Andrology-Open Access

Yumura et al., Andrology (Los Angel) 2017, 6:2
DOI: 10.4172/2167-0250.1000194

Research Article Open Access

Cisplatin, Methotrexate and Bleomycin for Advanced Recurrent or Metastatic Penile Squamous Cell Carcinoma

Yumura Y*, Kasuga J, Kawahara T, Miyoshi Y, Hattori Y, Teranishi J, Takamoto D, Mochizuki T and Uemura H

Department of Urology and Renal Transplantation, Yokohama City University Medical Center, Japan

***Corresponding author:** Yasushi Yumura, Departments of Urology and Renal Transplantation, Yokohama City University Medical Center, Japan, Tel: +81452615656; Fax: +81452531962; E-mail: yumura@yokohama-cu.ac.jp

Received date: December 11, 2017; **Accepted date:** December 15, 2017; **Published date:** December 22, 2017

Abstract

Objective: This study aimed to evaluate the efficacy and toxicity of cisplatin, methotrexate, and bleomycin (CMB) chemotherapy in patients with advanced, recurrent, or metastatic penile squamous cell carcinoma (PSCC).

Methods: The CMB regimen was administered to 12 patients with advanced (n=7), recurrent (n=4), or metastatic (n=1) PSCC. Patients received a total of 21 cycles of CMB between 2002 and 2009, and were retrospectively reviewed for treatment efficacy and toxicity of the drugs. The mean patient age was 61 (61.0 ± 8.7) years. Patients received 20.0 mg/m^2 of cisplatin intravenously on days 2-6; 200.0 mg/m^2 of methotrexate intravenously on days 1, 15 and 22; and 10.0 mg/m^2 of bleomycin as a bolus on days 2-6. The CMB regimen consisted of 21-28 days of treatment per cycle. Survival after CMB therapy and frequency and magnitude of adverse effects were assessed.

Results: Of the 7 patients with advanced disease who received the CMB regimen as neoadjuvant and/or adjuvant treatment, 5 survived, 1 died of local recurrence and lung metastasis, and 1 died of interstitial pneumonia. Three of the 5 patients with recurrent or metastatic disease died of PSCC. One patient died of interstitial pneumonia due to CMB. Only 1 patient with inguinal lymph node metastasis after penectomy who underwent adjuvant CMB regimen had survived. Eight patients who were disease free survived longer than those who still had the disease. No adverse hematological effects of Grade 3 or higher were observed.

Conclusion: The CMB regimen might be effective for advanced PSCC, but not for recurrent or metastatic PSCC. Two patients died of interstitial pneumonitis due to chemotherapy. Hence, we believe that the CMB regimen should not be used as a first-line treatment option in patients with advanced-stage or metastatic PSCC.

Keywords: Bleomycin; Cisplatin; Combination chemotherapy; Methotrexate; Penile cancer; Squamous cell carcinoma

Introduction

Penile squamous cell carcinoma (PSCC) is relatively rare in Japan, with an incidence of 0.4 per 100,000 of the male population [1]. The majority of PSCCs are diagnosed when they are still localized. Although localized PSCC has a good prognosis after radical resection, cases of unrespectable, recurrent, and metastatic disease, with a poor prognosis, can also be seen [2-5]. The penile cancer guidelines of the National Comprehensive Cancer Network (NCCN) recommend neoadjuvant chemotherapy, radiotherapy, or chemoradiotherapy followed by consolidation surgery for the management of advanced and recurrent disease, provided that the disease is stable or a clinical response is demonstrated [6]. However, there are currently no guidelines for the management of PSCC in Japan. Hence, many Japanese urologists treat PSCC patients based on the guidelines from NCCN or European Association of Urology [2,6].

Chemotherapy regimens for PSCC have switched from monotherapy with a single anticancer agent to cisplatin-based combination chemotherapy. We used a combination regimen of cisplatin, methotrexate, and bleomycin (CMB) for advanced, recurrent, or metastatic PSCC patients (n=12) between 2002 and 2009. The CMB regimen was first described by Corral et al. [7]. Sixteen of the 29 advanced-stage genitourinary SCC patients treated with this regimen had an objective response and the median overall survival (OS) of patients who were disease free following surgery or external beam radiotherapy was significantly longer than that of patients who were not disease free [7]. Subsequently, this regimen has been widely used as one of the effective chemotherapy regimens for advanced PSCC. In this study, we retrospectively analyzed the efficacy and toxicity of CMB chemotherapy in PSCC patients.

Patients and Methods

The CMB regimen was administered to 12 patients with advanced, recurrent, or metastatic PSCC in our department at Yokohama Municipal Citizen's Hospital, National Sagamihara Hospital, and Yokosuka Kyosai Hospital between February 2002 and July 2009. Patients received 20.0 mg/m^2 of cisplatin intravenously on days 2-6; 200.0 mg/m^2 of methotrexate intravenously on days 1, 15, and 22; and a bolus of 10.0 mg/m^2 of bleomycin on days 2-6 [7]. The CMB regimen consisted of 21-28 days of treatment per cycle.

Of the 12 patients included in this study, 7 had advanced-stage PSCC and 5 had recurrent (n=4) or metastatic (n=1) PSCC. Four advanced-stage PSCC patients received 1 cycle of neo adjuvant CMB therapy followed by surgical resection and 1 or 2 cycles of adjuvant

CMB therapy. The remaining advanced-stage PSCC patients (n=3) received 1 cycle of adjuvant CMB therapy.

The 5 patients with recurrent or metastatic PSCC received 1 or 2 cycles of CMB therapy. Of these, 1 patient had inguinal lymph node and lung metastases. The remaining 4 patients had local recurrence or lymph node metastasis after the initial surgery. One patient received adjuvant CMB therapy after inguinal metastatic lymph node dissection. Four patients with recurrent or metastatic PSCC, who responded to CMB or had stable disease during CMB treatment, were continued on CMB until there was evidence of disease progression or adverse effects were observed (Table 1).

S.No	Age	Cinical TNM	Neoaduvant CMB cycles	Adjuvant CMB cycles	Effect of CMB	Result	Overall survival (mo)
1	54	cT2N1M0	0	1	NA	NED	118.47
2	58	cT1N2M0	1	1	PR	NED	146.63
3	46	cT2N2M0	1	2	PR	NED	54.8
4	65	cT1N1M0	0	1	NA	NED	53.7
5	60	cT2N0M0	0	1	NA	Death from Therapy	3.97
6	53	cT2N3M0	1	2	MR	DOD	14.2
7	65	cT2N2M0	1	2	MR	NED	39.6

Recurrent/metastatic group								
-	Age	Cinical TNM	Treatment before CMB	Recurrence/ Metastatic	Site of recurrence	CMB cycles	Effect of CMB	Results	Overall survival (mo)
8	57	cT4N1M0	Total penectomy+ILND	Recurrence	Local and ILN	1	SD	DOD	27.9
9	56	cT2N1M0	Partial penectomy+ILND +PLND	Recurrence	Local	2	PD	DOD	10.6
10	74	cT4N1M1	EBRT,CDDP+5FU	Metastatic	-	1	SD	Death from therapy	6.4
11	74	cT3N3M0	Partial penectomy+ILND EBRT	Recurrence	Paraaortic LN,pelvic LN	1	MR	DOD	52.17
12	70	cT1N0M0	Partial penectomy	Recurrence	Inguinal LN	2 (post ILND)	NA	NED	81.07

Table 1: Patient characteristics and outcomes [NA: Not Applicable; PR: Partial Response; MR: Minor Response; SD: Stable Disease; PD: Progressive Disease; NED: No Evidence Disease; DOD: Died of Disease; LN: Lymph Node; ILND: Inguinal Lymph Node Dissection; PLND: Pelvic Lymph Node Dissection; EBRT: External Beam Radiation Therapy; CMB: Cisplatin, Methotrexate Bleomycin].

A maximum of 3 courses of this regimen were administered to avoid exceeding the maximum permissible dose for bleomycin. Adverse effects were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0 [8]. When patients had disease in an evaluable region, the response was assessed after each cycle of chemotherapy, according to changes in the radiographic evidence of the disease. Responses were classified as follows: a complete response, a partial response (>50.0% reduction), a minor response (25.0-50.0% reduction), stable disease, or progressive disease, using the sum of the products of the perpendicular diameters of the measured lesions [9].

The surviving patients were followed-up and assessed at 3-month intervals for the first 2 years and at 6 month intervals thereafter. The cancellation criteria for CMB were as follows: (1) development of progressive disease after treatment; up to 3 courses were administered for stable disease; (2) occurrence of an adverse event of Grade 3 or higher. Patients were staged according to the 2009 edition of the TNM classification system [10]. OS was measured from the date the initial cycle of CMB therapy was started to the date of the last follow-up. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test.

All statistical analyses were conducted using Statistical Package for the Social Sciences for Macintosh, software version 22.0 (IBM Corp., Armonk, NY, USA). A p value <0.05 was considered statistically significant. This study protocol was approved by the appropriate Ethical Review Board committee of Yokohama City University Medical Center (Yokohama, Japan) (IRB approval number D1209028). Research was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. All participants provided informed written consent.

Results

Patients' characteristics, effects of the CMB regimen, and survival information are summarized in Table 1 and 2.

Statistics	Adjuvant/Neoadjuvant Cases	Recurrent/Metastatic Cases
Number of patients	7	5
Best response	2 PR	1 MR
Death from disease	1	3
Death from therapy	1	1
No evidence of disease	5	1

Table 2: Effect of cisplatin, methotrexate, and bleomycin (CMB) chemotherapy on our cases.

The mean age of the 12 patients enrolled in our study was 61 (61.0 ± 8.7) years and the median follow-up duration was 50.8 ± 45.2 (range, 6.4-146.6) months. A total of 21 cycles of CMB therapy were administered. Of the 7 patients with advanced disease who received 14 cycles of CMB therapy as neoadjuvant and/or adjuvant treatment, partial and minor responses were each observed in 2 patients (33.3%). Five patients (41.7%) survived and 1 patient died of local recurrence and lung metastasis after treatment. One patient (8.3%) died of interstitial pneumonia due to adjuvant chemotherapy. In 5 patients with recurrent or metastatic PSCC, only 1 patient exhibited a minor response (8.3%). Progressive and stable diseases were observed in 1 (8.3%) and 2 patients (16.7%), respectively. Three of these 4 patients died of PSCC. One patient with lung metastasis died of interstitial pneumonia, after just 1 cycle of CMB therapy. Only 1 patient in this group survived with no evidence of disease for 81 months after receiving 2 cycles of adjuvant chemotherapy following inguinal metastatic lymph node dissection.

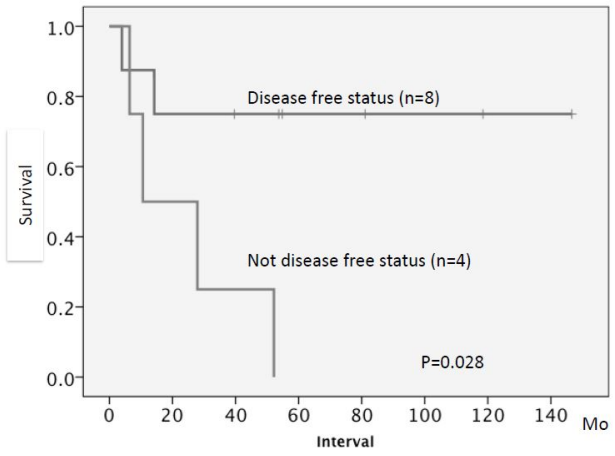

Figure 1: Kaplan-Meier curve of overall survival for penile squamous cell carcinoma patients who were disease free (n=7) and those who were not (n=5).

A Kaplan-Meier curve for OS of the 12 patients included in this study is displayed in Figure 1. The median OS of the 8 patients who were disease free was significantly longer than that of the 4 patients who still had the disease (54.3 months *vs.* 19.3 months, p=0.028). Across the 21 cycles administered no adverse hematological effects of Grade 3 or higher were observed. Non-hematological toxicities of Grade 3 or higher included interstitial pneumonia in 2 patients (9.5%), urticaria in 1 patient (4.8%), nausea in 1 patient (4.8%), anorexia in 1 patient (4.8%), and stridor (diagnosis was not interstitial pneumonia) in 1 patient (4.8%). Two patients (9.5%) with interstitial pneumonia died (Table 3).

Hematological toxicity	Grade: No of cases
Anemia	G1: 1
Leukocytopenia	G1: 2
Non-hematological toxicity	-
Liver dysfunction	G1: 1
Renal dysfunction	G2: 2
Hypokalemia	G1: 1
Urticaria	G3: 1
Fever (not FN)	G1: 1
Wound infection	G2: 1
Nausea	G2: 1, G3: 1
Anorexia	G3: 1
Stridor	G3: 1
Interstitial pneumonia	G5: 2 +
+Two patients died	

Table 3: Adverse effects of cisplatin, methotrexate, and bleomycin (CMB) treatment observed in our study.

Discussion

There are currently no guidelines for the management of PSCC patients in Japan. A treatment system for PSCC has recently been developed through the introduction of the European Association of Urology [2] and NCCN [6] guidelines in Japan.

According to the European Association of Urology guidelines [2], adjuvant chemotherapy is recommended for patients with N2-3 metastases. In patients with bulky or fixed inguinal lymph node metastasis or distant metastasis, neoadjuvant chemotherapy followed by surgery is also recommended. Cisplatin-based chemotherapy regimens have been shown to improve outcomes in patients with advanced-stage disease compared to non-cisplatin-based chemotherapy regimens [2,11]. Furthermore, taxanes can enhance the efficacy of the regimen [2,12].

Conversely, according to the NCCN guidelines [6], neoadjuvant chemotherapy should be considered as the standard treatment for patients with initially unresectable primary tumors or inguinal lymph nodes of >4 cm, if fine needle aspiration is positive. The NCCN guidelines recommend paclitaxel, ifosfamide, and cisplatin combination therapy [6], with regimens containing bleomycin no longer recommended [12]. Although the outcomes of adjuvant chemotherapy are yet insufficient to support its use, it is reasonable to

administer 4 cycles of the paclitaxel, ifosfamide, and cisplatin regimen in an adjuvant setting [6].

The CMB regimen was first described by Corral et al. [7]. The authors treated 29 advanced-stage genitourinary SCC patients with the CMB regimen. Sixteen patients (55.2%) had an objective response and the median OS of patients who were disease free following surgery or external beam radiotherapy was significantly longer than that of patients who were not disease free (34.4 *vs.* 7.0 months) [7].

Haas et al. reported the effects of combination chemotherapy with CMB in 45 patients with advanced or metastatic PSCC [13]. Although the drug dose and schedule of administration were different from those reported by Corral et al. [7], of the 45 patients enrolled, 5 exhibited a complete response and 8 exhibited a partial response, giving a total response rate of 32.5%. However, 5 patients died due to the toxicity of the regimen [13]. Hakenberg et al. treated 13 patients with advanced or metastatic PSCC with a similar regimen to ours, and reported that 3 of the 8 patients treated with adjuvant chemotherapy had no evidence of disease [14]. However, 5 patients with metastatic PSCC died of the disease. The authors also reported that 2 patients died of pulmonary toxicity due to chemotherapy.

Our study comprised 7 patients with advanced-stage PSCC and 5 patients with recurrent or metastatic PSCC. Although 5 of the 7 (71.4%) patients who received adjuvant and/or neoadjuvant CMB therapy survived without evidence of recurrence, 4 of the 5 patients with recurrent or metastatic disease who were treated with CMB therapy died of their disease with little effect of the CMB regimen. Patients who achieved a disease-free status survived significantly longer than those who did not.

Our study had some limitations, including the small sample size (12 patients) and the retrospective nature. However, in Japan, patients with PSCC are extremely rare [1] and there have been limited studies about PSCC. Hence, we believe that collaborative multi-center research is necessary to determine new treatments for advanced PSCC in Japan.

In conclusion, our findings suggest that the CMB regimen is effective as adjuvant and/or neoadjuvant chemotherapy for advanced-stage PSCC patients, but not for recurrent or metastatic PSCC patients, corroborating the findings by Hakenberg et al. [14]. Additionally, 2 patients died of interstitial pneumonitis due to chemotherapy. Although generally only bleomycin is considered to induce interstitial pneumonitis, methotrexate has also been reported to induce pulmonary toxicity [15]. Given that pulmonary toxicity is a life threatening adverse effect and safer and comparably effective treatments are emerging [16], we recommend that the CMB regimen should not be used as a first-line treatment option in patients with advanced-stage or metastatic PSCC.

Acknowledgements

We wish to thank Editage (www.editage.jp) for English language editing.

Disclosure Statement

The authors declare no conflict of interest and no funding has been received for this work.

References

1. Kamidono S (1992) Cancer of the penis and its treatment. Jpn J Urol 83: 1-15.
2. Hakenberg OW, Compérat EM, Minhas S, Necchi A, Protzel C, et al. (2015) EAU guidelines on penile cancer: 2014 update. Eur Urol 67: 142-150.
3. Horenblas S (2011) Lymphadenectomy in penile cancer. Urol Clin North Am 38: 459-469.
4. Horenblas S (2001) Lymphadenectomy for squamous cell carcinoma of the penis. Part 2: The role and technique of lymph node dissection. BJU Int 88: 473-483.
5. Sánchez-Ortiz RF, Pettaway CA (2003) Natural history, management, and surveillance of recurrent squamous cell penile carcinoma: A risk-based approach. Urol Clin North Am 30: 853-867.
6. National Comprehensive Cancer Network®: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Penile Cancer Version I. 2014.
7. Corral DA, Sella A, Pettaway CA, Amato RJ, Jones DM, et al. (1998) Combination chemotherapy for metastatic or locally advanced genitourinary squamous cell carcinoma: A phase II study of methotrexate, cisplatin and bleomycin. J Urol 160: 1770-1774.
8. National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.
9. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, et al. (2009) New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247.
10. Sobin LH, Gospodarowicz MK, Wittekind C (2009): TNM Classification of Malignant Tumours (7th ed) Wiley-Blackwell, Hoboken, NJ, USA.
11. Pond GR, Di Lorenzo G, Necchi A, Eigl BJ, Kolinsky MP, et al. (2014) Prognostic risk stratification derived from individual patient level data for men with advanced penile squamous cell carcinoma receiving first-line systemic therapy. Urol Oncol 32: 501-508.
12. Pagliaro LC, Williams DL, Daliani D, Williams MB, Osai W, et al. (2010) Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy for metastatic penile cancer: A phase II study. J Clin Oncol 28: 3851-3857.
13. Haas GP, Blumenstein BA, Gagliano RG, Russell CA, Rivkin SE, et al. (1999) Cisplatin, methotrexate and bleomycin for the treatment of carcinoma of the penis: A Southwest Oncology Group study. J Urol 161: 1823-1825.
14. Hakenberg OW, Nippgen JB, Froehner M, Zastrow S, Wirth MP (2006) Cisplatin, methotrexate and bleomycin for treating advanced penile carcinoma. BJU Int 98: 1225-1227.
15. Atzeni F, Boiardi L, Sallì S, Benucci M, Sarzi-Puttini P (2013) Lung involvement and drug-induced lung disease in patients with rheumatoid arthritis. Expert Rev Clin Immunol 9: 649-657.
16. Trabulsi EJ, Hoffman-Censits J (2010) Chemotherapy for penile and urethral carcinoma. Urol Clin North Am 37: 467-474.