Preoperative chemotherapy with irinotecan and mitomycin for FIGO Stage IIIb cervical squamous cell carcinoma: A pilot study

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Summary

Purpose of investigation: Patients with FIGO Stage IIIb cervical cancer show cancer propagation to pelvic side walls from the uterus, and the tumors cannot be completely removed by radical hysterectomy. Here, we examined the effects of preoperative irinotecan HCl (CPT-11)-combined chemotherapy on patients with unresectable Stage IIIb cervical squamous cell carcinoma.

Methods: Eleven patients agreed to participate in the pilot study and received preoperative chemotherapy.

Results: Cervical tumors of all 11 patients showed partial responses in tumor reduction, and radical hysterectomy was successfully performed in ten patients treated with CPT-11 and mitomycin C (MMC). One patient treated with CPT-11 and cisplatin had a 68% reduction of the primary cervical lesion but could not undergo radical surgery because of retroperitoneal cancer progression during chemotherapy.

Conclusion: These results indicate that chemotherapy with CPT-11 and MMC could be a useful preoperative treatment for unresectable Stage IIIb cervical squamous carcinoma.

Key words: Irinotecan, CPT-11; Cervical cancer; Squamous cell carcinoma.

Introduction

Radical hysterectomy is a curative pelvic surgery for locally advanced cervical cancers that removes the whole uterus with bilateral parametria and cardinal ligaments from the pelvic cavity. In Japan, this surgical therapy has been applied to FIGO Stage I and II cervical cancer patients. Since patients with FIGO Stage IIIb cervical cancers show cancer propagation to the pelvic side walls through either the parametrium or the cardinal ligament, radical hysterectomy cannot be primarily applied to these cases. If radical hysterectomy is excessively performed in Stage IIIb patients, cancer cells in the parametria or cardinal ligaments can spread into the retroperitoneal space, and lethal massive bleeding can result in the operative fields. In order to perform radical surgery for Stage IIIb patients, these patients must undergo certain preoperative treatments to change Stage IIIb tumors into resectable tumors as small as those found in most Stage IIb lesions.

Advanced cervical cancer patients whose primary tumors cannot be completely removed by radical hysterectomy have usually been treated with primary chemotherapy or radiotherapy. Radiotherapy alone may not be radical enough for advanced cancer patients with extrauterine micrometastatic lesions because radiotherapy is a local therapy. Since Stage IIIb cervical cancer patients usually have more than 4 cm in diameter of bulky tumor, such a large tumor is very difficult to be radically cured by radiotherapy alone [1-4]. It is also very difficult to kill the bulky cervical tumor cells completely using chemotherapy alone due to severe intolerable adverse effects of anticancer drugs because more than 4 cm in diameter of bulky cervical tumor needs much larger amounts of anticancer drugs, to be cured by chemotherapy alone. Therefore, to treat Stage IIIb bulky cervical tumors with cancer extension to the pelvic side walls by radical hysterectomy, preoperative chemotherapy or radiotherapy must be used to eradicate cancer cells that have extended to the pelvic side walls from the uterus. In this study, we investigated whether preoperative chemotherapy for Stage IIIb advanced squamous cell carcinoma (SCC) patients could reduce the primary lesion to a significant resectable size to be radically removed.

In order to completely remove the primary lesion in Stage IIIb cervical cancers by radical surgery, preoperative therapy must remarkably reduce cancer extended lesions to the pelvic side walls in the parametria and cardinal ligaments within a short time. Our recent clinical experience to treat advanced cervical cancer patients with irinotecan HCl (CPT-11)-combined chemotherapy revealed remarkable tumor-reduction effects in cervical SCC patients within one to two months. Therefore, in this study, we investigated chemotherapeutic effects on increasing resectability rate using preoperative CPT-11-combined chemotherapy for unresectable locally advanced Stage IIIb cervical SCC patients.

Patients and methods

All the patients in this study were treated in the University Hospital. From January 2000 to December 2004, 11 patients with bulky Stage IIIb cervical SCC tumors agreed with informed consents to participate in the present pilot study to receive preoperative CPT-11-combined chemotherapy. One

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patient had one course of chemotherapy, eight patients had two courses and two patients had three courses (Table 1). Age of patients ranged from 33 to 72 years old (mean age: 51 years old). Diagnosis of FIGO Stage IIIb was done by magnetic resonance (MR) analysis and gynecologic pelvic examinations performed by two gynecologists. All patients treated with the present regimens showed apparent cancer invasion to unilateral or bilateral pelvic side walls that could not be removed by primary radical hysterectomy. Chemotherapy was stopped when primary tumors were diagnosed as resectable lesions by both gynecologic examinations and MR findings within three courses of chemotherapy.

Chemotherapy with CPT-11 and cisplatin (CDDP) (CPT-11/CDDP) was performed according to the same regimen as that reported by Sugiyama *et al.* [5]. Briefly, an intravenous infusion of CPT-11 (60 mg/m^2 over 90 min) was given on days 1, 8 and 15. After completion of CPT-11 infusion on day 1, CDDP (60 mg/m^2 over 120 min) was administered intravenously. This treatment schedule was repeated every four weeks. Chemotherapy with CPT-11 and mitomycin C (MMC) (CPT-11/MMC) was performed according to the same regimen as that reported by Umesaki *et al.* [6]. Briefly, an intravenous infusion of CPT-11 (100 mg/m^2 over 90 min) was given on days 1, 8 and 15. After completion of CPT-11 infusion on day 1, MMC (10 mg/m^2) was administered as an intravenous bolus. This treatment schedule was also repeated every four weeks.

Criteria for assessment of tumor response were as follows: partial response (PR) was defined as > 50% reduction in the sum of the length x width product of cervical lesions before surgery. Whether the primary tumor could be resected by radical hysterectomy or not was determined following MR findings and gynecologic pelvic examinations by the two gynecologic oncologists (two authors). When the primary tumor was diagnosed as an unresectable cervical tumor with extrauterine extensions even after three courses of chemotherapy, radiotherapy was performed. In this study, all radical surgeries were done by an experienced gynecologic oncologist.

Results

Experimental results for all 11 patients are summarized in Table 1. Chemotherapy with CPT-11/MMC was performed in ten out of 11 Stage IIIb patients and chemotherapy with CPT-11/CDDP was performed in the remaining patient. Cervical cancer lesions reduced in size following chemotherapy and tumor response to chemotherapy was defined as PR in all 11 patients, indicating a 100% efficiency rate. All ten patients treated with CPT-11/MMC showed remarkable reductions of extrauterine cancer invasions that were diagnosed by pelvic examinations and MR studies, and they could undergo radical hysterectomy. Therefore, standard radical hysterectomy that is usually applicable to Stage I and II cervical cancer patients was successfully performed in all ten patients treated with CPT-11/MMC. However, radical hysterectomy was not applied to patient 11 who had been treated with CPT-11/ CDDP because unilateral obstruction of the ureter had progressed during chemotherapy even though the primary cervical lesion was reduced showing PR efficiency (68% reduction). This patient was treated with radical radiotherapy after three courses of chemotherapy. In the present study, no patient had their preoperative chemotherapy treatment interrupted due to severe adverse effects of anticancer drugs.

Table 1. — *Results of preoperative chemotherapy with CPT-11 for FIGO Stage IIIb cervical squamous cell carcinoma patients.*

Patient	Age	Histology*	Stage	Chemotherapy	Course	Cervical lesion**	Surgery***
1	39	SCC	IIIb	CPT-11/MMC	1	PR	RTH
2	53	SCC	IIIb	CPT-11/MMC	2	PR	RTH
3	69	SCC	IIIb	CPT-11/MMC	2	PR	RTH
4	53	SCC	IIIb	CPT-11/MMC	2	PR	RTH
5	42	SCC	IIIb	CPT-11/MMC	3	PR	RTH
6	63	SCC	IIIb	CPT-11/MMC	2	PR	RTH
7	51	SCC	IIIb	CPT-11/MMC	2	PR	RTH
8	72	SCC	IIIb	CPT-11/MMC	2	PR	RTH
9	33	SCC	IIIb	CPT-11/MMC	2	PR	RTH
10	44	SCC	IIIb	CPT-11/MMC	2	PR	RTH
11	42	SCC	IIIb	CPT-11/CDDP	3	PR	not done

*SCC: squamous cell carcinoma; **PR: partial remission; ***RTH: radical total hysterectomy and pelvic lymphadenectomy.

Discussion

The present pilot study showed that CPT-11-combined chemotherapy for 11 Stage IIIb cervical SCC patients had a 100% partial response (PR) on cervical tumor reduction. However, one patient could not undergo radical hysterectomy after chemotherapy even though cervical tumor reduction was evaluated as PR (68% reduction). This patient was preoperatively treated with three courses of CPT-11/CDDP without any delay but extrauterine cancer cells progressed during chemotherapy resulting in unilateral obstruction of the ureter and mild hydronephrotic changes. Therefore, retroperitoneal invasive cancer lesions of this patient were evaluated as unresectable tumors by radical hysterectomy. In conclusion, radical hysterectomy could be completed in ten out of 11 (91%) Stage IIIb cervical SCC patients because preoperative chemotherapy could markedly reduce cancer propagation in the parametria and cardinal ligaments to resectable lesion sizes. These results indicate that CPT-11-combined chemotherapy might be a recommended preoperative therapy for Stage IIIb cervical SCC patients who cannot receive primary radical hysterectomy.

In the present pilot study we performed either of two treatment regimens for preoperative CPT-11-combined chemotherapy. CPT-11/MMC chemotherapy was used in ten out of 11 patients with Stage IIIb cervical SCC, and CPT-11/CDDP chemotherapy was used in only one patient. We cannot determine which regimen is better as preoperative chemotherapy from this pilot study alone. Actually, patient 11 who was treated with CPT-11/CDDP was the first patient in this pilot study, and she could not undergo radical surgery. Therefore, the other patients were treated with CPT-11/MMC. CPT-11/MMC results in much lower degrees of subjective adverse effects such as nausea and vomiting compared with CPT-11/CDDP. The CPT-11/MMC regimen does not need hydration and can be easily applied to outpatients because of a short time infusion therapy. Therefore, patients in this study

preferred CPT-11/MMC treatment. Radical hysterectomy was performed after chemotherapy in all ten patients treated with CPT-11/MMC. In conclusion, pre-operative chemotherapy with CPT-11/MMC can be used as a recommended treatment for Stage IIIb locally advanced cervical SCC lesions that are unresectable by radical hysterectomy due to extrauterine cancer invasions.

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