

## Original article

# Intraarterial chemotherapy with gemcitabine and cisplatin in locally advanced or recurrent penile squamous cell carcinoma

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## Abstract

The prognosis of locally advanced or recurrent squamous cell carcinoma (SCC) of the penis after conventional treatment is dismal. This study aimed to evaluate the therapeutic effects of intraarterial chemotherapy with gemcitabine and cisplatin on locally advanced or recurrent SCC of the penis. Between April 1999 and May 2011, we treated 5 patients with locally advanced penile SCC and 7 patients with recurrent disease with intraarterial chemotherapy. The response rate and toxicity data were analyzed, and survival rates were calculated. After 2 to 6 cycles of intraarterial chemotherapy with gemcitabine and cisplatin, 1 patients with locoregionally advanced disease achieved a complete response, and 4 achieved partial response. Of the 7 patients with recurrent disease, 2 achieved complete response, 3 achieved partial response, 3 had stable disease, and 1 developed progressive disease. An objective tumor response was therefore achieved in 10 of the 12 patients. The median overall survival for the patients was 24 months (range, 10–50 months). Three out of 10 patients who responded were long-term survivors after intraarterial chemotherapy. Intraarterial chemotherapy with gemcitabine and cisplatin may be effective and potentially curative in locoregionally advanced or recurrent penile SCC. The contribution of this therapy in the primary management of advanced or recurrent penile SCC should be prospectively investigated.

**Key words** Penile squamous cell carcinoma, intraarterial chemotherapy, gemcitabine, cisplatin

Penile squamous cell carcinoma (SCC) is rare in developed countries but comprises 10% of male malignancies in developing countries<sup>[1]</sup>. Overall, 30% of patients with penile SCC are diagnosed with advanced disease<sup>[2]</sup>. Advanced disease has a very poor prognosis, with 5-year survival rates of only 5%–20% in patients with locoregional lymph node extension<sup>[3–5]</sup>. Therapy for fixed inguinopelvic or lymph node involvement in patients with recurrent disease is well characterized but usually ineffective. Radiotherapy may be of some

benefit, but local sequelae are usually severe, and wound healing after combined surgery and radiotherapy is severely impaired<sup>[1]</sup>. On the other hand, several chemotherapeutic agents may be effective in the treatment of locally advanced or recurrent penile SCC<sup>[1,6]</sup>. Methotrexate-bleomycin-cisplatin (BMP) and cisplatin-5-fluorouracil (5-FU) systemic chemotherapy has shown response rates between 25% and 72%<sup>[7–9]</sup>. Combination chemotherapy using gemcitabine and cisplatin has demonstrated encouraging responses in metastatic disease<sup>[10]</sup>. However, systemic chemotherapy has limited applications in advanced and recurrent penile SCC due to its short duration of response and its association with morbidity and mortality<sup>[11]</sup>.

Intraarterial administration of chemotherapy has been attempted in locally advanced penile SCC to deliver high concentrations of anticancer drugs to the entire pelvic area and to induce rapid shrinkage of the primary lesion and metastatic lymph nodes while reducing toxicities. This modality has the unique advantage of preserving the structure and function of the penis<sup>[12–14]</sup>. Most reported results have shown that intraarterial chemotherapy

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induced a higher response rate and a lower level of toxicity than systemic chemotherapy in other genitourinary tumors<sup>[15,16]</sup>. In this study, we report the encouraging results of combination intraarterial chemotherapy with gemcitabine and cisplatin for 12 patients with locally advanced or recurrent penile SCC.

## Patients and Methods

### Patients and their characteristics

Between April 1999 and May 2011, 12 men with histologically confirmed advanced (5 cases) or recurrent (7 cases) penile SCC were treated with intraarterial infusion therapy using gemcitabine and cisplatin. The patient ages ranged from 29 to 78 years (median age, 53 years), and all underwent at least two courses of intraarterial chemotherapy. The median follow-up duration was 23.6 months (range, 5–50 months). Tumor staging and restaging were determined by computed tomography (CT) of the abdomen and pelvis as well as by chest plain films. Pathologic stage was categorized according to the 2002 American Joint Committee on Cancer TNM classification system<sup>[17]</sup>.

### Intraarterial chemotherapy

The patients were given intraarterial infusions of 900 mg/m<sup>2</sup> gemcitabine plus 30 mg/m<sup>2</sup> cisplatin over 15 to 20 min every 7 days. All medications were administered by a percutaneous catheter system (PCS), which was placed by a modified Seldinger technique into the right thigh. Dexamethasone and antiemetics were administered at the same time. Three weeks of treatment followed by 1 week of rest was defined as a cycle. Patients were adequately hydrated with intravenous fluids as necessary pre- and post-treatment to ensure that urine output was >2,500 mL per 24 h.

### Follow-up and evaluation

Efficacy was grossly evaluated in every patient 4 weeks after the start and at the completion of chemotherapy according to the Response Evaluation Criteria in Solid Tumors (RECIST)<sup>[18]</sup>. All patients were followed up closely at an outpatient clinic. The overall survival (OS) was measured from the date of starting chemotherapy until death; the median time to disease progression (TTP) was measured from the date of starting chemotherapy until disease progression or death. Survival curves and probabilities were determined using the Kaplan-Meier method. Adverse effects of intraarterial chemotherapy were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0<sup>[19]</sup>.

### Statistical analysis

The primary efficacy of intraarterial chemotherapy, determined as a combination of OS and TTP, was assessed by using Kaplan-Meier survival analysis with the log-rank test for significance. A value of  $P < 0.05$  was considered statistically significant. Statistical analysis

was performed with the SPSS statistical software package (standard version 13.0; SPSS, Chicago, IL, USA).

## Results

### Patient outcomes

The clinical status, TNM stage or restage, treatment, and outcome of 12 patients with penile SCC are summarized in Table 1. The patients had no history of systemic chemotherapy or local radiotherapy prior to undergoing intraarterial chemotherapy. All patients had a good bone marrow reserve (white blood cell count  $\geq 4.0 \times 10^9/L$ , hemoglobin concentration  $\geq 120$  g/L, platelet count  $\geq 100 \times 10^9/L$ ) and normal renal function (serum creatinine level  $<100$   $\mu\text{mol/L}$ ). Two patients had painless lower limb edema and 4 had unilateral lower limb edema with pain (grade 3 in 3 patients and grade 4 in 1 patient) prior to intraarterial chemotherapy. Lower limb pain disappeared between 10 days and 1 cycle after starting chemotherapy, and lower limb edema resolved after 2 to 3 cycles of chemotherapy. Of the 10 patients who responded, 3 achieved a complete response (CR) and 7 had a partial response (PR). Of the 2 remaining patients, 1 achieved stable disease (SD) and 1 developed progressive disease (PD). The overall response rate was 83.3%. Among the 3 patients with a CR, patient No. 1 had previously undergone a partial penectomy and bilateral inguinal lymphadenectomy followed 9 months later by intraarterial chemotherapy with gemcitabine and cisplatin for a biopsy-proven relapse in the right inguinal lymph nodes. The patient achieved CR after 3 cycles of treatment and remained disease-free 43 months later. Patient No. 4 underwent a complete resection as the primary treatment in July 2001, which consisted of a total penectomy and bilateral inguinal lymphadenectomy. Two lymph nodes in the left inguinal region and 1 on the right were positive, and the disease was staged as pT2pN2. In June 2002, an excision biopsy from the left groin was positive for tumor deposits, and the patient was started on intraarterial chemotherapy. The patient achieved CR after 4 cycles of treatment and died of a myocardial infarction 37 months later. Patient No. 5 refused surgery, citing concerns about the cosmetic and functional integrity of his penis. The patient reached CR after 6 cycles of intraarterial chemotherapy and remained complete remission 50 months later.

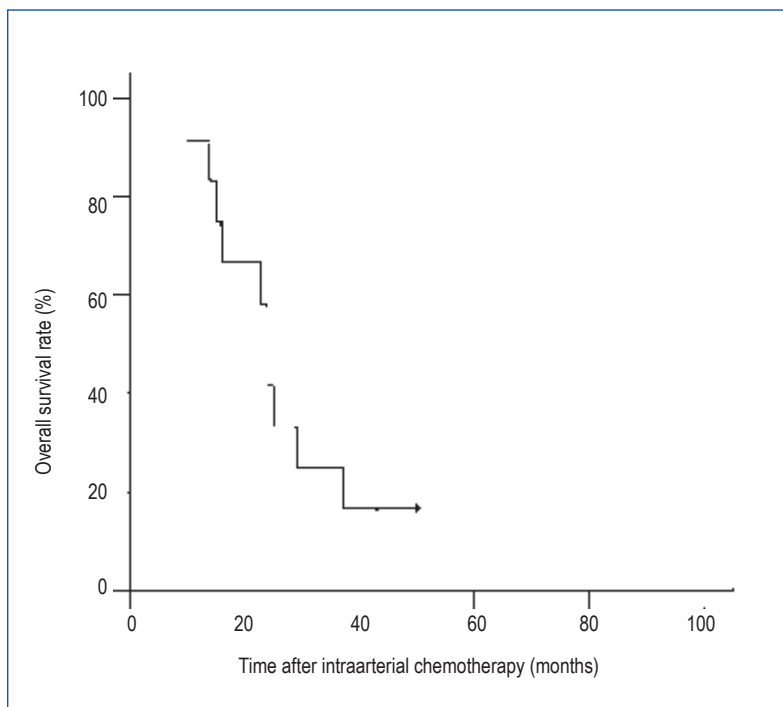
### Survival analysis

The median follow-up duration was 23.6 months (range, 5–50 months). The median OS time was 24 months (**Figure 1**), and the median TTP was 20 months. One CR patient (No. 4; Table 1) died of a non-tumor-related cause 37 months after chemotherapy. The other 2 CR patients survived for 43–50 months (median, 46.5 months) and were disease-free at the time of the last follow-up visit. The 7 PR patients developed disease progression and died between 14 and 29 months (median, 22.1 months) after chemotherapy. The 2 PD or SD patients survived for only 10 and 15 months, respectively, after intraarterial chemotherapy, compared to a median survival time of 24 months for CR + PR patients.

**Table 1. Disease status, treatment regimens, and outcomes of patients with penile squamous cell carcinoma**

Case	Age	Previous therapy	Tumor status at start of IA chemotherapy	TNM stage or restage	IA treatment cycles (n) and response	TTP (months)	OS (months)	Outcome
1	78	PP+BLAD	Right inguinal relapses	T2N2M0	3, CR	>43	>43	Alive and tumor-free
2	40	None	Small penile primary and fixed left inguinal nodes	TxN2M0	2.7, PR	20	23	Dead due to cancer
3	45	TP+BLAD+IPLAD	Ipsilateral pelvic relapses	T2N3M0	3.3, PD	7	10	Dead due to cancer
4	63	TP+BLAD	Left inguinal relapses	T2N2M0	4, CR	37	37	Dead of non-tumor cause
5	43	None	Small penile primary and bilateral inguinal nodes	TxN2M0	6, CR	>50	>50	Alive and tumor-free
6	75	PP+BLAD	Bilateral inguinal relapses	T1N2M0	2, SD	13	15	Dead due to cancer
7	53	PP+BLAD	Right inguinal relapses	T2N2M0	3.3, PR	19	24	Dead due to cancer
8	29	PP	Fixed bilateral inguinal nodes	T2N2M0	2.7, PR	21	25	Dead due to cancer
9	53	PP	Fixed bilateral inguinal nodes	T3N2M0	5.0, PR	24	29	Dead due to cancer
10	48	TP+BLAD	Right inguinal relapses	T1N2M0	4.3, PR	14	16	Dead due to cancer
11	59	PP+BLAD	Left inguinal relapses	T2N2M0	2.7, PR	22	24	Dead due to cancer
12	60	None	Penile primary and fixed right inguinal nodes	TxN2M0	3.3, PR	12	14	Dead due to cancer

PP, partial penectomy; TP, total penectomy; BLAD, bilateral inguinal lymphadenectomy; IPLAD, ipsilateral pelvic lymphadenectomy; RT, external radiation therapy; IA, intraarterial; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TTP, time to progression; OS, overall survival.



**Figure 1. Kaplan-Meier survival curve of the 12 patients with penile squamous cell carcinoma. All these patients underwent intraarterial chemotherapy with gemcitabine and cisplatin for locally advanced or recurrent penile squamous cell carcinoma.**

**Toxicity of intraarterial chemotherapy**

The toxicities observed in patients were expected. The most

severe adverse events were myelosuppression ( $n = 2, 16.7\%$ ) and abnormal renal function ( $n = 1, 8.3\%$ ). Leukocytopenia was observed in 2 patients (16.7%) and anemia was diagnosed in 1 patient

**Table 2. Cytotoxicities of intraarterial chemotherapy**

Cytotoxicity	No. of patients (%)	Duration (days)	Cytotoxicity grade
Nausea/vomiting	2 (16.7)	2–3	1–2
Anorexia	2 (16.7)	3–4	1–2
Leukocytopenia	3 (25.0)	3–5	2–3
Anemia	2 (16.7)	2–4	1–2
Thrombocytopenia	1 (8.3)	2	3–4
Abnormal renal function	1 (8.3)	4–5	1

(8.3%). Grade 3/4 thrombocytopenia occurred in 1 patient (8.3%). Dysfunction of the digestive system occurred in 2 patients (16.7%) 2–3 days after treatment, and this lasted for 3–4 days. All subjective intolerances and clinical complications were transient and moderate in severity. The details and grade of the toxicities in all patients are shown in **Table 2**.

## Discussion

The prognosis of patients with locally advanced and recurrent penile SCC is extremely poor, and the most appropriate therapy remains controversial. The treatment of locally advanced and recurrent penile SCC should incorporate surgery, radiotherapy, and chemotherapy. Consequently, multidisciplinary, urological, oncology-based patient clinics may be effective forums to arrive at rational consensus recommendations for individual patients<sup>[20]</sup>.

Lower abdominal aortic infusion chemotherapy, which has the main advantage of delivering a high concentration of anticancer drugs to the entire pelvic area including the penis, is useful for this localized lesion, even in cases of advanced penile carcinoma<sup>[12,21]</sup>. Intraarterial chemotherapy was introduced for the treatment of penile cancer by Sheen<sup>[21]</sup> in 1988. With the development of techniques and the regeneration of drugs, intraarterial chemotherapy has become an important therapy for penile cancer, and encouraging results have been reported in several studies<sup>[12–14]</sup>. Moreover, Roth *et al.*<sup>[22]</sup> reported 8 patients with locally advanced or recurrent penile carcinoma treated with intraarterial chemotherapy. Three patients obtained CR and 3 PR. Among the CR patients, 2 were reported to be alive and disease-free 5 and 15 years after treatment.

Penile cancer is a chemoresponsive disease. Cisplatin is the only single agent that has been properly assessed in a multi-institutional phase II trial, and response rates of up to 25% have been observed<sup>[23]</sup>. Our results show that the combination of gemcitabine and cisplatin administered by the intraarterial route in patients with advanced and recurrent penile SCC resulted in good outcomes

since 1999. This combination is well tolerated and is an established regimen in patients with non-small cell lung cancer, head and neck cancer, and bladder cancer<sup>[24–26]</sup>. The present study demonstrated that this strategy could be applied for penile SCC with relatively low toxicity rates.

The drug adverse effects were mild and tolerable, and both the drugs and administration method may be suitable for elderly patients, such as the 78-year-old described in this study. Most importantly, this strategy can prolong survival and could be a potential curative treatment. However, it should be mentioned that the present results were based on a retrospective collection of data, and we only analyzed the toxicities and efficacy of intraarterial chemotherapy with gemcitabine and cisplatin for locally advanced or recurrent penile SCC.

## Conclusions

Our results suggest that intraarterial chemotherapy with gemcitabine and cisplatin may be effective and potentially curative in locoregionally advanced or recurrent penile SCC. The contribution of this therapy in the primary management of advanced or recurrent penile SCC should be prospectively investigated.

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