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FULL PAPER

Concurrent weekly cisplatin *versus* triweekly cisplatin with radiotherapy for locally advanced squamous-cell carcinoma of the cervix: a retrospective analysis from a single institution

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Objective: To compare patients with cervical cancer who were primarily treated with concurrent chemoradiotherapy (CCRT) using 20 mg m⁻² CDDP for 5 days every 3 weeks with weekly regimens of 40 mg m⁻².

Methods: We retrospectively analyzed 185 patients with Stage IB–IVA squamous-cell carcinoma of the cervix who were treated with CCRT between 2005 and 2013 at our hospital. The CCRT regimen consisted of cisplatin (CDDP) at 20 mg m⁻² for 5 days every 3 weeks or 40 mg m⁻² weekly, administered concomitantly with RT.

Results: The median age was 50 years (range: 22–70 years) in the triweekly group and was 50.5 years (range: 28–70 years) in the weekly group. The 5-year overall survival rate in the triweekly and weekly groups

were 82.0% and 83.3%, respectively ($p = 0.851$); their disease-free survival rate was 79.6% and 78.1%, respectively ($p = 0.672$). In the triweekly group, 56 patients (50.9%) had grade 3/4 leukopenia, which was significantly higher than that of 11 patients (15%) in the weekly group ($p < 0.0001$).

Conclusion: The weekly CDDP regimen for CCRT seems better in patients with International Federation of Gynecology and Obstetrics Stages IB–IVA squamous-cell carcinoma of the cervix.

Advances in knowledge: The weekly CDDP regimen for CCRT seems better in patients with International Federation of Gynecology and Obstetrics Stages IB–IVA squamous-cell carcinoma of the cervix.

INTRODUCTION

The National Cancer Institute released a clinical alert¹ and reported higher survival rates after concurrent chemoradiotherapy (CCRT) for locally advanced cervical cancer at different stages from the International Federation of Gynecology and Obstetrics (FIGO) Stage IB1 with a relatively good prognosis to Stage IVA with poor prognosis. CCRT has proven effective in the definitive treatment of more advanced-stage diseases.^{2–6}

Regarding a sensitizing agent for CCRT, cisplatin (CDDP) at a dose of 40 mg m⁻² weekly is used globally as a standard regimen.^{2–6} In Japan, a Japanese Gynecologic Oncology Group (JGOG) 1066 Phase II trial of CCRT using a high-dose-rate intracavitary brachytherapy (HDR-ICBT) with CDDP at a dose of 40 mg m⁻² weekly achieved equivalent outcomes to those by global

radiotherapy (RT) dose schedules (cumulative linear quadratic equivalent dose, 85 Gy), although with a lower incidence of late toxicity.⁷ Although CDDP-based CCRT for locally advanced cervical cancer is accepted as the standard treatment, optimal treatment plan is yet to be established.

In the present study, we retrospectively analyzed data of patients with FIGO Stages IB–IVA carcinoma of the uterine cervix who were primarily treated with CCRT between 2005 and 2013 at University of the Ryukyus Hospital. CCRT using 20 mg m⁻² CDDP for 5 days every 3 weeks^{8,9} was a routine regimen until 2009. Thereafter, we changed the administration schedule of CDDP to weekly regimens of 40 mg m⁻² according to the JGOG 1066 protocol.⁷ We analyzed the efficacy of CCRT for squamous-cell carcinoma of the cervix. The present

retrospective study with a small series of patients might provide useful information for future appropriate treatment strategies.

METHODS AND MATERIALS

We retrospectively analyzed 185 patients with Stages IB–IVA squamous-cell carcinoma of the cervix who were treated with CCRT between 2005 and 2013 at our hospital. None of the patients had received prior treatment. All patients provided written informed consent. Patient charts were reviewed for clinicopathological data. This retrospective study was approved by the institutional review board of our university on 1 September 2016 (#989).

RT was performed as described in a previous study.¹⁰ All patients were treated with anteroposterior and posteroanterior parallel-opposed ports, or with the four-field technique of whole-pelvic (WP) external beam RT (EBRT). A 50-Gy dose of WP-EBRT was delivered in 25 fractions. A centre shield (4-cm wide at the midline) was used in some patients after delivery of the 40-Gy dose. HDR-ICBT was delivered once per week at a fractional dose of 6 Gy which was given one to three times at Point A for a total dose of 6–18 Gy. Boost EBRT doses of 6–20 Gy in one to four fractions were applied to the pelvic walls and/or nodal metastases (≥ 10 mm in a short-axis diameter) for patients with

nodular parametrial involvement. The CCRT regimen consisted of CDDP at $20 \text{ mg m}^{-2} \text{ day}^{-1}$ for 5 days triweekly^{9,10} or 40 mg m^{-2} weekly,⁷ administered concomitantly with RT. The Common Terminology Criteria for Adverse Events v. 4.0 and Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer criteria were used for the grading of acute and late toxicities, respectively. Follow-up examinations were performed every month for the first year, every other month for the second year and then every 3–6 months. The survival curves were estimated by Kaplan–Meier method, and the differences were assessed using the log-rank test; a p -value of <0.05 was considered significant.

RESULTS

Patient characteristics are shown in Table 1. In this retrospective analysis, 185 patients were treated with CCRT in which the triweekly CDDP regimen was used for 110 patients and weekly CDDP regimen for 75 patients. The median follow-up period was 68 months (range: 5–135 months) for the triweekly group and was 36 months (range: 2–88 months) for the weekly group. The median age was 50 years (range: 22–70 years) in the triweekly group and was 50.5 years (range: 28–70 years) in the weekly group. The median total CDDP dose was 200 mg m^{-2} (range: $100\text{--}300 \text{ mg m}^{-2}$) in the triweekly group and was 200 mg m^{-2} (range: $80\text{--}280 \text{ mg m}^{-2}$) in the weekly group

Table 1. Patient characteristics

Clinicopathological variable	Triweekly ($n = 110$)	Weekly ($n = 75$)	p -value
Median age (range) (years)	50 (22–70)	50.5 (28–70)	0.274
FIGO stage			
IB1	5	11	0.550
IB2	22	13	
IIA	7	7	
IIB	44	22	
III	29	21	
IVA	3	1	
Median tumour size (range) (mm)	50 (22–90)	49 (20–113)	0.320
Pelvic lymph node enlargement			
0	64	41	0.445
1	23	21	
2	16	9	
≥ 3	2	4	
ND	5	0	
Median pre-treatment Hb (g dl^{-1})	11.9 (4.2–14.8)	11.5 (4.2–15.7)	0.579
Median pre-treatment SCC (ng ml^{-1})	4.4 (0.8–283)	5.6 (0.7–51.8)	0.97
Median total CDDP dose (mg m^{-2})	200 (100–300)	200 (80–280)	0.129
Median course of chemotherapy (courses)	2 (1–5)	5 (4–6)	NA
Median overall treatment time (days)	48 (37–68)	51 (45–67)	0.135
Median follow-up period (months)	68 (5–135)	36 (2–88)	<0.0001

CDDP, cisplatin; FIGO, the International Federation of Gynecology and Obstetrics; Hb, haemoglobin; SCC, squamous cell carcinoma antigen; NA, not applicable.

($p = 0.129$). The median course of triweekly CDDP was two courses (range, 1–5 courses); the median course of weekly CDDP was five courses (range, 4–6 courses); and the median overall treatment time, including HDR-ICBT and boost EBRT, was 48 days (range, 37–68 days) in the triweekly group and 51 days (range, 45–67 days) in the weekly group, respectively ($p = 0.135$). No significant differences were observed in dose intensity of chemotherapy and the overall treatment time of radiation therapy. No statistically significant differences were observed in the distribution of FIGO staging classification, pre-treatment haemoglobin level, tumour size, lymph node status and serum squamous cell carcinoma antigen level.

The 5-year overall survival (OS) rate in the triweekly and weekly groups were 82.0% and 83.3%, respectively ($p = 0.851$) (Figure 1); their disease-free survival (DFS) rate was 79.6% and 78.1%, respectively ($p = 0.672$) (Figure 2). The 5-year local DFS rates in the triweekly and weekly groups were 88.5% and 87.0%, respectively ($p = 0.782$), and the distant DFS rates were 83.9% and 84.1% ($p = 0.938$). Regarding recurrence, 24 patients (21.8%) in the triweekly group and 16 patients (21.3%) in the weekly group developed recurrence (Table 2). A total of 15 of the 110 patients in the triweekly group and 9 of the 75 patients in the weekly group experienced locoregional recurrence. A total of 19 patients in the triweekly group and 11 patients in the weekly group experienced distant recurrence. No significant difference was observed in the distribution of the site of recurrence between the groups.

Adverse events of CCRT in each group are described in Table 3. In the triweekly group, 56 patients (50.9%) had grade 3/4 leucopenia, which was significantly higher than that of 11 patients (15%) in the weekly group ($p < 0.0001$). There was no significant difference in other haematologic adverse effects. In non-haematologic adverse events, grade 3/4 nausea/vomiting and diarrhoea were observed in 13 (11.8%) and 16 (14.5%) patients in the triweekly group, respectively while in only 2 (2.6%) and 3 (4%) patients in the weekly group, respectively, and those were significant ($p = 0.028$ and 0.025 , respectively). In terms of late

adverse events (Table 4), one patient (0.9%) suffered from grade 4 radiation enterocolitis with required intestinal surgery, and two patients experienced bone fracture (pubic bone and lumbar vertebra) both in the triweekly group on the basis of toxicity criteria of Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer. Grade 2 radiation enterocolitis was observed in six patients (the triweekly group) and three patients (the weekly group), respectively. Grade 2 radiation cystitis was seen in two patients only in the triweekly group. No death due to toxicities occurred during the study period.

DISCUSSION

Our retrospective study demonstrates that there is no significant survival difference, including OS, DFS, local DFS and distant DFS, among patients treated with CCRT using 20 mg m^{-2} CDDP for 5 days every 3 weeks and CCRT using 40 mg m^{-2} CDDP weekly. Although the CDDP dose intensity and overall treatment time are important in CCRT for cervical cancer, no significant difference was observed in CDDP dose intensity and overall treatment time.¹¹ However, acute adverse events, namely grade 3/4 leucopenia, nausea/vomiting, and diarrhoea were significantly higher in the triweekly group. The weekly CDDP regimen for CCRT seems better in patients with FIGO Stage IB–IVA squamous-cell carcinoma of the cervix in our institutions.

So far, several clinical trials have investigated alternative CDDP dose and dosing schedules to weekly CDDP-based chemoradiation. Einstein et al¹² reported in their retrospective study that the weekly group had a 3.43 times higher risk of developing acute toxicities than the 5-day group in advanced-stage patients with a significantly shorter 3-year progression-free survival (PFS). Regarding acute toxicity, they mentioned that most of the early toxicities seen in weekly patients were gastrointestinal-related. Significant gastrointestinal-related toxicity in the triweekly group may have been masked by the use of inpatient intravenous fluids and intravenous antiemetic medications.

Figure 1. The 5-year overall survival rate in the triweekly and weekly groups were 82.0% and 83.3%, respectively ($p = 0.851$). CDDP, cisplatin.

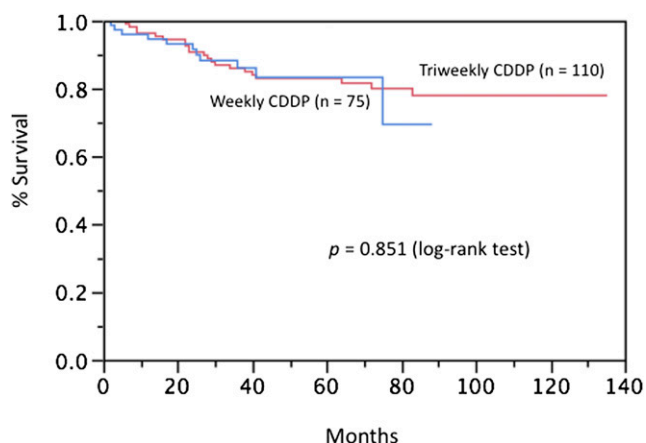


Figure 2. The 5-year disease-free survival (DFS) rate in the triweekly and weekly groups were 79.6% and 78.1%, respectively ($p = 0.672$). CDDP, cisplatin.

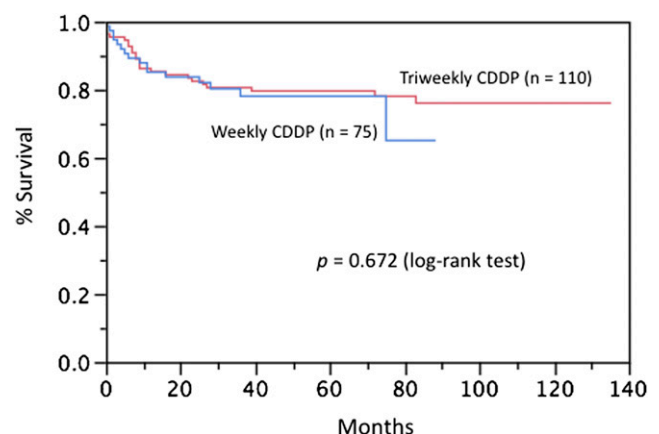


Table 2. Site of recurrence

Site of recurrence	Triweekly (<i>n</i> = 110)	Weekly (<i>n</i> = 75)	<i>p</i> -value
Recurrence (total)	24 (21.8%)	16 (21.3%)	0.544
Locoregional	5 (20.8%)	5 (31.3%)	0.482
Distant	9 (37.5%)	7 (43.8%)	
Locoregional + distant	10 (41.7%)	4 (25.0%)	

In an open-label, randomized trial from the Republic of Korea,¹³ 104 patients with Stages IIB–IVA cervical cancer were randomly assigned to weekly (weekly CDDP 40 mg m⁻², six cycles) and triweekly (CDDP 75 mg m⁻² every 3 weeks, three cycles) chemotherapy arms during concurrent RT. This study postulated that higher peak concentration of CDDP is more critical in enhancing the synergy of chemoradiation than the weekly CDDP exposure. Also, the high peak concentration might effectively eliminate small clumps of micrometastases, which leads to decrease in local failure and distant metastasis, and thus, to improvement in survival. However, without appropriate pharmacokinetic analysis of peak CDDP levels in both CDDP doses, we cannot clarify that the observed difference is due to higher peak levels of serum CDDP concentration in triweekly administration. Furthermore, the advantages of chemotherapy may not be due to true sensitization but rather by inhibiting tumour repopulation during RT; it is therefore possible that shorter schedules may not require chemotherapy support.¹⁴ The Korean group study¹³ suggested that another explanation for this result is that the possible role of CDDP administration during brachytherapy enhances the chemoradiation effect. However, because the third cycle of chemotherapy was delivered on average 10 days before brachytherapy in that study, there was no way of deducing what proportion of the CDDP acted as a radiosensitizer during brachytherapy. Based on the result of the trial, Triweekly Cisplatin-Based Chemoradiation in Locally Advanced Cervical Cancer Phase III randomized clinical trial is ongoing by the Korean Gynecologic Oncology Group.¹⁵

A randomized Phase 3 trial comparing two CDDP dose schedules (CDDP, 20 mg m⁻² per day, on Days 1–5 every 21 days, and CDDP, 40 mg m⁻² per day weekly) concluded that the 21-day CDDP regimen was superior regarding local efficacy and less toxic than the weekly chemotherapy regimen.¹⁶ Owing to the

acute toxicity, the proposed CDDP dose was delivered only in 79% of the patients from the triweekly CDDP and in 70% of the patients from the weekly CDDP groups. This underdose in weekly CDDP can be one of the causes of the better results obtained by the triweekly CDDP regimen. However, nodal status was included neither in the randomization criteria nor in the results evaluation. Another limitation of the study is the inclusion of surgery in the therapeutic protocol, deciding optionally on surgery after pre-operative CCRT. These above-mentioned reports recommend triweekly CDDP regimen of CCRT for cervical cancer.

Meanwhile, a randomized clinical trial comparing three monthly cycles of fluorouracil (1000 mg m⁻² day⁻¹ intravenously) plus CDDP (20 mg m⁻² day⁻¹ intravenously) for 5 days with six cycles of weekly CDDP (30 mg m⁻² intravenously) for CCRT showed that CCRT by weekly CDDP improves compliance with treatment and reduces acute haematological adverse effects without spoiling response and survival rates.¹⁷ An analysis of seven studies between 1995 and 2011¹⁸ and a meta-analysis of five randomized controlled trials between 1995 and 2015 to compare weekly and triweekly CDDP combined RT,¹⁹ established that weekly CDDP has a lower risk of haematological toxicity than triweekly CDDP with concurrent RT in the treatment of cervical cancer with no differences in PFS and OS. Clinicians and patients may choose either weekly CDDP or triweekly CDDP combined RT for cervical cancer.

Furthermore, a retrospective analysis comparing CCRT with weekly CDDP with CCRT with monthly CDDP and 5-fluorouracil for two cycles followed by additional consolidation chemotherapy for two cycles with the same regimen²⁰ showed that there were no statistically significant differences in PFS and OS. They also found that both regimens seemed to have similar

Table 3. Acute adverse events

Adverse event	Triweekly (<i>n</i> = 110)		Weekly (<i>n</i> = 75)		<i>p</i> -value
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	
Leukocytopenia	25	56	15	11	<0.0001
Anaemia	50	8	29	6	0.533
Thrombocytopenia	29	13	5	3	0.052
Nausea/vomiting	57	13	15	2	0.028
Diarrhoea	51	16	26	3	0.025
Radiation dermatitis	3	1	6	1	0.648

Table 4. Late adverse events

Organ tissue	Triweekly (n = 110)		Weekly (n = 75)	
	Grade 3	Grade 4	Grade 3	Grade 4
Small/large intestine	4	1	3	0
Bladder	2	0	0	0
Bone	0	2	0	0

efficacy for patients with locally advanced cervical cancer, but the weekly CDDP was better tolerated. Sonoda et al,²¹ through their retrospective study, also demonstrated that CCRT with both triweekly and weekly CDDP appeared to have similar efficacy for cervical cancer patients, but the toxicities were better tolerated with weekly CCRT. The results from these later four reports are consistent with our analysis.

One of the limitations of our study is that the retrospective nature of the study is inevitable, which can be affected by recall bias and difficulties with data abstraction from charts. The other limitation is that only patients with squamous-cell carcinoma were analyzed in our study, which might affect our results because patients with both squamous-cell carcinoma and adenocarcinoma were investigated in the other reports. Actually, the Gynecologic Oncology Group (GOG) 120 study demonstrates that weekly CDDP at 40 mg m⁻² is equally effective and less toxic than CDDP and 5-fluorouracil regimens.² However, data from previous Phase I trials did not lead to the choice of weekly CDDP 40 mg m⁻² for Phase III CCRT trials, and the maximum tolerated dose of weekly CDDP during CCRT has not been determined.

Thus, which regimen is better for CCRT in cervical cancer patients remains controversial. However, a recent meta-analysis²² showed that for locally advanced cervical cancer, CCRT with platinum-based doublet regimen contributed to improvements of prognosis, compared with CCRT with weekly CDDP. Therefore, because platinum-based combination therapy should be the preferred treatment over weekly CDDP during CCRT for Stage IB–IVA cervical cancer, we need to develop CCRT with new regimens, such as paclitaxel and CDDP.^{23,24} Furthermore, CDDP and radiation therapy with or without carboplatin and paclitaxel in patients with locally advanced cervical cancer trial²⁵ and induction chemotherapy plus chemoradiation as first-line treatment for locally advanced cervical cancer trial²⁶ are ongoing. We should consider the additional systemic chemotherapy to CCRT. We believe that a well-designed prospective, randomized trial is necessary to develop a novel CCRT strategy for locally advanced cervical cancer.

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