

Evaluation of Paclitaxel, Ifosfamide, and Cisplatin (TIP) Regimen on Penile Cancer in Adam Malik Medan: A Single Center 2 Years of Experience

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Abstract

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BACKGROUND: Penile tumour is a rare tumour in the genitourinary system, account for 0.4-0.6%. Although rare, patients are often unaware and come in late stage, so the use of chemotherapy agents is becoming crucial.

AIM: This study was conducted to evaluate responses and overall survival rate of Paclitaxel, Ifosfamide, and Cisplatin (TIP) regimen in penile cancer with nodal involvement.

METHODS: We included all medical records of penile squamous cell carcinoma patients associated with nodal involvement who acquired TIP regimen in Adam Malik Hospital between 2014 and 2016. We administered 175 mg/m² of Paclitaxel on day 1, 1200 mg/m² of Ifosfamide on days 1 to 3, and 25 mg/m² of Cisplatin on days 1 to 3 as our standard TIP regimen. The regimen was re-administered every 21-28 days. Characteristics of the patient including age, history of circumcision, races, primary lesion of the tumour and TNM staging were noted. Adverse event, clinical responses, and overall survival were assessed and evaluated.

RESULTS: We extracted data from 17 patients of penile cancer with nodal involvement who acquired TIP regimen with a mean age of 44.18 ± 11.13 years old from our medical records. Only 10 patients completed the full 4 cycles of the regimen. Four patients died before completion, two patients refused to continue the regimen, and 1 patient is still on the second cycle. Total penectomy was the most frequent procedure had taken, and clinical stage T4 and N3 was the most findings at initial diagnosis. There was no complete response noted. Six patients were noted as partial response, and 1 patient was noted as progressive disease. The Kaplan-Meier curve shows an overall 6 months (95% CI: 4.4-7.6 months) of survival with a median of follow-up time was 7 (1-11) months. In subgroup analysis, we found that the responder group has significantly better overall survival than the non-responder group (log-rank test, p = 0.004).

CONCLUSION: Paclitaxel, Ifosfamide, and Cisplatin (TIP) regimen give significant clinical benefit in penile cancer with nodal involvement.

Introduction

The penile tumour is a rare tumour of the genitourinary system, found only 0.4-0.6 % from all incidence of malignancy among men in Europe and the United States of America. However, it made up 10 % of all incidence of malignancy among men in Asian, South America, and Africa countries [1], [2]. In Indonesia, there is no clear data yet regarding the incidence of penile cancer. In eleven years (1994-2005), there were 69 patients of penile cancer that recorded in Dr Cipto Mangunkusumo General Hospital

and Dharmas National Cancer Center Hospital Jakarta [3]. In Sanglah Hospital Bali, there were 46 patients of penile cancer during 8 years (1993-2001) [4]. Meanwhile, at Haji Adam Malik General Hospital Medan, the incidence of penile cancer during the last four years (2012-2015) was 34 patients [5]. Squamous cell carcinoma (SCC) of the penis was the most frequently found type of penile cancer [2], [5], [6].

The principle of management for penile cancer is to remove the tumour with as much organ preserved as possible, by either partial or total penectomy, as an effort to reduce recurrence. Aside

from treating the primary tumour, the involvement of lymph nodes is also an important factor to improve the patient's prognosis. Penile cancer is an aggressive disease, and the success of local lesion treatment is only when it is treated during the early stages. Meanwhile, penile cancer in late stages, accompanied by the involvement of regional lymph nodes or distant metastases, is still considered as a challenging problem for euro-oncologists [7].

Patients with unilateral lymph nodes metastasis, without extranodal involvement or involvement of pelvic lymph nodes, had a low recurrence rate of 10% to 20% after surgical management only. The recurrence rate was higher in patients with metastasis of bilateral lymph nodes, extranodal involvement, or the involvement of pelvic lymph nodes; which was 80% to 90% [8], [9]. The multi-modality approach, an approach combining chemotherapy and aggressive surgical management, might be effective, even though the local recurrence rate and progressivity were still high. Zou et al. reported that the administration of chemotherapy before lymphadenectomy on penile cancer patients with the involvement of regional lymph nodes (N3) showed great benefits. The administration of combination chemotherapy of bleomycin, methoprene, and cisplatin before lymphadenectomy resulted in 5-year overall survival rate 45.8%. This result statistically was greater in patients who were responsive to chemotherapy compared to those who were unresponsive (73.3% vs 0%, $p < 0.001$) [10]. Sarma et al. provided chemotherapy as adjuvant chemotherapy for patients with penile cancer after the removal of pelvic lymph nodes. The research showed an improvement in overall survival [11]. In cases where there were systemic metastases, chemotherapy was the choice of treatment [7], [12].

Various chemotherapy regimens were used as part of the management for penile cancer, either as neoadjuvant or adjuvant therapy. Cisplatin, bleomycin, and methotrexate were first used as single anti-tumour agents for penile cancer in the year 1975. However, the response rate was still low, with severe adverse effects; especially for bleomycin which was toxic for lungs [13].

Therefore, to improve the response rate of chemotherapy in penile SCC, various combinations of chemotherapy regimens were tested, the combinations usually consisted of two to three drugs [14]. The use of combined chemotherapy regimens was first reported by Shmmas et al., using 1000 mg/m² 5-fluorouracil (5-FU) and 100 mg/m² cisplatin with three weeks intervals. Results from the research showed partial responses in two out of a total of eight cases treated, with adverse effects including septicemia, decreased renal function, nausea, and vomiting [15].

Regimen of taxane-based chemotherapy has been successfully used to treat SCC from two

different locations. Combination chemotherapy using paclitaxel has been used to treat penile SCC since early 2000. Bermejo et al., used a combination of paclitaxel as neoadjuvant chemotherapy on two patients, resulting in prolonged post-chemotherapy survival rate followed by the removal of lymph nodes [16].

Joerger et al. reported significant remission in one of the patients with advanced disease after three cycles of paclitaxel/carboplatin [17]. The two types of research reported that the regimens were well tolerated [16], [17]. Pagliaro et al. conducted a phase two clinical trial of taxane-based chemotherapy regimen as neoadjuvant chemotherapy for penile SCC with the involvement of lymph nodes; the results showed that taxane-based chemotherapy had good response towards penile cancer with metastases to lymph nodes [12].

Reports regarding the use of taxane-based regimen for the management of penile SCC, either as neoadjuvant or adjuvant chemotherapy, were still limited so far. This condition might be due to the small number of penile SCC cases. At Haji Adam Malik General Hospital, the use of taxane as part of the chemotherapy regimen for penile SCC has been started since 2014. This study aims to evaluate the response for the administration of chemotherapy paclitaxel, ifosfamide, and cisplatin (TIP) regimens as well as to evaluate the overall survival (OS) rate.

Methods

This research is a retrospective, descriptive analytic study. Samples were collected from the year 2014 to 2016. Samples were patients with penile SCC which has been confirmed with histopathological examination results: enlargement of either unilateral or bilateral lymph nodes > 4 cm, with no signs of distant metastases. Patients with enlargement of pelvic lymph nodes found through computed tomography (CT) scan imaging were also included in the study, with or without biopsy results.

We used chemotherapy regimen TIP consisting of four cycles of paclitaxel 175 mg/m² on day 1, ifosfamide 1200 mg/m² on day 1 to 3, and cisplatin 25 mg/m² on day 1 to 3 with duration of 21-28 days. Patient's characteristics including age, ethnic, primary lesion, and TNM staging were noted. Occurring adverse effects, clinical response rate post-chemotherapy based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria [18] and overall survival rate were also noted.

Results

There were 17 patients of penile cancer with the involvement of lymph node, who received chemotherapy regimen consisting of paclitaxel, ifosfamide, and cisplatin from June 2014 to December 2016 at Haji Adam Malik General Hospital Medan. Out of a total of 17 patients, only 10 patients who managed to receive the full regimen of chemotherapy completely. Meanwhile, four patients passed away before completing chemotherapy, two patients refused to continue receiving chemotherapy, and one patient was still on the second cycle of chemotherapy in December 2016. Patients' characteristics were shown in table 1.

In this research, we found that the mean age of patients was 44.18 ± 11.13 years old. All samples were Batakese, and 16 patients (94.1%) were uncircumcised. Primary tumour lesion was found on the penile shaft (58.8%) and penile base (35.3%), with pathological results showing that 35.3% tumour had invaded surrounding tissues (T4) and had fixated nodules (N3) in 10 patients (58.8%). There was no patient found with distant metastases when diagnosed. Three patients had tumour staging Tx because they underwent an operation at other hospitals and their histopathological assessment results did not describe the T staging of their tumour.

Table 1: Baseline characteristics of patients (N = 17)

Characteristics	Number of patients	Percentage
Age (year)		
Mean	44.18 ± 11.13	
Circumcision		
Yes	1	5.9
No	16	94.1
Ethnic		
Batak	17	100
Location of the primary tumour		
Penile glans	1	5.9
Penile shaft	10	58.8
Penile base	6	35.3
Tumour Staging		
T1a	0	0
T1b	1	5.9
T2	3	17.6
T3	3	17.6
T4	7	35.3
Tx	3	35.3
Nodule Staging		
N0	0	0
N1	3	17.6
N2	4	23.5
N3	10	58.8
Metastasis	0	0
Type of operation		
Partial penectomy	6	35.3
Total penectomy	11	64.7
Histopathological type		
SCC	17	100

Eleven patients (64.7%) who received chemotherapy with paclitaxel, ifosfamide, and cisplatin underwent total penectomy while 6 patients (35.3%) underwent partial penectomy; the histopathological type of all tumour (100%) was squamous cell carcinoma (SCC).

Table 2: Response to chemotherapy after four cycles of TIP

Response towards chemotherapy	Frequency	Percentage
Complete response	0	0
Partial response	6	60
Stable	3	30
Progressive	1	10

There was no patient with a complete response. However, there were six patients with partial responses, three patients with a stable response, and one patient showed progressive disease.

Table 3: Adverse effects during chemotherapy of TIP

Adverse effects	Frequency (n)	Percentage (%)
Neutropenia	8	47.1
Thrombocytopenia	7	41.2
Anaemia	14	82.4
Mucositis	6	35.3
Nausea	12	70.6
Diarrhoea	2	11.8
Constipation	0	0
Alopecia	15	88.2
Allergy	0	0

Eleven out of 17 patients receiving chemotherapy passed away with median overall survival (OS) of 6 months (95% CI: 4.4-7.6 months). The median time for follow up was seven months (ranging from 1 to 11 months).

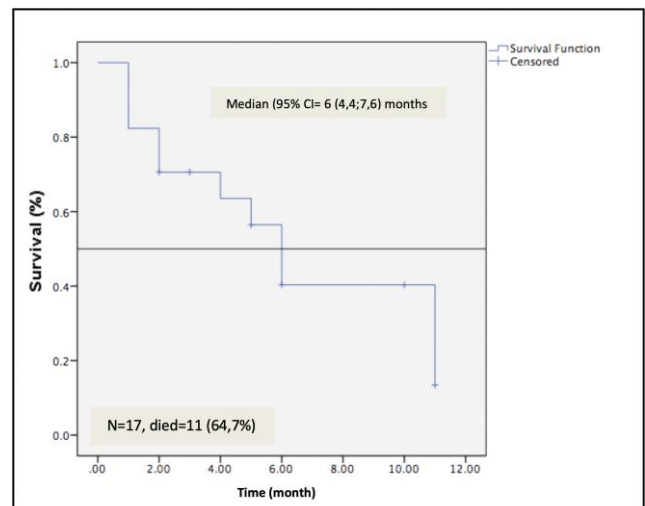


Figure 1: Kaplan-Meier graph overall survival rate (OS)

We conducted subanalysis towards the responsive and unresponsive sub-groups regarding the administration of paclitaxel, ifosfamide, and cisplatin-based chemotherapy. Eight patients passed away in the unresponsive group, while only two patients passed away in the responsive group. The overall survival rate was significantly higher in responsive patients compared to unresponsive patients (log-rank test, $p = 0.004$).

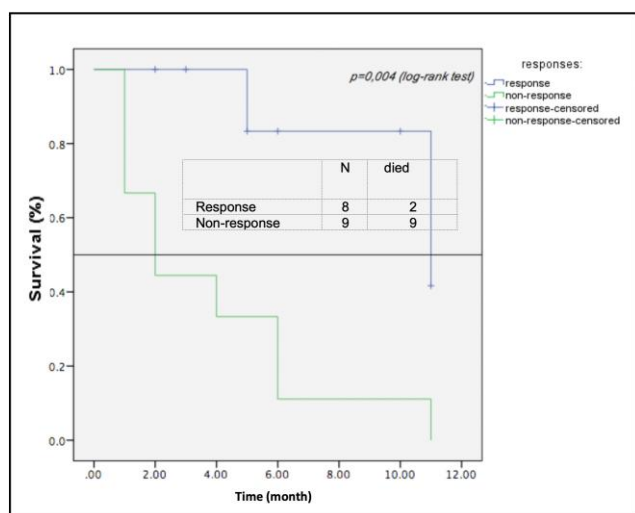


Figure 2: Kaplan-Meier graph overall survival rate (OS) of responsive and unresponsive sub-groups

Discussion

Based on our experiences in using paclitaxel, ifosfamide, and cisplatin-based chemotherapy as part of penile cancer management in Haji Adam Malik General Hospital, Medan, we found 17 patients who received the regimen from June 2014 to December 2016. Penile cancer is an aggressive disease, in which success for local lesion management could only be achieved during the early stages. The success of penile cancer management with regional and systemic metastases is still a challenge for urologists. In situations where there were metastases on regional lymph nodes, administration of chemotherapy combined with aggressive surgical management might be effective, even though the recurrence rate and progressivity were still high. In cases where systemic metastasis was found, chemotherapy becomes the only choice of treatment [7].

Most penile cancers are squamous cell carcinoma (SCC). In this research, the histopathological type of all samples was SCC (100%) with T4 (35.3%) and N3 (58.8%) as the most common staging results. Thus, it can be concluded that most patients who came to Haji Adam Malik General Hospital Medan were already in the late stages of the disease. This condition is commonly found in patients with penile SCC, as also found in the research by Lynch and Krush, which reported 15-50% patients delayed up to one year before they are finally looking for treatment [19].

There were six patients with partial responses after four cycles of chemotherapy in our research; however, there was no sample which showed a complete response. In the research by Pagliaro, there

were found three patients with complete response and twelve patients showing the partial response from total research samples of 30 patients; 13.6% of all patients showing a complete pathological response (pCRs) [12]. Other researches which used a taxane-based combination as neoadjuvant chemotherapy in advance stage penile cancer resulted in 60% responsive patients, with 4% showing complete pathological response [20]. Kubota et al. reported that the TIP combination was effective for penile cancers with the involvement of lymph nodes [21].

The administration of chemotherapy for penile cancer with lymph nodes metastases is quite common. Both adjuvant and neoadjuvant chemotherapy could increase overall survival [12], [16], [22], [23]. The largest prospective research by the Southwest Oncology Group (SWOG) reported of patients receiving a combination of bleomycin, methotrexate, and cisplatin. In the research, the overall survival rate was 32.5% with median overall survival of 28 weeks. Even though the overall survival rate for the regimen was quite high, it was not well tolerated since there was also a high mortality rate due to chemotherapy (13.9%) [23]. Our study showed an overall survival of 6 months. This result was lower when compared to the results from the study by Pagliaro, which was OS 17.1 months [12]. This difference might be caused by the fact that in this research, the intervention was only chemotherapy; there was no patient who underwent inguinal lymphadenectomy (ILND).

Sub-group analysis of patients who were responsive and unresponsive to chemotherapy showed a statistically significantly higher overall survival in patients who were responsive to chemotherapy (11 months vs 2 months, $p = 0.004$). The response towards chemotherapy might be used as predictors for chemotherapy success as part of management for penile cancer.

There were a few adverse effects occurring during the administration of TIP. In this study, the most commonly found adverse effects included alopecia, nausea, and anaemia. The alopecia was temporary and will subside once the chemotherapy was stopped. Djajadiningrat et al. discovered a few adverse effects during the administration of taxane-based combination chemotherapy in each patient and concluded that the adverse effects of taxane-based combination chemotherapy were less well-tolerated [20].

In conclusion, the administration of paclitaxel, ifosfamide, and cisplatin-based chemotherapy is effective, showing improvement in overall survival of patients with penile cancer, with the involvement of regional lymph nodes. Patients who were responsive to chemotherapy had longer overall survival, although, a combination of chemotherapy and surgical management will show better results.

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