

Carboplatin and paclitaxel as an initial treatment in patients with stage IVb cervical cancer: a report of 7 cases and a review of the literature

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Objective: The aim of this study is to evaluate the efficacy of carboplatin-paclitaxel (TC) as an initial treatment in patients with the International Federation of Gynecology and Obstetrics (FIGO) stage IVb cervical cancer.

Methods: We retrospectively reviewed seven patients with stage IVb cervical cancer who have been primarily treated with TC. The activity and the toxicity were evaluated. Response rate was the main endpoint.

Results: Overall, the treatment of TC was well tolerated. The overall response rate was 71.4% (2 complete response, 3 partial response). Although grade 3-4 hematologic toxicities were observed in 3 out of 7 patients (42.8%), no patients experienced grade 3-4 non-hematologic toxicities. When we combined our present results with the previous reports, the overall response rate of TC is 63.6%.

Conclusion: TC is active and well tolerated in patients FIGO stage IVb cervical cancer. This combination may be considered as an initial treatment regimen in this patient population.

Key Words: Stage IVb, Cervical cancer, Carboplatin, Paclitaxel

INTRODUCTION

Patients with the International Federation of Gynecology and Obstetrics (FIGO) stage IVb cervical cancer have a dismal prognosis.^{1,2} Systemic chemotherapy and individualized radiotherapy have been proposed as initial treatments for these patients.³ On the basis of phase III clinical trials, cisplatin-containing combination chemotherapy; i.e., cisplatin plus paclitaxel (TP), has become the standard treatment for recurrent or advanced cervical cancer.⁴ Although the combination of carboplatin-paclitaxel (TC) was demonstrated to be equally effective as and less toxic than TP in ovarian cancer,⁵ information on the use of TC in patients with advanced cervical cancer is limited. We herein describe our experiences with 7 cases of stage IVb cervical cancer that were primarily treated with TC.

MATERIALS AND METHODS

Permission to proceed with data acquisition and analysis was obtained from the Osaka University Hospital's institutional review board. Seven patients with stage IVb cervical cancer that were primarily treated with TC at the Osaka University Hospital from 2007 to 2009 were identified and retrospectively reviewed. For all patients, clinical data on the following characteristics were collected: initial stage, maximal tumor diameter, cell type, performance status, primary treatment, site of recurrent disease, disease free interval (DFI), chemotherapy regimen, response, and progression free survival (PFS). PFS was measured from the start of chemotherapy to the progression of disease. The maximal tumor diameter was measured three-dimensionally based on T2-weighted magnetic resonance imaging (MRI). The longest diameter was considered valid as the maximal tumor diameter. TC was administered on a monthly basis in all patients: Carboplatin at an area under the curve (AUC) of 5 given as a 1 hour infusion, and paclitaxel at 175 mg/m² given as a 3 hours infusion every 28 days. The response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumors after every three cycles of each regimen. A complete response (CR) was defined as the disappearance of all target and non-target lesions and no new lesions being documented after two assessments that were at least 4 weeks apart. A partial response (PR) was defined as at least a 30% decrease in the sum

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of the longest dimension of the target lesions, which was also documented in two assessments that were at least 4 weeks apart. Progressive disease (PD) was defined as a 20% increase in the longest dimension of the sum of the target lesions or the development of new lesions. Stable disease (SD) implies that none of the above applies. Performance status (PS) was graded according to the Eastern Cooperative Oncology Group performance status criteria. Toxicity related to treatment was graded according to the NCI Common Terminology Criteria for Adverse Events, ver. 3.0.

RESULTS

The patient's characteristics and clinical data are summarized in Table 1. The median age at the time of treatment was 60. Five women had squamous cell carcinoma, and two had adenocarcinoma. All patients had stage IVb disease with metastasis to distant organs including the lungs, liver, peritoneal dissemination, para-aortic lymph node, or other distant lymph node. All patients received TC as an initial treatment.

TC was administered on a monthly basis in all patients: Carboplatin at an AUC of 5 given as a 1-h infusion and paclitaxel at 175 mg/m² given as a 3-h infusion every 28 days. The median courses of TC administered was 6 (range, 3 to 12). As predicted, the administration of TC was generally well tolerated without any significant delays or dose reduction. Although grade 3-4 hematologic toxicities were observed in 3 out of 7 patients (42.8%), no patients developed febrile neutropenia. No patients experienced grade 3-4 non-hematologic toxicities. As shown, 2 patients showed CR, 3 showed PR, 1 showed SD, and 1 demonstrated PD. The overall response rate was 71.4%. Two patients who had achieved clinical CR to chemotherapy were further examined, and proven to be with no cytological evidence of disease in the primary site.

Three out of 5 responders and 1 non-responder received salvage

radiotherapy consisting of external beam radiotherapy and high dose rate-intracavitary brachytherapy with curative intent following treatment with TC. One complete responder refused to receive additional treatment such as radiotherapy after the initial chemotherapy. Because of the rapid progression of the systemic disease, two non-responders did not receive further treatment following the treatment with TC. At the time of this study, 5 out of 7 patients were alive, and 2 of these 3 had not suffered recurrence after a median follow-up period of 21 months.

DISCUSSION

Surgery and concurrent chemoradiotherapy (CCRT) have achieved significant success in the treatment of cervical cancer both in patients with early stage cervical cancer, and in those with locally advanced cervical cancer.⁶ However, in patients with stage IVb disease, no standard treatment has been established. Although systemic chemotherapy and individualized radiotherapy have been proposed as initial treatments,² the patients given these regimens showed a poor prognosis with a reported 5-year survival of less than 10%.⁷

Since stage IVb cervical cancer is a systemic disease, theoretically, chemotherapy is required for these patients. Based on previous phase III clinical trials, cisplatin-containing combination chemotherapy; i.e., cisplatin plus paclitaxel or topotecan, had become the standard treatment for recurrent or advanced cervical cancer.^{4,8} Subsequently, a Gynecologic Oncology Group (GOG) phase III clinical trial (protocol GOG 204) comparing the efficacy of four cisplatin-based combination chemotherapies including TP, cisplatin-topotecan, cisplatin-vinorelbine, and cisplatin-gemcitabine has been conducted. In this study, although not statistically significant, TP showed the most favorable clinical activity with regard to the response rate, progression free survival, and overall survival in patients with FIGO stage IVb, recurrent, and persistent cervical cancer.⁹ A recent retrospective

Table 1. Synopsis of patients with stage IVb cervical cancer treated with paclitaxel-carboplatin

Case	Age (yr)	Performance status	Histology	Maximum tumor diameter (cm)	Site of metastasis	Pelvic sidewall fixation	Course of chemotherapy	Response	Grade 3-4 toxicity	Subsequent treatment	PFS (mo)	Site of recurrence	Outcome
1	50	0	SCC	6	Liver, lung, spleen, peritoneum	No	4	SD	No	Non	3	Liver, lung, spleen, peritoneal dissemination	DOD
2	74	0	SCC	7	PALN, lung	No	3	PR	Yes	RT	9	Lung	AWD
3	60	0	SCC	6	PALN, lung	No	3	PD	Yes	RT	0	PALN, lung	AWD
4	71	0	SCC	3	Lung	No	6	CR	No	Non	12	PALN	AWD
5	37	0	SCC	4	SCLN	No	6	PR	No	RT	20	No	AWOD
6	57	0	Adeno	3.5	Liver	No	6	PR	No	Non	8	Liver	DOD
7	70	0	Adeno	2	Peritoneum, PALN	No	12	CR	Yes	RT	30	No	AWOD

PFS: progression free survival, SCC: squamous cell carcinoma, SD: stable disease, DOD: died of disease, PALN: para-aortic lymph node, PR: partial response, RT: radiotherapy, AWD: alive with disease, PD: progressive disease, CR: complete response, SCLN: supraclavicular lymph node, Adeno: adenocarcinoma, AWOD: alive without disease.

Table 2. Paclitaxel-carboplatin as an initial treatment in patients with stage IVb cervical cancer

Article	Target disease	Dose of chemotherapy	Total no. of patients	Stage IVb patients	Response		
					No. of CR	No. of PR	Rate (%)
Piver et al. ¹⁵ (1999)	R or A	Paclitaxel: 135 m ² Carboplatin: 300 mg/m ² Every 4 wk	3	2	0	1	50
Tinker et al. ¹⁶ (2005)	R or A	Paclitaxel: 175 m ² Carboplatin: AUC 5-6 Every 4 wk	25	2	0	1	50
Moore et al. ¹⁷ (2007)	R or A	NA	48	5	NA	NA	NA
Current study (2010)	A	Paclitaxel: 175 m ² Carboplatin: AUC 5 Every 4 wk	7	7	2	3	71.4
Evaluable patients				11	2	5	63.6

CR: complete response, PR: partial response, R: recurrent cervical cancer, A: advanced-stage cervical cancer, AUC: area under the curve, NA: not available.

review of four randomized phase III GOG clinical trials suggested that advanced or recurrent cervical cancer patients who had been previously treated with radiosensitizing-cisplatin showed poorer response to platinum-based chemotherapy than those who had not.¹⁰ With the aim to investigate the effectiveness of non-platinum containing chemotherapy in the same population, GOG has recently initiated a phase III trial (protocol 240) comparing TP versus non-platinum doublet (paclitaxel- topotecan), with or without bevacizumab.¹¹

Although the combination of TC was demonstrated to be equally effective as and less toxic than TP in ovarian cancer,⁵ information on the use of TC in cervical cancer is limited. Except for several case reports, to the best of our knowledge, only six retrospective studies on the value of TC in 3-48 recurrent or advanced cervical cancer patients have been reported.¹²⁻¹⁷ Since the vast majority of patients enrolled in these studies were treated for recurrence after either radiotherapy or surgical treatment, the effectiveness of TC against stage IV disease as an initial treatment is largely unknown. Of the six retrospective studies, the total number of patients treated for stage IVb disease as an initial treatment was 9. Of these, detailed information regarding the treatment outcome was only available for 4 patients (Table 2).

We have demonstrated that TC is effective in patients with stage IVb cervical cancer. Our overall response rate of 71.4% is very similar to our previously reported response rate of 67.9% in patients with recurrent cervical carcinoma after definitive radiotherapy.¹² Moreover, when we combined our present results with the previous reports, as shown in Table 2, the overall response rate in a total of 11 patients was 63.6%.

As predicted, TC was well tolerated. Although grade 3-4 hematologic toxicities were observed in 3 out of 7 patients, no patients developed febrile neutropenia. This favorable toxicity profile of TC demonstrated in the current study may have been, at least in part, due to the treatment schedule employed in our institution: TC was administrated every 28 days as this

dosing schedule had demonstrated significant clinical activity in patients with recurrent cervical cancer.¹² However, on the basis of the concept of dose-density, we believe that we should try every 21 days administration of TC, which may result in better treatment outcome.

Although this study was retrospective and involved a relatively small number of patients, given the advantages of patient convenience and tolerance as well as the significant activity shown, we believe that TC is a reasonable treatment option for patients with stage IVb cervical cancer. To address the clinical benefit of TC compared with TP in stage IVb, persistent, or recurrent cervical cancer, the Japan Clinical Oncology Group (JCOG) is currently conducting a randomized phase III trial of their JCOG 0505 protocol.¹⁸ In addition, since this combination chemotherapy demonstrated significant effectiveness as an initial treatment, TC may also hold promise in a CCRT or neoadjuvant chemotherapy setting in patients with cervical cancer. To establish a more effective and less toxic treatment strategy for patients with advanced cervical cancer, further studies are needed.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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