CASE REPORT

Clinical features of 4 patients who underwent neoadjuvant chemotherapy for the locally advanced penile cancer

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Abstract Of 32 patients with penile cancer who underwent medical treatment in our institute between 1999 and 2016, 4 with locally advanced penile cancer received penectomy, neoadjuvant chemotherapy, and lymphadenectomy for regional lymph node metastases. The median age and follow-up period were 46 years and 79 months. Clinical lymph node (N) stages cN1, cN2, and cN3 were observed in 1, 2, and 1 patient, respectively. Except for 1 patient who had partial penectomy, all received total penectomy for the primary tumors. All pathological findings were squamous cell carcinoma. Among the specimens at the time of the primary tumors, 1, 2, and 1 were classified as pT1, pT2, and pT3, respectively. Neoadjuvant chemotherapy composed of 5-fluorouracil and cisplatin in 2 cases and paclitaxel, ifosfamide, and cisplatin in 2 cases was performed for lymph node metastases. After chemotherapy, lymphadenectomy was performed for all patients and the pathological findings were pN0. During the follow-up period, all patients survived with no metastases and no recurrence.

Keywords Penile cancer · Lymph node metastasis · Neoadjuvant chemotherapy

Introduction

The 5-year cancer-specific survival rates for patients who have penile cancer with regional lymph node metastases

range from 29 to 40% [1]. Because penile cancer accounts for less than 1% of all cancers in men [2], it is difficult to conduct a randomized controlled clinical trial to determine whether neoadjuvant chemotherapy affects the pathological findings of lymphadenectomy and cancer-specific survival. Considering this background, the National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) developed guidelines for the treatment of penile cancer. According to the NCCN guidelines, cisplatin (CDDP)-based neoadjuvant chemotherapy composed of 5-fluorouracil (5FU) and CDDP (5FU + CDDP), and paclitaxel, ifosfamide, and CDDP (TIP) should be considered for patients who present with inguinal lymph node metastasis ≥ 4 cm diagnosed by fine-needle aspiration or excisional biopsy. On the other hand, the EAU guidelines exclusively recommend CDDP and taxane-based neoadjuvant chemotherapy for patients with fixed inguinal nodal masses (cN3).

In the present work, we report the clinical features of patients with locally advanced penile cancer who achieved long-term progression-free survival after neoadjuvant chemotherapy followed by lymphadenectomy.

Case report

We retrospectively reviewed the medical charts of 32 patients with penile cancer who received medical examination and treatment at our institute from April 1999 through June 2016. We included the patients who had regional lymph node metastases and no distant metastases assessed by palpation and computed tomography (CT) at the first visit. Finally, the clinical features of 4 patients were evaluated.

After diagnosis of penile cancer by tumor biopsy, total or partial penectomy was performed. Before

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lymphadenectomy, all patients underwent multiple courses of neoadjuvant chemotherapy for regional lymph node metastases. From 1990 to 2000, the regimen of neoadjuvant chemotherapy was composed of 5FU and CDDP. 5FU 1000 mg/m² on days 1–5 and CDDP 100 mg/m² on day 1 were administered at 21-day intervals. From 2001, the regimen for neoadjuvant chemotherapy was changed to the combination of paclitaxel, ifosfamide, and CDDP. We administered paclitaxel 175 mg/m² on day 1, and ifosfamide 1200 mg/m² and CDDP 25 mg/m² on days 1–3 at 21-day intervals. The tumor responses of regional lymph node metastases were assessed by CT after the chemotherapy. In this study, we re-evaluated the responses using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and adverse events of chemotherapy using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. After evaluation of the response to neoadjuvant chemotherapy, inguinal lymph node dissection and/or pelvic node dissection were performed. Considering the pathological results, adjuvant chemotherapy was added as necessary.

The characteristics of the patients are shown in Table 1. The median age and follow-up period were 46 years (range 41–62) and 79 months (range 14–125), respectively. One patient dropped out of follow-up for 14 months. Three patients were diagnosed with bilateral inguinal (cN2: 2, cN3: 1) metastases and one had

unilateral (cN1) node metastasis. Of the 3 patients with bilateral inguinal node metastases, 1 had pelvic node metastases (common iliac node and internal iliac node). Partial penectomy and total penectomy were performed for 1 and 3 patients, respectively, for the primary tumors. All pathological findings revealed squamous cell carcinoma. Among the specimens at the time of surgery for the primary tumors, 1, 2, and 1 were classified as pT1, pT2, and pT3, respectively. Neoadjuvant chemotherapy for regional lymph node metastases was conducted for all patients. 5FU + CDDP therapy was completed for 2 patients and TIP therapy for 2 patients. The reduction rates of neoadjuvant TIP therapy were 50% (case 3) and 44% (case 4), respectively (Fig. 1a–d). Hematological adverse events of grade 3 or more occurred in all patients. All patients had decreased neutrophil counts (grade 4:3, grade 3:1). Moreover, a grade 3 platelet count decrease occurred in 1 of the 4 patients. On the other hand, non-hematological adverse events of grade 3 or more did not occur in the 4 patients.

All pathological findings of lymphadenectomy were no residual tumor after neoadjuvant chemotherapy. Only one patient (case 1) underwent consolidation chemotherapy, which consisted of two courses of 5FU + CDDP, after lymphadenectomy. During the follow-up period, all patients were alive without local recurrence or distant metastasis.

Table 1 Patients and tumor characteristics

	Case 1	Case 2	Case 3	Case 4
Age	47	45	62	41
Tumor size (mm)	20	88	55	45
SCC (ng/ml)	No data	1.7	1.9	2.9
Palpable inguinal lymph node	Bilateral	Rt	(–)	Bilateral
Clinical <i>N</i> stage	cN2	CM	CN2	CN3
Operative procedure	Partial	Total	Total	Total
Histological type	SCC	SCC	SCC	SCC
Pathological <i>T</i> stage	pT2	pT1	pT2	pT3
NEOADJUVANT chemotherapy	5FU+CDDP	5FU +CDDP	TIP	TIP
Course	2	3	2	5
RECIST response	No data	No data	50% (PR)	44% (PR)
Adverse events of chemotherapy	Neutrophil count decreased (G3)	Neutrophil count decreased (G4) Platelet count decreased (G3)	Neutrophil count decreased (G4)	Neutrophil count decreased (G4)
Lymphadenectomy	Bil. inguinal+pelvic	Bil. inguinal	Bil. inguinak+pelvic	Bil. inguinak+pelvic
Pathological findings	pNO	pNO	pNO	pNO
Cancer free survival (M)	119	10	91	58
Follow-up duration (M)	125	14	95	63
Recurrence and metastasis	(–)	(–)	(–)	(–)
Clinical outcome	Alive	Alive	Alive	Alive

Fig. 1 **a, c** Inguinal lymph node metastasis before neoadjuvant chemotherapy in case 3 and 4. **b, d** After neoadjuvant TIP therapy for 2 and 5 courses, inguinal lymph node metastases were achieved PR

Discussion

There is no standard regimen of neoadjuvant chemotherapy for locally advanced penile cancer because of the lack of evidence due to penile cancer being a rare disease. In our clinic, neoadjuvant 5FU + CDDP therapy and TIP therapy were administered in reference to previous cases and small-scale reports [3, 4].

Our two patients who underwent neoadjuvant TIP therapy had surgical CR with lymphadenectomy and long progression-free survivals without local recurrence or distant metastasis. Bermejo et al. reported 5 patients with regional lymph node metastases who underwent neoadjuvant TIP therapy. Four of the five achieved CR and 3 of them had no nodal metastases in lymphadenectomy. In the follow-up period, 2 of them had no evidence of disease [5]. Pagliaro et al. conducted a non-randomized phase II clinical trial of neoadjuvant TIP therapy. Thirty patients who had N2 or N3 penile cancer without distant metastasis received neoadjuvant TIP therapy. Fifteen of them (50%) achieved objective responses (CR: 2, PR: 12). The median time to progression (TTP) and overall survival (OS) were 8.1 months and 17.1 months, respectively. Comparing the TTP and OS between responders and non-responders to neoadjuvant TIP therapy, TTP and OS were significantly improved in responders [6]. According to the results of this phase II study, neoadjuvant TIP therapy should be considered in the NCCN guidelines for penile cancer.

In our institute, 5FU + CDDP neoadjuvant chemotherapy was performed for 2 patients. Because cases 1 and 2 were treated in 1999, all of the CT images were discarded. Therefore, we could not evaluate the response rate according to RECIST 1.1 in either case. Furthermore, when cases 1 and 2 were treated in our institute, neoadjuvant chemotherapy was performed without the needle biopsy of inguinal lymph nodes recommended by the 2016 NCCN guidelines. According to the medical charts, the inguinal lymph node metastases were reduced in size compared to before neoadjuvant chemotherapy.

The pathological finding for lymphadenectomy was pN0. During the follow-up period, both patients remained alive with no recurrence and no metastasis. There are no prospective reports suggesting the effectiveness of neoadjuvant 5FU + CDDP therapy for penile cancer. In SCC of the head and neck, randomized phase III trials suggested the better effectiveness of 5FU + CDDP therapy with paclitaxel added than for 5FU + CDDP alone [7]. Pizzocaro et al. treated 6 patients with locally advanced penile cancer with neoadjuvant paclitaxel, cisplatin, and 5FU (TPF) therapy. In 3 of them, pathological CR was achieved in lymphadenectomy [8]. On the other hand, Djajadiningrat et al. reviewed 26 patients who underwent taxane-based combination neoadjuvant chemotherapy composed of docetaxel, 5FU, and CDDP. Pathological CR was observed only 1 of them (4%). Therefore, they

concluded that the regimen was not sufficient and other treatment options should be considered [9].

A limitation of this study is that it is a retrospective study with a small patient population. However, this is the first report indicating the possibility that Japanese patients with penile cancer with regional lymph node metastases can obtain a surgical complete response and long-term survival via treatment using neoadjuvant chemotherapy recommended in guidelines and lymphadenectomy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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