Cisplatin-gemcitabine as palliative chemotherapy in advanced squamous vulvar carcinoma: report of two cases

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Summary

Vulvar cancer (VC) is a rare disease, usually diagnosed in a stage still amenable to potentially curative treatments, including surgery and/or radiation therapy with or without chemotherapy. Several patients however present at diagnosis with metastatic disease and another 30-50% will relapse. Prognosis of metastatic or recurrent disease not amenable to salvage surgery or radiotherapy is very poor. Evidence about the efficacy of chemotherapy in this setting is limited and its role still remains unclear. At present there is no standard treatment for advanced VC and patients are usually treated with schedules adopted for chemoradiation or extrapolated from cervical cancer. We report our experience using a cisplatin-gemcitabine regimen in two cases of metastatic squamous cell VC. No response was obtained with this schedule. No other data are available in the literature about the choice of a cisplatin-gemcitabine regimen in this patient subset. The paucity of evidence about the role of palliative chemotherapy in metastatic VC justifies any effort to implement knowledge. For this reason we think it is notable to also report a negative experience. It is not possible for us to conclude that this chemotherapy would be unable to provide any benefit in a larger sample of patients; nonetheless we think that new agents, rather than combinations of older drugs, could hopefully provide more benefit.

Key words: Vulvar cancer; Chemotherapy; Gemcitabine.

Introduction

Vulvar cancer (VC) is a rare disease which mostly affects elderly women; it represents about 4% of all gynecological malignancies with an incidence of about two cases for every 100,000 women per year [1].

Usually VC has a squamous cell carcinoma histology and is diagnosed in a stage still amenable to potentially curative treatments, including surgery and/or radiation therapy with or without chemotherapy [2]. Several patients however present with metastatic disease at diagnosis and another 30-50% will develop a relapse within two years; recurrences are usually located in the groin [3].

Prognosis of metastatic or recurrent disease that is not amenable to salvage surgery or radiotherapy is very poor. Evidence about the role of chemotherapy in this setting is limited and its role still remains unclear, also because results remain disappointing [4].

While chemotherapy has shown activity on chemonaive patients in the neo-adjuvant setting [5-9], many single agents (cisplatin, mitoxantrone, bleomicyn, piperazinedione) have shown no response or short duration response in pretreated women with recurrent VC [2, 9]. Furthermore, only a modest activity with a response rate of 14% was achieved by the administration of a 3-weekly schedule of paclitaxel in recurrent or metastatic VC women in a phase II trial conducted by EORTC-GCC [10] while Olawaiye et al. [2] and recently Bacha et al. [11] reported an interesting activity of erlotinib in two and one cases, respectively.

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Cormio *et al*. [4] found that combination chemotherapy with the doublet cisplatin-vinorelbine was an active and well tolerated regimen, also in previously irradiated women reporting a 40% overall response rate. Nonetheless, at present there is no standard treatment for advanced VC. This may be in part explained by the rarity of the disease and in part by the fact that patients are usually elderly and frequently present with important comorbidities, such as impairment of renal and cardiac function in particular [9], thus they are not ideal candidates for clinical studies.

The difficulties in enrolling patients and the lack of a standard treatment represent an obstacle in planning and conducting randomized controlled trials. Thus patients are usually treated with schedules adopted for chemoradiation or extrapolated from cervical cancer therapy.

In a phase III GOG trial on advanced cervical carcinoma Monk et al. [12] randomized 513 patients to receive four cisplatin containing doublets (with gemcitabine or vinorelbine or topotecan or paclitaxel, respectively) to assess the toxicity and efficacy. Though cisplatin combined with paclitaxel showed a favorable trend over other treatment arms, no significant difference in OS was found in this study [12], while a lower hematological toxicity was observed in the gemcitabine containing arm. Therefore the authors suggested that differences in chemotherapy scheduling and pre-existing morbidity are important in individualizing therapy [12].

We think it is noteworthy to report our experience about the use of a cisplatin-gemcitabine regimen in two cases of advanced squamous cell VC. To the best of our knowledge this is the first report in this patient subset.

Case Reports

Case 1

A 65-year-old woman with various comorbidities (congestive heart failure, hypertension, atrial fibrillation, diabetes mellitus and Graves' disease) who experienced a left groin recurrence of squamous VC was treated with a palliative chemotherapy consisting of 75 mg/m^2 cisplatin on day 1 and 1000 mg/m^2 gemcitabine on days 1 and 8 every three weeks. She was previously submitted to a left hemivulvectomy with inguinal-femoral lymph node dissection and, because of her comorbidities, to adjuvant concurrent chemotherapy with cisplatin and radiation therapy (CT + RT) for a poorly differentiated carcinoma which was staged as pathological T1b N2c M0 (FIGO Stage IIIC). The treatment was well tolerated and only G2 neutropenia was observed. Treatment was stopped after two cycles because of local disease progression.

Case 2

A 73-year-old woman with a poor performance status due to cancer symptoms, also affected by hypertension and atrial chronic fibrillation, was treated with the same chemotherapy schedule (75 mg/m^2 cisplatin on day 1 and 1000 mg/m^2 gemcitabine on days 1 and 8 every three weeks). She presented with metastases to the left supra-clavicle lymph nodes and with left groin disease progression. She experienced disease progression during concurrent adjuvant cisplatin and capecitabine CT + RT. She had previously undergone radical vulvectomy with bilateral inguinal-femoral lymph node dissection for a moderately differentiated squamous VC, staged as pathological T1b N2c M0 (FIGO Stage IIIC). Treatment was relatively well tolerated (G2 anemia and G3 neutropenia were respectively observed) but despite a sizable reduction of the palpable left supraclavicular nodal metastases treatment was stopped after three cycles because of pulmonary progression of the disease.

Discussion

Commonly a patient with metastatic vulvar cancer presents with one or more comorbidities and a relatively unfavorable performance status, resulting in a major vulnerability to chemotherapy side effects. Therefore, decision making about the preferred treatment is difficult because chemotherapy in the palliative setting should mostly provide improvement in quality of life and disease control.

We chose a cisplatin-gemcitabine combination therapy which is effective against various cancer types (i.e., squamous non-small cell lung cancer, bladder, biliary tract), considering the favorable hematological toxicity profile reported [12] compared with other regimens and initial data of promising activity against cervical cancer [13].

Unfortunately, despite a manageable toxicity profile this regimen has shown no positive activity in our experience. The disheartening lack of response and paucity of evidence about the role of palliative chemotherapy in metastatic VC justify any effort to implement knowledge. For this reason we think it noteworthy to also report a negative experience.

It is not possible for us to conclude that this chemotherapy would be unable to provide any benefit in a larger sample of patients, nonetheless we think that new agents, rather than combinations of older drugs, could hopefully provide more benefit.

An interesting option may probably be offered in the near future by the use of agents such as anti-EGFR targeted therapy, i.e., erlotinib [2, 11] or erbitux [14], which seem to be active and with a different toxicity profile than chemotherapy (mostly cutaneous side effects).

References

[1] Jemal A., Center M.M., Ward E., Thun M.J.: "Cancer occurrence". *Methods Mol. Biol*., 2009, *471*, 3.

[2] Olawaiye A., Lee L.M., Krasner C., Horowitz N.: "Treatment of squamous cell vulvar cancer with the anti-EGFR tyrosine kinase inhibitor Tarceva". *Gynecol. Oncol*., 2007, *106*, 628.

[3] Fonseca-Moutinho J.A.: "Recurrent vulvar cancer". *Clin. Obstet. Gynecol*., 2005, *48,* 879.

[4] Cormio G., Loizzi V., Gissi F., Serrati G., Panzarino M., Carriero C., Selvaggi L.: "Cisplatin and vinorelbine chemotherapy in recurrent vulvar carcinoma". *Oncology*, 2009, *77*, 281.

[5] Durrant K.R., Mangioni C., Lacave A.J., George M., van der Burg M.E., Guthrie D. *et al*.: "Bleomycin, methotrexate, and CCNU in advanced inoperable squamous cell carcinoma of the vulva: a phase II study of the EORTC Gynaecological Cancer Cooperative Group (GCCG)". *Gynecol. Oncol*., 1990, *37,* 359.

[6] Benedetti-Panici P., Greggi S., Scambia G., Salerno G., Mancuso S.: "Cisplatin (P), bleomycin (B), and methotrexate (M) preoperative chemotherapy in locally advanced vulvar carcinoma". *Gynecol. Oncol*., 1993, *50,* 49.

[7] Geisler J.P., Manahan K.J., Buller R.E.: "Neoadjuvant chemotherapy in vulvar cancer: avoiding primary exenteration". *Gynecol. Oncol*., 2006, *100*, 53.

[8] Wagenaar H.C., Colombo N., Vergote I., Hoctin-Boes G., Zanetta G., Pecorelli S. *et al*.: "Bleomycin, methotrexate, and CCNU in locally advanced or recurrent, inoperable, squamous-cell carcinoma of the vulva: an EORTC Gynaecological Cancer Cooperative Group Study. European Organization for Research and Treatment of Cancer". *Gynecol. Oncol*., 2001, *81,* 348.

[9] Domingues A.P., Mota F., Durão M., Frutuoso C., Amaral N., de Oliveira C.F.: "Neoadjuvant chemotherapy in advanced vulvar cancer". *Int. J. Gynecol. Cancer*; 2010, *20*, 294.

[10] Witteveen P.O., van der Velden J., Vergote I., Guerra C., Scarabeli C., Coens C. *et al*.: "Phase II study on paclitaxel in patients with recurrent, metastatic or locally advanced vulvar cancer not amenable to surgery or radiotherapy: a study of the EORTC-GCG (European Organisation for Research and Treatment of Cancer-Gynaecological Cancer Group)". *Ann. Oncol*., 2009, *20,* 1511.

[11] Bacha O.M., Levesque E., Renaud M.C., Lalancette M.: "A case of recurrent vulvar carcinoma treated with erlotinib, an EGFR inhibitor". *Eur. J. Gynaecol. Oncol*., 2011, *32*, 423.

[12] Monk B.J., Sill M.W., McMeekin D.S., Cohn D.E., Ramondetta L.M., Boardman C.H. *et al*.: "Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study". *J. Clin. Oncol*. 2009, *27,* 4649.

[13] Brewer C.A., Blessing J.A., Nagourney R.A., McMeekin D.S., Lele S., Zweizig S.: "Cisplatin plus gemcitabine in previously treated squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group". *Gynecol. Onco1*., 2006, *100,* 385.

[14] Richard S.D., Krivak T.C., Beriwal S., Zorn K.K.: "Recurrent metastatic vulvar carcinoma treated with cisplatin plus cetuximab". *Int. J. Gynecol. Cancer,* 2008, *18*, 1132.

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