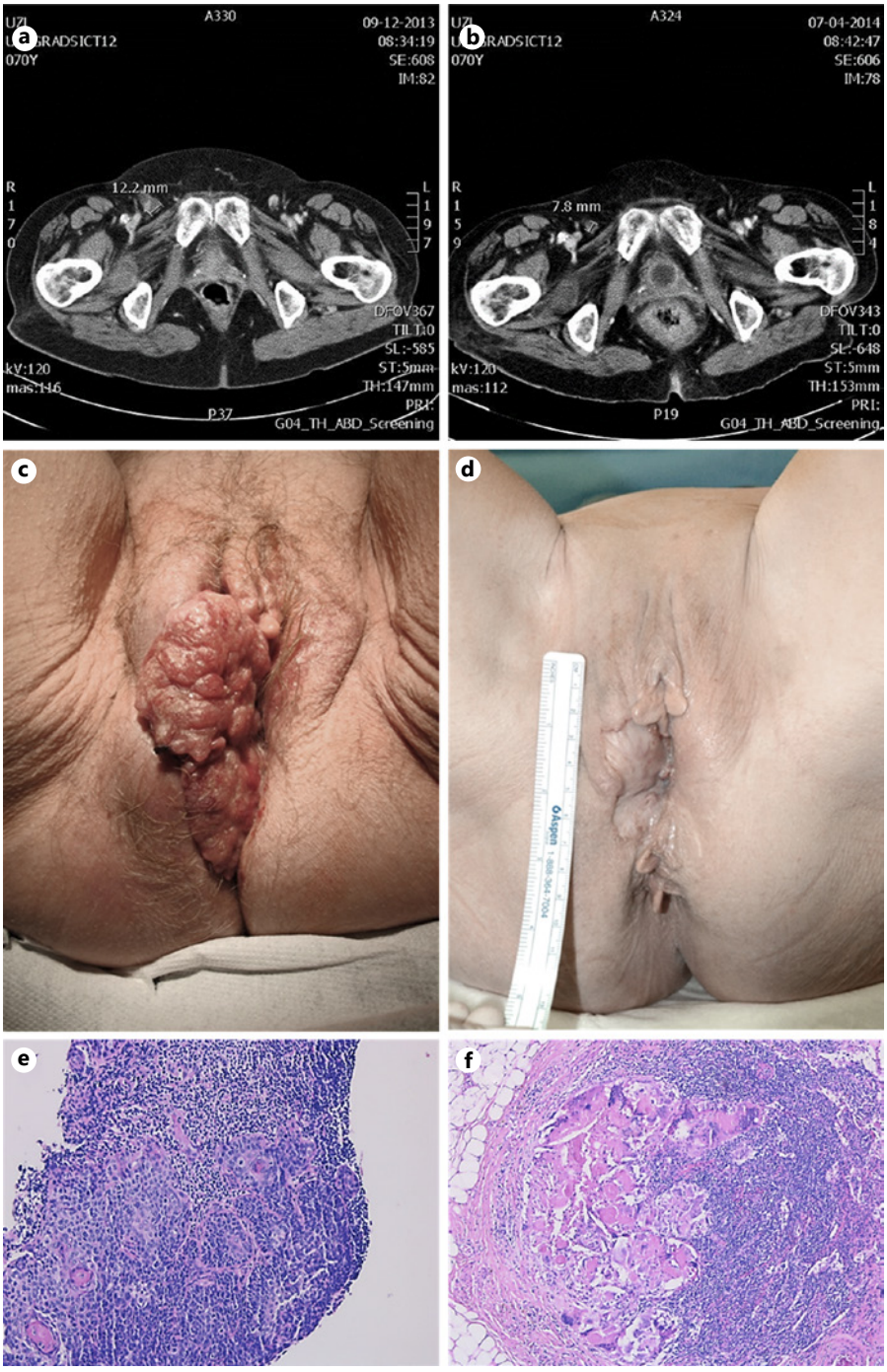

Fig. 1. MRI study, macroscopic appearance and microscopic appearance of advance vulvar cancer before and after 4 cycles 3-weekly paclitaxel and carboplatin in patient 1. **a**, **b** MRI. **a** Inguinal node measuring 12.2 mm before chemotherapy. **b** Inguinal node measuring 7.8 mm (Partial remission according to RECIST). **c**, **d** Macroscopic appearance. **c** At diagnosis an exophytic tumor originating from the right labium growing from peri-urethral to anus measuring, 7 × 5 cm (with invasion of the rectal mucosa). **d** Apart from a small residual tumor, no macroscopic tumor is visible. **e**, **f** Microscopic appearance. **e** Core needle biopsy of an inguinal lymph node before chemotherapy containing a metastasis of a squamous cell carcinoma (HE 100×). **f** Inguinal lymph node after chemotherapy completely cleared from viable tumor, showing only a foreign body reaction to residual keratin.

subtype), with several microinvasive lesions (diameter <3 mm). The underlying stroma showed a fibro-inflammatory reaction associated with hemosiderin-laden macrophages and foreign body giant cells. The tumor resection margins were free, with a minimal tumor free margin of 7 mm.

Four out of 13 lymph nodes contained metastatic disease with a diameter ranging from 1.5 to 5 mm, without extracapsular growth. One node was completely cleared from viable tumor, showing only a remaining foreign body reaction to residual keratin. Adjuvant vulvar and inguinal radiotherapy (50 Gy in 25 fractions of 2 Gy) was administered until July 2014. In January 2015, a right-sided hemivulvectomy was performed for a local recurrence. Microscopic examination revealed a moderately differentiated squamous cell carcinoma measuring 1.8 cm with a depth of invasion of 0.3 cm. The tumor resection margins where free and adjuvant treatment was not necessary. She remained disease free till May 2017 when she presented with a local recurrence.

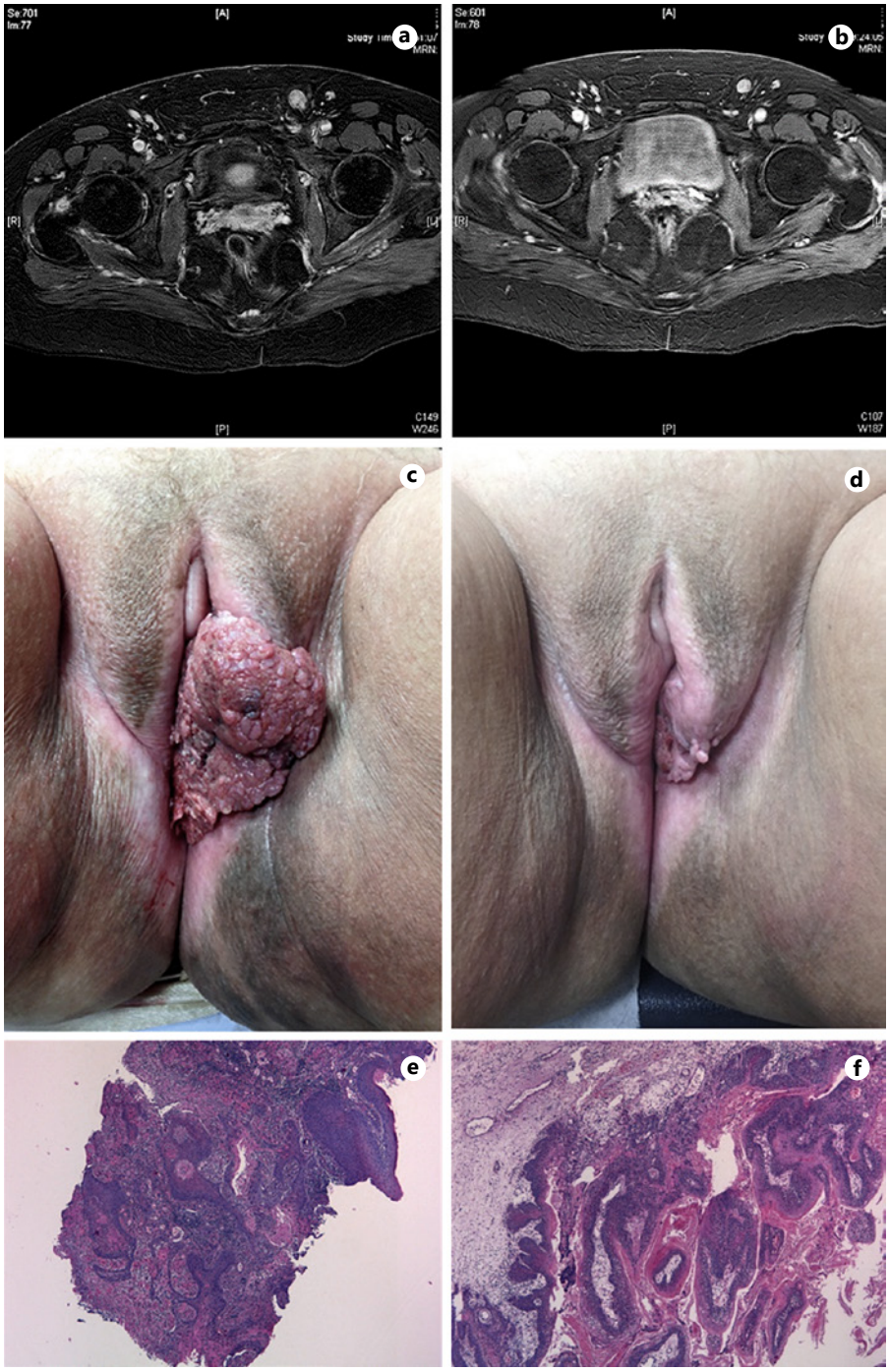

Fig. 2. MRI study, macroscopic appearance, and microscopic appearance of advance vulvar cancer before and after 6 cycles 3 weekly paclitaxel and carboplatin in patient 2. **a**, **b** MRI. **a** The inguinal node is suspect due to a clear enlargement and irregular delineation before the start of chemotherapy. **b** After chemotherapy, the inguinal node is sharply delineated with an otherwise unsuspected appearance. **c**, **d** Macroscopic appearance. **c** An exophytic tumor arises from the left labium major, measuring 10 cm in diameter and extending to the anal sphincter. **d** After chemotherapy, the tumor is dramatically reduced and a safe margin to the anal sphincter was obtained. **e**, **f** Microscopic appearance. **e** Diagnostic vulvar biopsy demonstrating a well differentiated keratinizing squamous cell carcinoma arising on a background of differentiated vulvar intraepithelial neoplasia. **f** The vulvectomy specimen after chemotherapy showed residual well differentiated keratinizing squamous cell carcinoma and differentiated vulvar intraepithelial neoplasia with an important fibro-inflammatory reaction in the underlying stroma.

Patient 2

A 69-year-old woman presented in April 2015 at the university hospital in Liège, Belgium, with a well differentiated vulvar squamous cell carcinoma (FIGO stage 2). The tumor originated from the left labium majus, measured 10 cm in diameter and extended to the anal sphincter. She had enlarged lymph nodes in the left inguinal area on MRI. Positron emission tomography (PET)-CT excluded distant metastases. Because of the size of the tumor and the extension to the anal sphincter, her treatment started with 6 cycles taxol (175 mg/m^2)-carboplatin (5 × AUC) from April 2015 until August 2015. MRI as well as macroscopic inspection showed partial remission making less extensive surgery possible (Fig. 2). In November 2015, a radical vulvectomy and left inguinofemoral lymphadenectomy were performed.

Microscopic examination revealed multifocal well differentiated keratinizing squamous cell carcinoma. The largest lesion measured 6 × 4 cm in diameter invading the stroma over a depth

Table 1. Studies with 3-weekly taxol carboplatin/cisplatin in locally advanced (inoperable) vulvar cancer

Author, year	Patients, *n*	Age, years	FIGO 2009 stage	Clinical response	Surgery	Adjuvant therapy	PFS, months	Relapse	OS, months	Status	Notes
Belotte et al. [10], 2012	1	_	IIIA	CR after 6 cycles	No	No	24	_	_	NED	Middle-age, HIV-positive patient. Because of toxicity, switched to docetaxel/ carboplatin for the last 3 cycles
Aragona et al. [11], 2012	6	_	II	PR after 3 cycles	Yes RV + BL	_	_	_	_	_	
		_	IVA	PR after 3 cycles	Yes RV + BL	_	70	_	_	_	
		_	IVA	PR after 3 cycles	Yes LRR + BL	_	_	_	_	_	
		_	IVA	PR after 3 cycles	Yes RV + BL	_	_	_	_	_	
		_	IVA	PR after 3 cycles	Yes LRR + BL	_	_	_	_	_	
		_	IVA	SD after 3 cycles	No	_	_	_	_	_	
Musella et al. [12], 2013	1	57	III	PR after 3 cycles	Yes LRR	No	4	_	_	NED	Intestinal-type vulvar adenocarcinoma
Deppe et al. [13], 2013	3	_	_	PR after 6 cycles	Yes LRR	_	_	_	_	_	
		_	_	PR after 6 cycles	Yes LRR	_	_	_	_	_	
		_	_	PR after 6 cycles	No	RT	_	_	_	_	Refused surgery
Mert et al. [14], 2014	3	57	_	CR after 6 cycles	No	No	3	Vulvar	36	AWED	
		57	_	PR after 4 cycles	_	_	_	_	_	_	Decided to discontinue after 4 cycles, then lost of follow-up
		41	_	CR after 6 cycles	No	No	10	_	_	NED	
Raspagliesi et al. [15], 2014	3	73	III	CR after 3 courses	Yes	RT	28	Vulvar	35	NED	
		78	IVB	PR after 3 courses	Yes	RT	5	Vulvar + liver	9	DOD	
		77	IVA	PD after 2 cycles	No	_	2	Liver	5	DOD	Switched to chemoradiation after 2 cycles due to lack of response
Current series	3	70	IVA	PR after 4 cycles	Yes RV + BL	RT	5	Vulvar	42	AWED	
		69	II	PR after 6 cycles	Yes RV + ML	No	20	_	20	NED	
		50	IVB	SD of the vulvar tumor, PD of the inguinal nodes	Yes RV+ BL	No	4	Vulvar + lung and bones	18	DOD	

AWED, alive with disease; BL, bilateral lymphadenectomy; CR, complete response; DOD, dead of disease; LRR, local radical resection; ML, monolateral lymphadenectomy; NED, alive with no evidence of disease; PD, progressive disease; PR, partial response; RV, radical vulvectomy; SD, stable disease.

of 2 cm. Tumor resection margins were negative for invasive cancer but positive for differentiated vulvar intraepithelial neoplasia. All 13 inguinofemoral lymph nodes were free of disease. Adjuvant treatment was not necessary. PET-CT showed no evidence of disease 20 months after diagnosis.

Patient 3

A 50-year-old woman presented in August 2015 with vulvar squamous cell carcinoma at the university hospital in Leuven. The vulvar lesion was 3 cm in diameter, with bilateral inguinal lymphadenopathy. PET-CT also showed lymphadenopathy in the left

iliac region. This was confirmed by a laparoscopic iliac lymphadenectomy, which showed 4/9 positive lymph nodes (FIGO stage IVb). Due to the iliac lymph node metastases that was found, it was decided to start treatment with 4 cycles taxol (175 mg/m^2)-carboplatin (5 × AUC) from September 2015 to December 2015. The vulvar tumor remained stable. Unfortunately, disease progression of the inguinal lymph nodes was found. After chemoradiation, a vulvectomy and bilateral inguinofemoral lymphadenectomy were performed.

Microscopic examination revealed a well differentiated squamous cell carcinoma with a largest diameter of 3 cm and an invasion depth of 5 mm. Tumor resection margins were negative. There were 3 positive lymph nodes on both sides, all of them being macrometastases and 3 of them showing extracapsular growth. Postoperative recovery was complicated by debilitating lymphedema and cellulitis. Local relapse and metastatic spread to the lung and bones were found 4 months after surgery. Palliative care was opted and she died 18 months after primary diagnosis.

Discussion

Two patients with locally advanced vulvar squamous cell carcinoma showed an impressive response after neoadjuvant 3-weekly paclitaxel-carboplatin. Complementation with standard vulvar surgery resulted in a long-term disease control. This observation warrants further exploration of this clinical approach. Although human papilloma virus status does not seem to influence the response rate at this moment, this also needs to be further explored.

Currently, chemoradiation is the only alternative treatment option to obtain tumor size reduction in patients with advanced stage vulvar cancer. Although this treatment regimen proved to be successful in several studies, treatment-related morbidity was high causing significant postoperative complications, including wound breakdowns and treatment-related death [6]. Another disadvantage of preoperative chemoradiation is that salvage radiotherapy is no longer a treatment option [2]. These results indicate the need of alternative treatment options.

In the treatment of cervical cancer, utilization of paclitaxel and carboplatin, with or without ifosfamide as neoadjuvant chemotherapy followed by radical surgery is currently being investigated by the EORTC [7]. A first report on the results in 30 cervical cancer patients showed a clinical overall response rate of 82.3%. Optimal pathological response was seen in 17.6% of the patients and suboptimal pathological response was 41.2%. However, recurrence occurred in 42.8% of the complete responders. Toxicity was acceptable [7]. Other studies also found promising results, especially for platinum-based chemotherapy in combination with paclitaxel for the treatment of invasive squamous cervical cancer [8, 9].

The effect of neo-adjuvant chemotherapy with paclitaxel and carboplatin or cisplatin has been described in previous case reports or larger series where paclitaxel-carboplatin was one of the treatment options for patients with locally advanced (inoperable) vulvar cancer. The results of these case reports are summarized in Table 1. In 17 out of 20 (85%) patients, complete or partial response was found after 3–6 cycles of paclitaxel-carboplatin. In 12 out of 20 (60%) patients, surgical treatment after chemotherapy was possible [10–15]. One advantage of the use of paclitaxel-carboplatin is the vast experience clinicians have in ovarian, cervical, and endometrial cancer.

In conclusion, the current data suggest that the combination of paclitaxel and carboplatin in a 3-weekly schedule deserves further exploration in patients with locally advanced and/or metastatic vulvar cancer in a prospective multicentric setting.

Disclosure Statement

The authors declare no conflicts of interest.

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