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Review

Systemic therapy in squamous cell carcinoma of the vulva: Current status and future directions

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HIGHLIGHTS

- Current treatment strategies have not led to improved survival in women with advanced-stage vulvar carcinoma.
- Knowledge of the pathogenesis and mutational profile of vulvar carcinoma may allow for the development of new treatment strategies.
- Future trials should use innovative designs, focus on quality of life, include elderly patients, collect biomarkers and incorporate targeted agents.

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ABSTRACT

Objective. The advances achieved in the surgical management of vulvar squamous cell carcinoma (SCC) have not been mirrored in systemic therapy options. The objective of this paper is to summarize current evidence regarding systemic therapy in vulvar cancer, review the latest research on the biology of this disease, and identify future strategies to improve patient management.

Methods. MEDLINE and EMBASE were searched for all relevant English-language articles from inception to December 10, 2012. Existing evidence regarding systemic therapy in vulvar SCC was synthesized descriptively, with an emphasis on prospective studies when available. Single-patient case-reports were excluded.

Results. We identified 12 studies of neoadjuvant chemoradiation, 8 studies of neoadjuvant chemotherapy alone, 18 studies of chemoradiation as primary therapy, 4 studies of chemotherapy in the adjuvant setting, and 8 studies of chemotherapy for recurrent or metastatic disease. Review of the biology of vulvar cancer was performed, and promising targets for the future were identified based on the two biologic pathways of disease development. New therapeutic strategies such as immune-therapy and targeted agents hold promise for the future.

Conclusions. Advances in systemic therapy for vulvar SCC are urgently needed, especially in the setting of recurrent and metastatic disease. A focus on the investigation of new targeted agents is encouraged and consideration of quality of life and sexual health issues is essential. International cooperation and adaptive trial designs are required to improve outcomes for this group of traditionally under-served women.

Contents

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Introduction

The incidence of vulvar cancer has been increasing over the past 20 years [1]. Vulvar cancer is diagnosed in an estimated 4,490 US women, and leads to 950 deaths annually [1]. One third of these women will be diagnosed with FIGO stage III and IV disease [2]. There has been no improvement in survival for those diagnosed with advanced or recurrent disease in the last 2 decades [2]. New approaches are therefore required to improve outcomes in patients with advanced disease.

Significant progress has been made in the surgical management of vulvar cancer over the past 20 years. Wide local excision has largely replaced radical vulvectomy for early-stage disease [3]. Assessment of groin lymph nodes has transitioned from en-bloc resection to separate inguinal incisions [4], and finally to sentinel lymph node biopsy in appropriately selected patients [5]. These modifications have maintained oncologic outcomes while significantly reducing morbidity. The development of effective systemic therapy options for patients with vulvar cancer, however, has not kept pace with these surgical advances.

Trials of systemic therapy for patients with vulvar cancer are difficult to perform. The rare nature of this disease makes randomized controlled trials (RCT) virtually impossible for single institutions, and even multicentre trials have difficulty meeting accrual targets. The patient population is predominantly elderly, and often suffering from medical comorbidities, making enrolment into phase I/II trials difficult. Significant improvements in systemic therapy for vulvar cancer will require new ways of thinking about, and investigating, therapeutic options, especially for those with advanced-stage disease. This review summarizes the current evidence for systemic therapy in vulvar cancer, highlighting the latest research on the biology of this disease and seeks to act as a catalyst for new initiatives in the gynecologic oncology community to facilitate the development of better strategies for patient management.

Methods

MEDLINE and EMBASE were searched from inception to December 10, 2012 to identify English-language publications of systemic therapy for squamous cell carcinoma (SCC) of the vulva. The search strategy was created in conjunction with a research librarian experienced in systematic reviews. Search terms included appropriate controlled vocabulary for each database and keyword searches including various terms for vulvar cancer in combination with terms such as “chemoradiation”, “chemotherapy”, “systemic therapy”, “targeted therapy”, and “biologic agents”. In addition, the PubMed related articles feature was used and reference lists of eligible articles were searched to ensure all relevant articles were identified. Articles describing treatment for melanoma or non-SCC histologies were excluded. Given the rarity of vulvar cancer, no limits were placed on study methodology, however, single-patient case series were excluded as were studies not providing clinical outcomes for patients given systemic therapy.

Current approaches to systemic therapy

Neoadjuvant chemoradiation

Chemoradiation has been evaluated as a strategy to allow for surgical resection in patients presenting with unresectable locally advanced vulvar cancer (LAVC) or to allow for more limited, and less morbid surgery, in patients who would otherwise require exenteration. Studies of neoadjuvant chemoradiation are summarized in Table 1. According to a survey of members of the Gynecologic Cancer Intergroup (GCIG), there is significant heterogeneity in the chemotherapy regimens used in the neoadjuvant setting along with radiation therapy (RT) [6]. The most commonly used chemotherapy regimen was weekly cisplatin (in 60% of GCIG groups) followed by cisplatin and 5-FU (in 31% of groups) [6]. No study has compared various chemotherapy agents in conjunction with standardized RT for the treatment of LAVC.

Maneo et.al. presented the results of an RCT comparing neoadjuvant chemoradiation to primary surgery in abstract form only; it is therefore not included in Table 1 [7]. Sixty-eight women with operable LAVC were randomized to either primary radical surgery followed by RT if more than one groin lymph node contained metastatic disease, or to neoadjuvant chemoradiation followed by surgery. Chemoradiation comprised 50 Gy neoadjuvant RT with concurrent infusional 5-FU 750 mg/m^2 days 1–5 and Mitomycin-C 15 mg/m^2 IV day 1, with two courses given three weeks apart. They found no difference in rates of morbidity or wound separation, and also no difference in recurrence or survival between groups at a mean follow-up of 42 months. Details regarding the extent of primary tumor and the complexity of surgical procedures required in each group are not provided, and quality of life (QOL) was not reported.

GOG 101 was a two-part prospective study by the Gynecologic Oncology Group (GOG) investigating the use of neoadjuvant chemoradiation for LAVC. The study separately investigated the role of concurrent RT and cisplatin/infusional 5-FU chemotherapy in patients with unresectable disease due to local tumor extent [8] or fixed or ulcerated inguinal lymph nodes [9]. RT was given in two courses separated by a 2 week break.

The first component of GOG 101 evaluated 71 patients with unresectable vulvar disease, or disease requiring exenteration [8]. Clinical CR occurred in 47% (34/71) of patients. Of the patients with clinical CR who had surgery, 70% (22/31) had a pathologic CR. Two of 71 patients (3%) had unresectable disease after chemoradiation, and three patients (4%) required exenteration. Although postoperative wound complications were frequent, morbidity related to surgery in the irradiated vulva was not excessive. Toxicity from chemoradiation was acceptable, although acute vulvar cutaneous reactions were almost universal. Four treatment-related deaths (5%) were reported. At a median follow-up of 50 months, recurrence was reported in 34% (24/69) of patients, while 56% of patients (40/71) were alive without evidence of disease.

The second component of GOG 101 evaluated 46 patients with unresectable nodal disease [9]. After chemoradiation, 38 patients (83%) were able to undergo surgery (37 with resectable nodal disease).

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