Original Study

A Combination of Cisplatin and 5-Fluorouracil With a Taxane in Patients Who Underwent Lymph Node Dissection for Nodal Metastases From Squamous Cell Carcinoma of the Penis: Treatment Outcome and Survival Analyses in Neoadjuvant and Adjuvant Settings

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Abstract

We addressed the use of perioperative chemotherapy in nodal metastases from penile cancer. Forty-seven N2 to 3 M0 patients received perioperative taxane, cisplatin and 5-fluorouracil (T-PF) and 38.3% are disease-free at 22 months. Neoadjuvant T-PF allowed 12 (43%) clinical responses and 4 (14%) complete pathologic remissions among 28 patients, and the 2-year disease-free survival (DFS) was 7.1%. The 2-year DFS was 36.8% after adjuvant T-PF. T-PF is active and is associated with long-term survival after surgery. Chemotherapy must be offered with caution in patients with resectable nodal metastases.

Background: The role of chemotherapy in nodal metastases from penile squamous cell carcinoma is not defined. We evaluated the efficacy of a combination of T-PF (a taxane, cisplatin, and 5-fluorouracil) in neoadjuvant and adjuvant settings. **Patients and Methods:** Since June of 2004, T-PF was administered to stage N2 to 3 patients. With time, neoadjuvant chemotherapy administration prevailed with respect to use in the adjuvant setting. Primary end points were progression-free (PFS) and overall (OS) survival. Secondary objectives were tolerability and activity in the neoadjuvant setting. Nonparametric tests, Kaplan–Meier, and regression analyses were performed. **Results:** As of October of 2012, 47 consecutive N2 to 3 M0 patients had undergone neoadjuvant ($n = 28$) or adjuvant ($n = 19$) T-PF: 18 patients (38.3%) remain disease-free after a median follow-up of 22 months (interquartile range, 17-42 months). The 2-year disease-free survivals were 36.8% (95% confidence interval [CI], 15.2-58.5) versus 7.1% (95% CI, 0-16.7) after adjuvant and neoadjuvant therapy, respectively. N3 metastases were associated with a poorer PFS, and bilateral metastases and mutated p53 were associated with a poorer OS. After neoadjuvant treatment, 43% clinical responses and 14% complete pathologic remissions were recorded, but responses were not associated with survival. Neutropenia (25.5%) was the most frequent Grade ≥ 2 toxicity. **Conclusion:** The T-PF regimen is well tolerated and compares with other regimens in terms of activity and efficacy in the neoadjuvant setting, and very long survivals have been recorded after adjuvant administration. The role of perioperative treatment in these patients remains controversial. Some caution in administering preemptive treatment in patients with resectable disease is needed.

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Introduction

Squamous cell carcinoma (SCC) of the penis is rare and does not exceed 1% of all malignancies in Western countries.[1] Nodal metastases represent a critical landmark where cure is still possible.[2,3] Most of the patients with minimal nodal involvement might be cured with radical surgery, and patients with bilateral disease, extranodal extension, or pelvic involvement have a very high risk of disease recurrence and finally death of disease.[4]

Available data showed that combination chemotherapy could exert moderate efficacy in penile SCC.[5-9] Cisplatin-based chemotherapies are most frequently used, although available data are few and heterogeneous. Neoadjuvant chemotherapy showed interesting clinical and pathologic response rates,[10,11] and adjuvant chemotherapy has been evaluated in single studies, with no control arm.[5,12] No strong data are available concerning the long-term benefits of pre- and postoperative chemotherapy.

Thanks to randomized clinical trials in ear, nose, and throat (ENT) SCC,[13-15] some experience showed promising results in metastatic penile SCC with use of a taxane with PF (cisplatin and 5-fluorouracil).[16] A prospective neoadjuvant trial reported complete pathologic remissions in 10% of patients after paclitaxel, cisplatin, and ifosfamide (TIP) treatment.[17] A recent study with docetaxel-PF reported a remission rate of 38% in metastatic penile SCC.[18]

In the present study we report the retrospective results of a combination of a taxane with PF administered before or after surgery with radical intent for $\geq$ N2 metastases in patients with SCC of the penis. Our aims were to evaluate results of adjuvant and neoadjuvant administration and predictive factors of survival.

Patients and Methods

Since June 2004, selected patients with histologically confirmed nodal metastases from SCC of the penis, an Eastern Cooperative Oncology Group performance status $\leq$ 2, and a written informed consent underwent treatment with a taxane with PF. The procedures were in accordance with the Declaration of Helsinki (2000) of the World Medical Association. The 2002 tumor, node, metastases (TNM) American Joint Committee on Cancer staging system (sixth edition) was used for classification.

Neoadjuvant chemotherapy was provided for clinical N3 (TNM, sixth edition) or bilateral disease and adjuvant chemotherapy was provided for all patients with $\geq$ pN2 SCC who received surgery. The regimen consisted of up to 4 cycles every 21 days with 120 mg/m^2 paclitaxel intravenously (I.V.) over 1 hour on day 1, 100 mg/m^2 cisplatin I.V. over 2 hours of infusion on day 1 followed by 96 hours of continuous I.V. infusion of 1000 mg/m^2/d of 5-fluorouracil.

Since January 2007, 75 mg/m^2 of docetaxel replaced paclitaxel and PF was reduced to 75 and 750 mg/m^2, respectively.

Since February 2010, all patients with $\geq$ N2 (TNM, sixth edition) disease were candidates for neoadjuvant therapy.

Patients must not have received previous radiation therapy or systemic chemotherapy for penile carcinoma containing cisplatin or taxanes.

No dose reduction was provided according to specific toxic events, which were tabulated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[19]

All patient stages were subsequently reclassified according to the seventh 2009 TNM edition.

Inguinal and pelvic lymph node dissections were aimed at full resection of palpable or visible disease with negative surgical margins.[20]

Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.1.[21]

p53 status was ascertained using chromogenic in situ hybridization (CISH) after the documented relationship between p53 mutation and poor response to cisplatin-based chemotherapy in ENT SCC.[22] CISH was done on 5-μm thick archival formalin-fixed paraffin-embedded tissue sections.[23]

After completion of treatment, patients were followed on a regular basis in the outpatient clinic.

Clinical End Points

The main end points of the study were progression-free survival (PFS) and overall survival (OS). Response rate and safety represented further objectives. The following covariates were considered: period of treatment (before and after 2008), treatment timing (at diagnosis vs. at relapse), age, N stage according to 2009 TNM staging system, size of measurable disease (diameter of largest node), laterality and presence of pelvic disease, p53 status, duration of treatment (computed as the interval between date of last surgery and start of chemotherapy for the adjuvant setting and as the interval between the date of starting chemotherapy and date of surgery for the neoadjuvant setting).

Progression-free survival and OS were calculated with Kaplan–Meier survival curves,[24] and a logistic model was developed to explore the effects of response according to RECIST criteria in the neoadjuvant group only.

Because of the retrospective nature of the study, we also evaluated if substantial differences between the patients who underwent neoadjuvant and adjuvant chemotherapy were appreciable with nonparametric Wilcoxon sum rank tests,[25] and *t* tests on logarithmically transformed variables (whose normality in distribution was ascertained via Shapiro tests). Associations among covariates were investigated via exact Fisher independence tests.[26]

All analyses were performed using R software.[27]

Results

Between June 2004 and October 2012, 47 consecutive patients underwent adjuvant (n = 19) or neoadjuvant (n = 28) treatment with T-PF (a taxane and PF). Characteristics are reported in Table 1.

Figure 1 shows Kaplan–Meier PFS (Figure 1A) and OS (Figure 1B) curves according to treatment in the adjuvant and neoadjuvant settings. A total of 18 (38.3%) patients were disease-free after a median follow-up of 22 months (interquartile range, 17-42 months). Table 2 shows the data in the 2 settings. The 2-year disease-free survival was 36.8% (95% confidence interval [CI], 15.2%-58.5%) in the adjuvant setting versus 7.1% (95% CI, 0%-16.7%) in the neoadjuvant setting.

We tested all covariates that we hypothesized could be informative of treatment outcome: treatment timing (at diagnosis vs. at relapse), disease extent (N3 vs. N < 3), laterality (bilateral vs. unilateral), pelvic disease (vs. inguinal only), and p53 status