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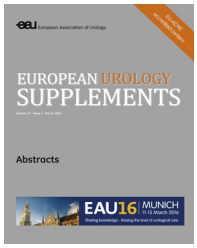

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Systemic Therapy for Penile Cancer

Andrea Necchi *

Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Article info

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Abstract

Penile squamous cell carcinoma (PSCC) is a very rare disease and its prognosis primarily depends on regional lymph node involvement. Although a cure can be obtained in patients with a low metastatic burden using surgery as standalone option, combined modality therapy is required for more advanced cases. In patients with multiple fixed or bulky inguinal lymph nodes, and in those with enlarged pelvic lymph nodes, chemotherapy is moderately effective, with an objective response rate of approximately 50% if a triple regimen of cisplatin, taxane, and ifosfamide or 5-fluorouracil is used. However, long-term survival rates are dismal irrespective of the possibility of administering the most effective treatments, and new drugs are warranted. Therefore, huge unmet medical needs remain in the management of patients with advanced disease. Among the limitations is the optimal timing of chemotherapy delivery in relation to lymphadenectomy. Targeted therapies against the EGFR pathway provided the most promising results in patients after chemotherapy failure. The next research efforts should focus on combining new drugs with standard therapy options, and on identification of biomarkers of clinical benefit and new prognostic factors to help physicians in orienting therapeutic strategies.

* Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Via G. Venezian 1, 20133 Milan, Italy. Tel. +39 02 23902402; Fax: +39 02 23903150.
E-mail address: andrea.necchi@istitutotumori.mi.it.

1. Introduction

In patients with regional lymph node involvement or distant metastases of penile squamous cell carcinoma (PSCC), the optimal timing for chemotherapy and radiotherapy administration with respect to lymph node dissection is unclear and efficacy results for chemotherapy from the available studies are conflicting. In this review, we critically summarize literature evidence on systemic therapy options and focus on the huge unmet medical needs that characterize clinical research in this field.

2. Role of neoadjuvant chemotherapy in locally advanced PSCC

Regional lymph node involvement represents the most frequent dilemma in the clinical management of patients with squamous cell carcinoma of the penis (PSCC), as it is far more frequent than the occurrence of distant metastases [1]. However, the prognosis is generally poor in the long term despite adequate treatment, and primarily depends on the extent of locoregional spread.

In fact, only a small proportion of patients with bulky or fixed inguinal lymphadenopathy will benefit from surgery

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as a standalone therapeutic option. Presurgical systemic therapy in these patients is currently recommended by the European Association of Urology (EAU) guidelines and represents an attractive strategy [2]. Neoadjuvant chemotherapy allows timely delivery of therapy in treating systemic disease, results in volume reduction for enlarged lymphadenopathies, and may facilitate subsequent surgical consolidation. Several retrospective studies using various chemotherapeutic agents reported objective response rates (ORRs) of ~50% and pathologic complete responses (pCRs) ranging from 10% to 15% among patients who underwent consolidative lymph node dissection [3]. These results are summarized in a large multicenter analysis of individual patient-level data for men who underwent perioperative chemotherapy and lymphadenectomy. It is important to note that despite initial moderate activity, combination chemotherapy was associated with 2-yr overall survival (OS) probability of only 35.8% in this analysis [4].

Among the available studies, a prospective US phase 2 trial evaluated the safety and activity of four cycles of neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy (TIP) [5]. Thirty patients received TIP in this trial, of whom 15 (50%) had an objective response and 22 (73.3%) underwent consolidative surgery. Three patients (10%) exhibited a pCR, which was a marginally significant predictor of improved survival. Nine patients (30%) remained alive and free of recurrence after median follow-up of 34 mo. The estimated median time to progression (TTP) was 8.1 mo and median OS was 17.1 mo. Univariable regression to identify favorable prognostic factors showed that objective response to chemotherapy and the absence of bilateral residual tumor, extranodal extension, or skin involvement were associated with longer TTP and OS. The combination of docetaxel, cisplatin, and 5-fluorouracil (TPF) has been investigated by several groups. In a UK phase 2 study (Cancer Research UK study 09/001), TPF was administered to 26 patients, including seven with distant (visceral) metastases [6]. The ORR was 38.5%, the median progression-free survival (PFS) was 7.1 mo, and OS was 13.9 mo. Disappointingly, the combination was quite toxic, as grade 3–4 adverse events were reported in 19 patients (65.5%). Results for the TPF combination (with paclitaxel instead of docetaxel in some cases) were also reported from retrospective studies: an ORR of 42.8% and pCR of 14.3% were reported in an Italian study including 28 patients [7]. A Dutch experience with the same regimen included 26 patients, with an ORR of 60% and pCR of 4% [8]. Safety results are hard to reproduce from such retrospective, and usually long-dated, series.

Interestingly, retrospective comparison of neoadjuvant TPF and PF chemotherapy did not show significant differences in RFS and OS, although inherent biases due to the retrospective nature of the data and the small numbers in each subgroup should be acknowledged [4].

Retrospective studies including limited numbers of patients have also evaluated alternative regimens, such as the combination of bleomycin, methotrexate, and cisplatin (BMP) [9–11].

There are no clinical or pathological factors that are useful in predicting the benefit from neoadjuvant chemotherapy to date. The strongest predictor of improved survival after preoperative chemotherapy and surgery remains achievement of a pCR [12]. Imaging biomarkers may also be useful for early assessment of the benefit during neoadjuvant chemotherapy, and some data are available regarding the role of [^{18}F]-fluorodeoxyglucose positron emission tomography [13]. In conclusion, there is a substantial need for new studies that might provide translational evidence towards predictive or prognostic biomarkers of the effect of chemotherapy, as well as a need for additional data on combined treatment approaches with radiotherapy to improve outcomes.

3. Data on the use of adjuvant chemotherapy

There are no prospective data on adjuvant chemotherapy; only small retrospective studies have been reported, as well as large retrospective and multicenter case series. There is level 2b evidence for adjuvant chemotherapy in the current EAU guidelines, and this should be regarded as a treatment option for patients with pathological N2 or N3 disease after lymphadenectomy [2].

Historically, long-term disease-free survival occurred in 84% of 25 consecutive node-positive patients treated with adjuvant vincristine + bleomycin + methotrexate chemotherapy during 1979–1990 in a single institution [14]. More recently, an international retrospective study focused on a subgroup of patients with pathological pelvic lymph node involvement and reported an OS improvement with adjuvant chemotherapy [15]. Disappointingly, no additional information can be obtained from such a retrospective study, in particular regarding the role of specific chemotherapy combinations, as mixed regimens were used. An Italian study by the Milan Cancer Institute showed intriguing long-term efficacy of TPF chemotherapy: among 19 treated patients, ten (52.6%) were still disease-free after median follow-up of 22 mo [7]. Of note, outcomes were compared between patients treated with adjuvant chemotherapy and patients treated preoperatively from the same institution. An apparent improvement in survival was reported but it did not reach statistical significance, although the authors could not fully account for the inherent biases of patient selection and the retrospective nature of the data.

Some evidence supports a role of biomarkers for patient selection in the adjuvant setting. In particular, intriguing early evidence from the Milan group showed that p53 immunohistochemical expression seemed to be associated the with shortest RFS and OS among 21 patients who received adjuvant TPF chemotherapy [16]. This information warrants additional studies and might be useful in improving prognostic stratification of these patients and allocating therapeutic options.

4. Chemotherapy for advanced disease

There is substantial variability in first-line regimens for patients with distant metastatic disease, and the outcomes

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