

# Intra-arterial Infusion of Chemotherapy in the Treatment of Penile Cancer

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**Objective:** Patients with penile cancer sometimes refuse surgery under the consideration of cosmetic and functional impact. The efficacy of intra-arterial (IA) chemotherapy for penile cancer has not been well defined.

**Methods:** Five patients with penile cancer, receiving at least two courses of IA chemotherapy, were analyzed from January 2005 to January 2009. These patients all refused surgery initially. The drug combinations were as follows: methotrexate, mitomycin C, bleomycin, cisplatin and 5-fluorouracil. Carboplatin was used instead of cisplatin for one patient with renal insufficiency.

**Results:** The overall response rate (complete or partial) was 100%. One case achieved complete remission and four cases achieved partial remission. Among the partial responders, three cases underwent subsequent partial penectomy to preserve partial appearance. Mild (Grades I–II) anorexia is the most common adverse effect of IA chemotherapy. Hematological toxicity included two episodes of Grade III anemia and one episode of Grade III febrile neutropenia.

**Conclusions:** Organ- and function-sparing approaches are proposed using combination therapies, especially for those with huge tumor burden. Our preliminary data indicated that a combination of IA neoadjuvant chemotherapy and surgery may have the potential to achieve the goal in the treatment of penile cancer with negative lymph node.

*Key words:* chemotherapy – intra-arterial – neoadjuvant – penectomy – penile cancer

## INTRODUCTION

Penile carcinoma is rare in developed countries. More than 95% of penile carcinomas are squamous cell carcinomas (SCCs). It usually arises on the coronal sulcus of the glans of the penis. Of the total number of penile cancer cases, 30% are diagnosed with advanced disease (1). Treatment includes penectomy, Mohs' surgery, laser, radiation therapy and systemic chemotherapy. Patients with penile cancer sometimes refuse total penectomy for huge tumor burden because of the consideration of cosmetic and functional impact. This led to consideration of alternative treatments.

Several systemic chemotherapy agents have been used for metastatic penile cancer, of which the most common are bleomycin, methotrexate and cisplatin. Previous reports

demonstrated that combination regimens have yielded objective responses in 25–72% of cases (2–4). A recent report demonstrated the efficacy of neoadjuvant chemotherapy followed by surgical consolidation with objective responses in 50% of patients with advanced penile cancer (5). However, there are a limited number of reports on the efficacy of intra-arterial (IA) chemotherapy for penile cancer. The aim of this study was to evaluate the efficacy and adverse effects of IA chemotherapy in the treatment of penile cancer.

## PATIENTS AND METHODS

We reviewed the records of 48 patients with penile cancer treated from January 2005 to January 2009. The inclusion criteria were those with initial refusal to receive operation, SCC type penile cancer and those receiving at least two courses of IA chemotherapy. The exclusion criteria included distant metastasis or prior systemic chemotherapy or prior

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radiotherapy. Positive regional lymph node was not excluded. A total of five patients met the criteria. The main reason for these patients choosing IA chemotherapy is refusal of operation in the beginning. The primary lesions were present in the coronal sulcus of the glans and were pathologically confirmed to be SCC. The median patient age was 61 years (range, 48–79 years). Tumor staging was determined by computerized tomography (CT) of the abdomen and pelvis as well as chest plain film. The duration of follow-up averages 24.2 months (range, 17–34 months).

Chemotherapy agents were administrated via a 4 or 5 F pigtail catheter inserted into the lower abdominal aorta with the distal pigtail located at the level above aortic bifurcation and below the inferior mesenteric artery orifice. The drug combinations were as follows (6): methotrexate (110 mg/m<sup>2</sup>/day), mitomycin C (4.5 mg/m<sup>2</sup>/day), bleomycin (15 mg/m<sup>2</sup>/day), cisplatin (35 mg/m<sup>2</sup>/day) and 5-fluorouracil (1200 mg/m<sup>2</sup>/day). The agents were infused continuously into the catheter for 2 days in each course. In addition, leucovorin, 50 mg/day, was also given intravenously for 2 days. For one patient with renal insufficiency, carboplatin (100 mg/m<sup>2</sup>/day) was used instead of cisplatin for IA chemotherapy and the doses of other regimens were adjusted to be 75% of regular dose. The interval of each course was 4 weeks.

All patients received a follow-up CT scan to assess the lymphadenopathy from 4 weeks to 5 months after response to IA chemotherapy. Primary lesion size was evaluated grossly for every patient on every visit for chemotherapy. According to the Response Evaluation Criteria in Solid Tumors (7), complete response (CR) was defined as the disappearance of all target lesions without lymphadenopathy >1.0 cm. Partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameter of target lesions with or without residual lymphadenopathy >1.0 cm. Adverse effects of IA chemotherapy were graded according to the National Cancer Institute Common Toxicity Criteria (8). Pre-IA chemotherapy assessment included complete blood counts and creatinine level/or creatinine clearance rate. If recurrent tumor was suspected, biopsy was performed for the histopathological examination.

## RESULTS

The response was quick and dramatic after the first two to three courses of IA chemotherapy (Fig. 1) and the overall response rate (PR or CR) was 100% in patients receiving at least two courses of IA chemotherapy. Four cases experienced partial remission (one case had nearly CR after two courses of IA therapy, Fig. 1) and one case (Case 2) achieved complete remission after five courses of IA therapy (Table 1).

Among four partial responders, one was lost to follow-up and three (Cases 3–5) received partial penectomy for small residual tumor after two to three courses of IA chemotherapy. In addition, Cases 4 and 5 both underwent bilateral inguinal lymphadenectomy due to initial presentation with positive inguinal lymph nodes.

During the follow-up period, tumor recurrence developed in three cases. In Case 2 (the only complete responder), tumor recurrence was observed 8 months after completion of the fifth course of IA chemotherapy; consequently, the patient underwent salvage partial penectomy. To date, there is no tumor recurrence observed for 15 months after surgery in this case. In three partial responders who received subsequent surgery, Case 3 did not experience tumor recurrence for 13 months after surgery. However, tumor recurrence was observed in Cases 4 and 5 who had initial positive lymph node 4 and 8 months after surgery, respectively. Consequently, they received additional courses of salvage IA chemotherapy and radiotherapy for recurrent tumor. Finally, Cases 4 and 5 died of metastatic diseases 15 and 6 months after they received last course of IA chemotherapy, respectively.

With regard to the adverse effects of IA chemotherapy (Table 2), mild (Grades I–II) anorexia is common in our series. Cases 1 and 5 developed Grade III anemia, and blood transfusion was necessary. Grade III febrile neutropenia was observed only in Case 3 and it was controlled with antibiotics treatment. Notably, Case 4 also received inguinal lymphadenectomy and salvage radiotherapy for left inguinal lymph node invasion and left acetabular bone metastasis.



**Figure 1.** Case 1, a 48-year-old male with lymph node-positive penile cancer, before and 3 months after intra-arterial chemotherapy.

**Table 1.** Patient with penile cancer: status and results

Case	Age	Previous therapy	Tumor status at start of IA chemotherapy	IA drugs	Cycles of IA treatment (n) and response	Therapy after response to IA chemotherapy	Loss of follow-up	Time to relapse after surgery or complete response to IA therapy (months)	Therapy after relapse	Final status
1	56	None	No inguinal LN invasion	MTX, BLM, MitoC, Carbo, 5-FU	4, PR	Loss of follow-up	Loss of follow-up			Loss of follow-up
2	70	None	No inguinal LN invasion	MTX, BLM, MitoC, Cis, 5-FU	5, CR		8	PP	Disease-free for 15 months	
3	61	None	No inguinal LN invasion	MTX, BLM, MitoC, Cis, 5-FU	3, PR	PP	No relapse		Disease-free for 13 months	
4	48	None	Left inguinal LN invasion	MTX, BLM, MitoC, Cis, 5-FU	3, PR (nearly complete response)	PP + LAD	4	Salvage IA C/T (2) and R/T	Expired 15 months after last IA C/T	
5	79	None	Right inguinal LN invasion	MTX, BLM, MitoC, Cis, 5-FU	3, PR	PP + LAD	8	Salvage IA C/T (2) and R/T	Expired 6 months after last IA C/T	

IA, intra-arterial; LN, lymph node; MTX, methotrexate; BLM, bleomycin; MitoC, mitomycin C; Carbo, carboplatin; 5-FU, 5-fluorouracil; Cis, cisplatin; PR, partial response; CR, complete response; PP, partial penectomy; LAD, lymphadenectomy; IA C/T (2), additional two courses of intra-arterial chemotherapy after relapse; R/T, radiation therapy.

**Table 2.** Adverse effects of IA chemotherapy (n = 5)

Case	Adverse effects
1	Gr. III anemia (2nd to 3rd week)
2	Gr. I–II anorexia (2nd to 4th day)
3	Gr. I–II anorexia (2nd to 5th day); Gr. III febrile neutropenia (2nd week)
4	Gr. I–II anorexia (2nd to 4th day)
5	Gr. I–II anorexia (1st to 4th day); Gr. III anemia (2nd to 3rd week)

Gr., grade (the emerging time of adverse effect after IA chemotherapy).

Post-operatively, pitting edema over the left lower extremity developed. Several months later, superficial ulcer with secondary infection developed over the left groin. Consequently, suspected peripheral arterial ischemia developed and required amputation of left lower extremity. Vascular insufficiency secondary to infection may contribute to the complication. We assumed that previous inguinal lymphadenectomy and radiotherapy should be responsible for the complication.

**DISCUSSION**

SCCs of the penis are chemosensitive and relatively radio-sensitive (9). In patients with penile cancer treated with radiotherapy, high doses of radiation may be required to eradicate the tumor. However, complications following radiotherapy are common. Urethral mucositis, secondary infection and late complications, such as superficial necrosis, urethral stricture, fistula formation and meatal stenosis, had been reported in some studies (10–13). Definitive treatment with surgery would be standard. However, patients sometimes hesitate to receive surgery under the consideration of cosmetic and functional impact. Chemotherapy was used as an organ preservation strategy in patients who exhibited no evidence of distant metastases. Systemic (intravenous) chemotherapy would not routinely be used in this setting due to the toxicity and relatively low response rate (14,15). Corral et al. (14) reported the toxicity of combination chemotherapy of methotrexate, cisplatin and bleomycin, including pulmonary toxicity (33%) resulting from bleomycin, significant neutropenia and/or thrombocytopenia (19%), renal toxicity (7%), stomatitis and toxic death (3%). Similar toxicity has also been reported in neoadjuvant chemotherapy for advanced penile cancer by Bermejo et al. (5).

In comparison with systemic (intravenous) chemotherapy, IA chemotherapy is a strategy for delivering chemotherapy preferentially to the pelvis with less systemic drug exposure. In our series, we positioned the IA catheter in the abdominal aorta via the femoral route, above the aortic bifurcation and below the inferior mesenteric artery. The rationale for this, presumably, is that infused drug does circulate systemically,

but with higher concentration in the pelvis and lower extremities, and so requires a lower dose to achieve a specific treatment effect. In our series, most adverse effects of IA chemotherapy were tolerable and manageable. Anorexia was the most common adverse effect and the symptom was resolved with medical therapy. There was no severe cutaneous or renal toxicity observed. Three cases (60%) experienced hematological toxicity, which included two cases that developed Grade III anemia and one case that developed Grade III febrile neutropenia. More attention should be paid to the doses of IA chemotherapy for patients with impaired renal function and the elderly.

For penile cancer with lymph node invasion, CR or PR achieved by IA infusion of chemotherapy had been reported in some reports (6,16,17). In addition, there is good response for penile verrucous carcinoma under IA chemotherapy in Taiwan (18).

Bermejo et al. (5) previously reported the efficacy of neoadjuvant chemotherapy followed by surgical consolidation for advanced penile cancer. A total of five patients (50%) achieved an objective response after chemotherapy. In our series, the overall response rate was 100% for advanced penile cancer. The response was quick and dramatic after the first two or three IA chemotherapy courses. However, in penile cancer without distant metastasis, inguinal lymph node metastasis is the predictor for prognosis (19,20). For those with nodal metastasis, the 5-year survival rates are 40–51% after groin lymph node dissection (20,21). In our series, two patients with initial inguinal lymph node metastasis died of metastatic diseases after 34 and 21 months of follow-up, respectively. Our series could not prove that IA chemotherapy could improve survival for penile cancer with positive lymph node.

From our preliminary outcomes, it showed the feasibility and efficacy of a combination of IA neoadjuvant chemotherapy and then partial penectomy for lymph node-negative penile cancer. Patients with partial remission after primary IA chemotherapy could undergo partial penectomy instead of total penectomy to preserve partial appearance of penis and voiding function. However, the limitation of this study is small number of patients. Further large-scale and prospective studies should be performed to evaluate the feasibility and safety of IA chemotherapy in the treatment of penile cancer as a curative or neoadjuvant therapy followed by surgery.

## CONCLUSIONS

Penile cancer, when localized, can be treated by surgery. However, organ- and function-sparing approaches are proposed using combination therapies, especially for those with huge tumor burden. IA chemotherapy is a known approach in case of solid tumors. Our preliminary data indicated that a combination of IA neoadjuvant chemotherapy and then surgery may have the potential to achieve the goal in the treatment of penile cancer with negative lymph node.

## Conflict of interest statement

None declared.

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