Activity and toxicity of paclitaxel in pretreated metastatic penile cancer patients

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The objective of this study was to evaluate the use of paclitaxel in patients with advanced squamous cell penile cancer previously treated with neoadjuvant cisplatin-based chemotherapy. This was a single-arm, phase II, multicenter study. Patients were treated with 175 mg/m^2 paclitaxel at a 3-week interval, until disease progression or irreversible toxicity. The primary end point was the objective response rate. Secondary end points were safety, progression-free survival, and overall survival. Twelve patients were enrolled. Partial responses were observed in 25% (3 of 12) of patients (95% confidence interval: 12–40%). Grade 3 neutropenia and oral mucositis were the most common side effects, each noted in three patients. Median progression-free survival was 4 months (range 2–6 months) and median overall survival was 6 months (range 3–10 months). Paclitaxel is well tolerated and associated with promising efficacy. Further trials, also in a neoadjuvant setting, are needed to corroborate our preliminary findings. *Anti-Cancer Drugs* 20:277–280 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Squamous cell (SC) penile carcinoma is a rare disease, accounting for less than 1% of malignant tumors in men in the Western hemisphere, whereas it is not uncommon in Africa, South America, and eastern Europe [1]. Owing to the rarity of this cancer, few trials have been published so far; the majority of published trials is retrospective and include limited samples.

Although ilioinguinal lymphadenectomy is required to control regional metastases, it is rarely curative for bulky disease, and the prognosis is poor. Several studies have shown that combination chemotherapy gives the greatest benefit, improving surgical resectability and maximizing survival in patients with large-volume metastases [2–4].

Since the introduction of the methotrexate–bleomycin–cisplatin (BMP) and cisplatin-5 fluorouracil (5FU) regimens, there has been limited improvement in the efficacy of chemotherapy on SC penile cancer [5–7]. These regimens show response rates in the range of 25–72%, with high toxicity for the BMP schedule [5]. Recently, combination chemotherapy using cisplatin/gemcitabine and cisplatin/irinotecan has shown that these regimens are well tolerated and are active regimens for metastatic penile cancer [8,9].

More recently, the activity of taxanes in combination with cisplatin in SC penile cancer, either in a neoadjuvant or advanced setting, has been evaluated in a small series [10,11]. However, no study has been published so far considering paclitaxel monotherapy only in advanced tumors. Our phase II trial was carried out to evaluate the activity and toxicity of paclitaxel monotherapy in pretreated patients with advanced SC penile cancer.

Patients and methods

Study population

Between April 2004 and March 2008, 12 patients from five different institutions were enrolled in the study. Main eligibility criteria included previous diagnosis of SC carcinoma of the penis; previous treatment with a platinum-based regimen in a neoadjuvant setting for lymphonode metastases and/or inoperable disease; prior treatment with surgery or radiotherapy; current metastatic disease; and normal renal and liver function. Prior adjuvant regimens were permitted. Written informed

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consent was required from all patients before enrolment. The protocol was approved by the Institutional Review Board.

Patients received a 3 h 175 mg/m^2 paclitaxel intravenous infusion repeated every 21 days. Oral dexamethasone at 8 mg was given 12 h before, immediately before, and 12 h after the paclitaxel infusion. If the patient developed febrile neutropenia in any treatment cycle, granulocyte colony-stimulating factor was allowed in subsequent cycles. Paclitaxel dose reductions of 20% were permitted for febrile neutropenia or grade 3–4 nonhematologic toxicity.

The baseline evaluation included complete history and physical examination, assessment of performance status, bone scan, and total-body computed tomography scans. The treatment was administered until disease progression. The primary end point was the assessment of response rate; secondary end points included toxicity, progression-free survival, and overall survival (OS). Patients were assessed for response to therapy every 3 cycles, according to the standard Response Evaluation Criteria in Solid Tumors [12]. Toxicity was graded according to the Common Toxicities Criteria, Version 3.0 [13].

The primary end point of the study was response rate (complete and partial response). We have used a phase II design with two stages (minimax design), with a minimal acceptable rate of activity of 5% (p_0), an adjective rate of activity of 20% (p_1), P=0.10 (error α), and a potency ($1-\beta$) of 90%, with 12 patients in the first stage. If one response was observed, the trial passed to the second stage, with 32 patients. We have decided to publish these preliminary results of the first stage, and considering that only five centers participated in the study, with slow enrollment, we do not know whether we will continue the trial to the second stage. Time to progression and OS were analyzed using the product-limit method (Kaplan–Meier).

Results

Patients' characteristics

Patients' characteristics are shown in Table 1. All patients were treated with neoadjuvant chemotherapy for fixed inguinal nodes or unresectable tumors and received primary local treatment (total and partial amputation in seven and three patients, respectively, and radiotherapy in two patients). Five patients also received bilateral radical inguinal lymphadenectomy, whereas recurrent inguinal lymphadenectomy was carried out in seven patients. Three patients had also received adjuvant chemotherapy. Note that the interval between the end of neoadjuvant chemotherapy and disease relapse was ≤ 6 or >6 months in seven and five patients, respectively. All patients had distant metastases and local relapse. Current sites of metastases were abdominal nodes and the lung in seven patients and liver, bone, and nodes in five patients.

Table 1 Patients' characteristics

Number of patients	12
Median age (range) (years)	63 (43–75)
WHO performance status (%)	
0	6 (50)
1	5 (42)
2	1 (8)
Prior local therapy (%)	
Total amputation	7 (58)
Partial amputation	3 (25)
Radiotherapy	2 (17)
Neoadjuvant chemotherapy	12 (100)
Basal bilateral radical inguinal lymphadenectomy	5 (42)
Adjuvant chemotherapy after basal lymphadenectomy	3 (25)
Recurrent bilateral radical lymphadenectomy	7 (58)
Neoadjuvant chemotherapy (%)	
Cisplatin/fluorouracil	9 (75)
Cisplatin/gemcitabine	1 (8)
Cisplatin/vinorelbine	1 (8)
Cisplatin/bleomycin	1 (8)
Interval from the end of the neoadjuvant chemotherapy to disease relapse (%)	
$\leq$ 6 months	7 (58)
>6 months	5 (42)
Current site of metastases (%)	
Abdominal lymph nodes	12 (100)
Lung	7 (58)
Liver	5 (42)
Bone	1 (8)

A total of 66 cycles of paclitaxel were given to the patients. The schedule resulted in a mean received dose intensity of 168 mg/m^2, or 96% of the planned dose intensity. A paclitaxel dose reduction of 20% was adopted in 13 cycles (19.7%) because of grade 3 hematologic and nonhematologic toxicities. Treatment was delayed in 7 cycles (10.6%). Reasons for delay were patient's request (2 cycles), grade 2 nonhematologic toxicity (3 cycles), and investigator's decision for lack of premedication (2 cycles). Of 12 patients, three, six, and one patients completed 3, 6, and 8 cycles, respectively. The median number of cycles was 6 (range 2–8).

Objective responses, progression-free survival, and overall survival

Partial objective responses were observed in three of the 12 patients (25%) (95% confidence interval: 12–40%) after 3 cycles (Table 2). The partial responses were found in liver (one patient), lung (two patients), and lymph nodes (three patients). The responder patients were treated for 6 and 8 cycles (two and one patients, respectively). Median progression-free survival was 4 months (range 2–6 months), with a median OS of 6 months (range 3–10 months). Median OS was 8 months in responder patients. Further computed tomography was administered to three patients after progression of disease (gemcitabine, capecitabine, and sunitinib in one patient each, respectively), whereas only supportive care was given to nine patients.

Table 2 Responses and survival rates according to the follow-up

Response	Number of patients (%)
Complete response	0 (0)
Partial response	3 (25)
Stable disease	3 (25)
Progression	6 (50)
95% Confidence interval	12–40%
Median number of cycles	6 (2–8)
Median progression free survival (range) (months)	4 (2–6)
Median overall survival (range) (months)	6 (3–10)
Median survival in responders (range) (months)	8 (5–10)

Response criteria as reported in Patients and methods.

Table 3 Toxicity data experienced per patient ($n=12$)

Toxicity	Grade 1–2 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	6 (50)	3 (25)	1 (8)
Anemia	3 (25)	2 (17)	–
Thrombocytopenia	2 (17)	2 (17)	–
Alopecia	5 (42)	1 (8)	–
Oral mucositis	5 (42)	3 (25)	–
Nausea/vomiting	7 (58)	1 (8)	–
Peripheral neuropathy	6 (50)	2 (17)	–
Constipation	4 (33)	1 (8)	–
Diarrhea	3 (25)	1 (8)	–

Toxicity

In general, treatment was well tolerated. No toxic deaths occurred. The most important grade 1–2 toxicities included nausea/vomiting and peripheral neuropathy in seven and six patients, respectively. Grade 3 hematologic toxicities included neutropenia, anemia, and thrombocytopenia in three, two, and two patients, respectively. The most common grade 3 nonhematologic toxicities included oral mucositis and peripheral neuropathy in three and two patients, respectively. Grade 4 toxicity was limited to neutropenia in one patient (Table 3).

Discussion

Several agents have been used for penile cancer in a neoadjuvant setting and in advanced disease, of which the most common is BMP [4–6,11]. Dexeus *et al.* [5] treated 14 patients with locally advanced or metastatic penile cancer with BMP, reporting a 72% response rate, but toxicity was severe. Haas *et al.* [6] conducted a phase II study using BMP in 45 patients with locally advanced or metastatic penile carcinoma. There were five complete and eight partial responses, for an overall 32.5% response rate; however, toxicity was severe, as evidenced by five treatment deaths. Recently, Hakenberg *et al.* [14] retrospectively evaluated the efficacy and toxicity of BMP in 13 patients, concluding that it has a limited effect on metastatic penile cancer and that toxicity is high, carrying a high risk of death.

Another regimen, cisplatin–5FU, was investigated in two very small series. Hussein *et al.* [4] studied six patients with either recurrent or unresectable SC penile and urethral cancer, who received chemotherapy with cisplatin, followed 24 h later by continuous intravenous infusion of 5FU for 5 days every 3–4 weeks. Five patients had a clinical response, and one had a complete response. The treatment was well tolerated, with mild mucositis, nausea, and vomiting [7]. Shammas *et al.* [15] treated eight patients with advanced SC cancer of the penis with a cisplatin-5FU regimen. Of those eight patients, two (25%) achieved a partial response and were disease-free at 32 and 57 months, respectively.

Recently, cisplatin was combined with other chemotherapeutic agents in two studies [8,9]. Power *et al.* [8] reported two cases of advanced penile cancer in which a sustained palliative response was observed with combination chemotherapy using cisplatin and gemcitabine. Theodore *et al.* [9] conducted a phase II study of irinotecan and cisplatin in locally advanced and metastatic penile carcinoma. Twenty-eight patients were included and evaluated for toxicity, and 26 eligible patients were evaluated for response. There were eight responses (two complete and six partial responses), with a response rate of 30.8%.

The activity of taxanes in combination with cisplatin in SC penile cancer, in both neoadjuvant and advanced settings, has been evaluated in a small series. Bermejo *et al.* [10] reported on five patients who were treated with surgical consolidation after stable, partial, or complete response to four or five courses of paclitaxel, ifosfamide, and cisplatin (PIC), and five patients treated with different regimens. Three of the five patients treated with the paclitaxel–ifosfamide–cisplatin regimen had a pathologically complete response, and two of the patients are long-term survivors.

Pizzocaro *et al.* [11] have recently reported their findings of six patients treated with paclitaxel or docetaxel in combination with cisplatin and 5FU. Note that four patients had unresectable disease, whereas two patients had recurrent nodal metastases. Despite a very limited sample, different schedules, and different stages of the disease, this combination was shown to be promising.

No earlier studies have been published with paclitaxel monotherapy in advanced pretreated penile cancer. We have treated 12 metastatic SC penile cancer patients with paclitaxel monotherapy. Note that although all patients were previously pretreated with cisplatin, a partial response rate of 25% was observed. In general, the treatment was well tolerated. No toxic deaths occurred. Grade 3 hematologic toxicities included neutropenia, anemia, and thrombocytopenia in three, two, and two patients, respectively.

Although the majority of studies have enrolled patients either in neoadjuvant or advanced settings, all our

patients were pretreated with chemotherapy before surgery/radiotherapy, and at the time of entry into the study, they were metastatic. The results of our study are promising, especially in terms of toxicity, when compared with previously used regimens [4–6,9].

As previously shown for the efficacy of sequential single agents, such as methotrexate, cisplatin, and bleomycin [16], efficacy improved with BMP, and based on our encouraging results with paclitaxel monotherapy, future trials might investigate a combination regimen of cisplatin–paclitaxel in neoadjuvant and metastatic settings.

Despite few enrolled patients, the originality of our study relies on several important key points: (i) there are no published articles using this regimen; (ii) there are no earlier reports of patients who were all metastatic and all previously pretreated in a neoadjuvant setting; (iii) the observed efficacy is encouraging; and (iv) the treatment was well tolerated. Findings from this paper are worthy of attention because they show that the use of paclitaxel in penile cancer deserves further assessment in advanced and also in neoadjuvant settings.

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