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ORIGINAL ARTICLE

Phase II study of a new multidisciplinary therapy using once every 3 week carboplatin plus dose-dense weekly paclitaxel before and after radical hysterectomy for locally advanced cervical cancer

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Abstract

Background We proposed a novel treatment strategy, consisting of triweekly cisplatin plus dose-dense weekly paclitaxel before and after radical hysterectomy without adjuvant radiation therapy to treat locally advanced cervical cancer. However, cisplatin-related severe non-hematologic toxicities were frequent during this strategy. This study aimed to assess the applicability of replacing cisplatin with carboplatin in our proposed strategy.

Methods Women with International Federation of Gynecology and Obstetrics (FIGO) 2008 stage IB2, IIA2, or IIB cervical cancer received three cycles of carboplatin (based on an area under the curve of six), each 21 days apart, starting on day 1, and 80 mg/m^2 of paclitaxel on days 1, 8, and 15 of each 21-day cycle before undergoing radical hysterectomy. Patients with one or more high-risk factors, including lymph vascular invasion, parametrial invasion, lymph-node metastasis, or positive margins, received three additional cycles of chemotherapy after hysterectomy. Concurrent chemoradiation therapy was only applied to those patients who failed to respond to neoadjuvant chemotherapy.

Results Between September 2014 and July 2016, 50 women (13 women with FIGO stage IB2, 5 with stage IIA2, and 32 with stage IIB) were enrolled in this study. The overall response rate to chemotherapy was 92%, including 22% with pathological complete response. Forty-nine women (98%) completed the planned radical hysterectomy, and 11 (22%) women with one or more high-risk factors received three additional cycles of chemotherapy. Only four women (8%) received concurrent chemoradiation therapy after surgery. The 2- and 3-year progression-free survival rates were 88.0% and 83.8%, respectively, and the 2- and 3-year overall survival rates were 98.0% and 95.4%, respectively. Only two patients reported grade 3 or higher non-hematologic toxicities including grade 3 nausea in one patient and grade 3 liver dysfunction in one patient.

Conclusions Replacement the platinum agent resulted in equivalent efficacy, with reduced toxicity, in women with locally advanced cervical cancer. This strategy could considerably diminish the application of radiation therapy without reduced survival. A study to identify those patients who will benefit from this new multidisciplinary strategy is warranted.

Keywords Cervical cancer · Chemotherapy · Carboplatin · Dose-dense paclitaxel

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Introduction

Cervical cancer is the fourth most common cancer and the fourth leading cause of cancer-related mortality in women worldwide. Approximately 570,000 women were diagnosed to be cervical cancer, and 311,000 deaths from the disease occurred in 2018 [1]. Although the global introduction of HPV vaccination and HPV-based screening has potential to make cervical cancer a rare disease in the near future, it is still the major public health problem.

According to the National Comprehensive Cancer Network clinical guidelines, concurrent chemoradiation therapy (CCRT) is the primary treatment recommendation (category 1), followed by radical hysterectomy with pelvic lymphadenectomy (category 2b), for locally advanced cervical cancer. CCRT is exclusively recommended for stage IIB cervical cancer [2]. However, some patients, particularly young or middle-aged patients, desire to avoid ovarian dysfunction, vaginal stenosis, or secondary carcinogenesis induced by radiation therapy (RT). The treatment strategy without RT may be one of the attractive options for these patients if it does not hamper prognosis.

We previously reported the promising results of a phase II study, to evaluate a novel treatment strategy, without the use of RT, for locally advanced cervical cancer (SGSG-013 study) [3]. Our previous study reported the applicability of a novel treatment strategy, consisting of triweekly cisplatin (75 mg/m^2) plus weekly paclitaxel (80 mg/m^2) (dose-dense TP therapy), followed by radical hysterectomy and adjuvant dose-dense TP therapy. Among the 51 patients studied, the clinical response and pathological complete response rates were 94% and 28%, respectively, and the 2-year progression-free survival (PFS) and overall survival (OS) rates were 88.2% and 94.1%, respectively. Due to the high response and favorable survival rates, we considered this novel treatment without RT represent a potential alternative to standard therapy, which includes radical hysterectomy, followed by RT or CCRT. Verifying the comparable effectiveness of this strategy with those of RT and standard therapy may make this new therapy an attractive option among patients who desire the avoidance of RT-related complications.

However, our original dose-dense TP therapy regimen was frequently associated with cisplatin-related, grade 3, or higher non-hematologic toxicity, including nausea (12%), appetite loss (10%), and fatigue (6%) [3]. Additionally, most gynecologic oncologists are not familiar with dose-dense TP therapy, which represents an obstacle to the wide application of this therapy regimen in clinical practice. In contrast, carboplatin induces milder nephropathy, reduced nausea/vomiting, and lower neuropathy compared with cisplatin [4]. The JCOG0505 trial demonstrated the non-inferiority of carboplatin relative to cisplatin, when combined with paclitaxel, to treat patients with advanced or recurrent cervical cancer [5]. In addition, triweekly carboplatin, plus dose-dense weekly paclitaxel (dose-dense TC therapy), has been extensively used to treat patients with epithelial ovarian cancer.

Therefore, we attempted to conduct a subsequent phase II study, examining the replacement of cisplatin with carboplatin. This study aimed to evaluate whether the newer multidisciplinary strategy, using a dose-dense TC therapy both before and after radical hysterectomy, had equivalent efficacy and reduced toxicity compared with dose-sense TP therapy, for the treatment of women with locally advanced cervical cancer.

Patients and methods

Patients

Eligible patients included women aged 20 years or older who met the following criteria: (1) A histologically confirmed diagnosis of cancer of the uterine cervix. (2) International Federation of Gynecology and Obstetrics (FIGO) stage IB2, IIA2, or IIB, based on the FIGO staging system revised in 2008 [6]. FIGO staging was determined via gynecologic examination, using pelvic magnetic resonance imaging (MRI). Abdominal metastasis and para-aortic lymph-node metastasis were examined, using abdominal computed tomography (CT) or positron emission tomography (PET)-CT scans. Distant metastases were examined using chest X-ray, chest CT, or PET-CT images. (3) An Eastern Cooperative Oncology Group performance status of 0–2. (4) A life expectancy of 3 months or longer. (5) Adequate bone marrow and organ function (neutrophil count of at least 1500 cells/mm^3 or more, platelet count of at least 100,000/mm^3 or more, serum transaminase levels up to two times the upper limit of the normal range, total bilirubin of 1.5 mg/dL or less, and serum creatinine of 1.5 mg/dL or less). And (6) a normal electrocardiogram. Women with brain metastasis, severe peripheral neuropathy of grade 2 or higher, or active concomitant malignancy were excluded. Patients with serious concomitant medical illnesses, including uncontrolled infections or angina, were also ineligible.

Chemotherapy regimen

The treatment protocol included the intravenous (IV) carboplatin administration, at a dose based on an area under the curve (AUC) of 6 (in 250 mL of saline, infused over 1 h), on day 1, and the IV administration of 80 mg/m^2 of paclitaxel (in 250 mL of saline, infused over 1 h), on days 1, 8, and 15 of a 21-day cycle. The carboplatin dose was calculated

using Calvert's method, and the glomerular filtration rate was estimated using the Cockcroft and Gault formula [7, 8]. All patients were administered standard antiemetic and antiallergic therapy with palonosetron hydrochloride, dexamethasone, and antihistamine.

Patients were required to maintain a minimum neutrophil count of 1000 cells/mm^3 and a minimum platelet count of 75,000/mm^3 to receive subsequent therapy cycles. The patients were also required to maintain a minimum absolute neutrophil count of 500 cells/mm^3 and a minimum platelet count of 50,000/mm^3 to receive paclitaxel on days 8 and 15. Treatment delays were allowed for a maximum of 3 weeks. If indicated, the doses of carboplatin and paclitaxel were reduced as follows: carboplatin, AUC 5 (level 1) or AUC 4 (level 2); paclitaxel, 70 mg/m^2 (level 1) or 60 mg/m^2 (level 2). Both carboplatin and paclitaxel dose levels were reduced in response to febrile neutropenia or a treatment delay between 15 and 21 days associated with prolonged toxicity, excluding peripheral neuropathy. Only the carboplatin dose was reduced when grade 4 thrombocytopenia occurred. The paclitaxel dose was reduced when grade 2 or higher severe peripheral neuropathy occurred. The treatment protocol was discontinued in patients experiencing any of the following: (1) a delay of treatment longer than 21 days, due to any toxicity; (2) requiring a dose reduction greater than level 2, due to any toxicity; (3) grade 4 non-hematological toxicity; (4) disease progression; and (5) patient refusal.

Treatment plan

Chemotherapy was repeated for three cycles if no disease progression and no severe toxicities were observed. After three cycles of dose-dense TC therapy, we performed a type III radical hysterectomy under open laparotomy within 6 weeks of the final dose. The operability of each patient after dose-dense TC therapy was determined by individual physicians.

The application of adjuvant therapy was selected based on the presence or the absence of the gross residual tumor after surgery and pathological high-risk factors. Patients with the gross residual tumors underwent postoperative CCRT, using weekly cisplatin. Patients without residual tumors and one or more high-risk factors, including lymph vascular invasion, parametrial invasion, lymph-node metastasis, or positive margins, received three additional cycles of dose-dense TC therapy. Patients without residual tumors or any high-risk factors completed protocol therapy without adjuvant chemotherapy.

Patients who could not complete three cycles of neoadjuvant dose-dense TC therapy, due to disease progression or severe toxicity, immediately received a type III radical hysterectomy. Subsequently, the patient received postoperative CCRT, using weekly cisplatin, if the patient had one or more high-risk factors including lymph vascular invasion, parametrial invasion, lymph-node metastasis, or positive margins. Patients without any high-risk factors completed protocol therapy, without adjuvant chemotherapy, regardless of the implementation status of neoadjuvant chemotherapy (NACT). Patient deemed unsuitable for surgery received CCRT as soon as possible after the cessation of chemotherapy.

Patients who required CCRT received 50.4 Gy at 1.8 Gy per fraction, of external-beam radiation therapy for the entire pelvic field, using the four-field box technique. Concurrently, they received 5–6 cycles of concurrent chemotherapy, consisting of weekly cisplatin (40 mg/m^2).

Evaluation plan

The primary endpoint was the 2-year PFS rate. The secondary endpoints were the 2-year OS rate, the clinical response rate, the pathological complete response (pCR) rate, and the safety and completion rates of the therapy protocol. The incidence of chemotherapy-induced toxicity was calculated using a self-reported questionnaire and graded in accordance with the Common Terminology Criteria for Adverse Events, version 4.0. Tumors were measured with an MRI, performed every treatment cycle, before radical hysterectomy. After radical hysterectomy, the patients were monitored with CT, every 3 months, for 2 years, and every 6 months after 2 years. The response to chemotherapy was evaluated based on the Response Evaluation Criteria in Solid Tumors 1.1. PFS was defined as the time from patient registration to disease progression, death, from any cause, or last contact. OS was defined as the time from patient registration to death, from any cause, or last contact. The sample size was calculated in the same manner as was SGSG-013 study. The calculation was based on the assumption that a 2-year PFS of 85% was promising, whereas a rate of 70% indicated futility. Based on a one-sided alpha-level of 5% and a power of 90%, the enrollment of 47 patients was deemed as necessary. PFS and OS were estimated by the Kaplan–Meier method, using GraphPad Prism graphing and statistics software (version 7.0a; GraphPad Software, Inc., La Jolla, CA).

Ethics statement

The protocol was approved by the local ethics committee of each participating center before initiating clinical trial recruitment. All patients provided their written informed consent. To ensure safety, we decided to suspend this study if three or more patients experienced incomplete radical hysterectomy, among 20 registered patients. This study was registered in the University Medical Information Network Clinical Trials Registry, as No. 000015184 and

was conducted in accordance with the ethical principles described in the Declaration of Helsinki.

Results

Patient characteristics

Between September 2014 and July 2016, 50 women were enrolled in this study, and their characteristics are displayed in Table 1. The median age was 46 years (range 30–78 years). Forty-six patients (92%) were performance status (PS) 0, and four patients were PS 1. Thirteen women were FIGO stage IB2, five were stage IIA2, and 32 were stage IIB. Histological classifications included 37 patients with squamous cell carcinoma (SCC), ten patients with adenocarcinoma, two patients with adenosquamous carcinoma, and one patient with large-cell neuroendocrine carcinoma. Forty-two patients (84%) had tumors of 40 mm or larger tumor at the cervix, and eight patients (16%) had enlarged pelvic lymph node(s).

Table 1 Patient characteristics

Age (median (range))	46 (30–78)
PS	
0	46
1	4
FIGO stage	
IB2	13
IIA2	5
IIB	32
Histology	
SCC*	37
Adenocarcinoma	10
Adenosquamous	2
LCNEC**	1
Tumor size (mm)	
–29	1
30–39	7
40–49	21
50–59	14
60–69	6
70–	1
Enlarged pelvic lymph node	
Yes	8
No	42

**SCC* squamous cell carcinoma

***LCNEC* large-cell neuroendocrine carcinoma

Efficacy

The overall response rate of dose-dense TC therapy was 92% [95% confidence interval (CI): 81–97%], including 18 with complete response, 28 with partial response, three with stable disease, and one with progressive disease (Fig. 1). Table 2 shows the pathological findings for the specimens obtained from the 49 patients who underwent radical hysterectomy, including 22% with a pathological complete response (ten patients with squamous cell carcinoma and 1 patient with large-cell neuroendocrine carcinoma). Fourteen (29%), 8 (16%), and 5 (10%) patients presented with lymph vascular space invasion, parametrial invasion, and lymph-node metastasis, respectively. No patient was found to have a positive margin.

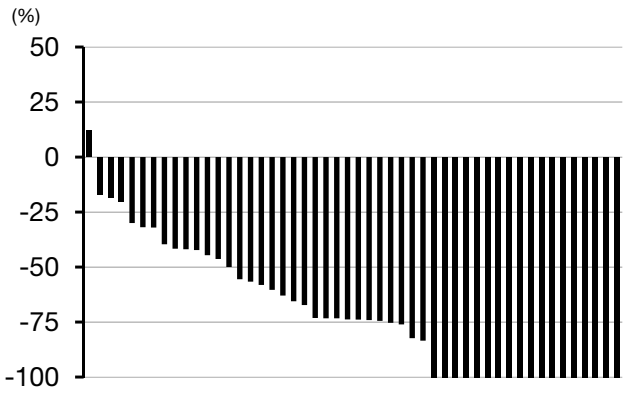

Fig. 1 Evaluation of tumor shrinkage rate by diameter

Table 2 Pathological findings of the specimens ($N=49$)

Residual tumor size (mm)	
0	11 (22%)
1–19	19 (39%)
20–39	12 (24%)
40–70	7 (14%)
Lymph vascular space invasion	
Positive	14 (29%)
Negative	35 (71%)
Parametrial invasion	
Positive	8 (16%)
Negative	41 (84%)
Lymph-node metastasis	
Positive	5 (10%)
Negative	44 (90%)
Margins	
Positive	0 (0%)
Negative	49 (100%)

Table 3 Patients without clinical response to neoadjuvant chemotherapy ($N=4$)

FIGO stage*	Histology	No. of chemotherapy	Clinical response	Surgery	High-risk factors				Adjuvant therapy	Survival
					LVI	Paramet	Stump	LN		
IB2	SCC	3	PD	Completed	+	+	−	−	CCRT	NED
IB2	SCC	3	SD	Incomplete	−	−	−	−	CCRT	NED
IIB	Adeno	1	SD	Completed	+	−	−	+	CCRT	NED
IIB	Adeno	2	SD	Completed	+	+	−	+	CCRT	NED

LVI lymph vascular invasion, *Paramet* parametrial invasion, *Stump* stump positive, *LN* lymph-node metastasis, *SCC* squamous cell carcinoma, *PD* progressive disease, *CCRT* concurrent chemoradiation therapy, *NED* no evidence of disease, *SD* stable disease, *Adeno*: adenocarcinoma

*FIGO staging system revised in 2008

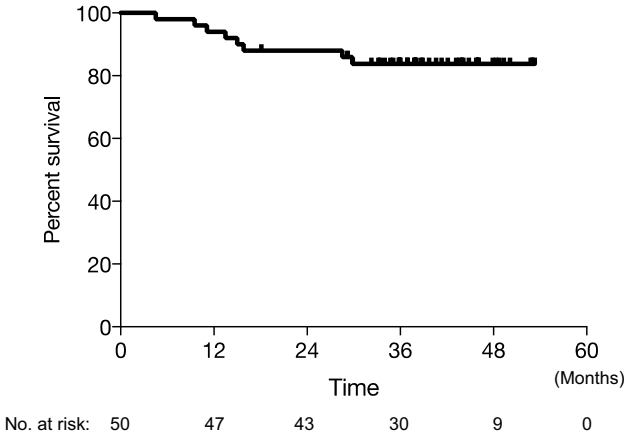

Fig. 2 Progression-free survival estimated by the Kaplan–Meier method

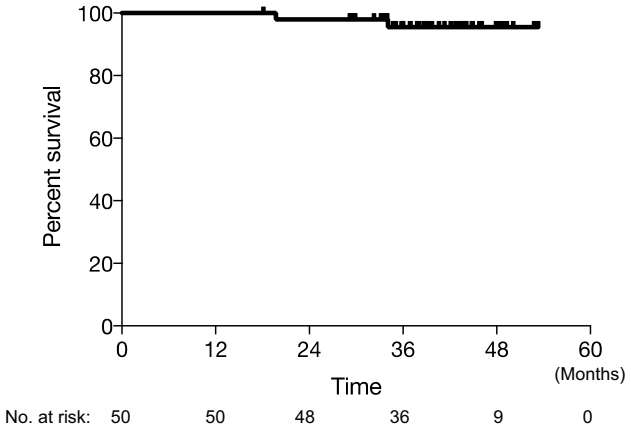

Fig. 3 Overall survival estimated by the Kaplan–Meier method

Three patients presented with stable disease and one presented disease progression following neoadjuvant dose-dense TC therapy. Table 3 displays the detailed clinical courses of these four patients. One patient with disease progression completed surgery, followed by the receipt of CCRT. One patient with stage IIA2 adenocarcinoma, whose clinical response to chemotherapy was stable disease, could not complete radical hysterectomy due to adhesion of the uterine cervix to the bladder wall. Subsequently, she received CCRT. The other two patients experienced grade 3 or 4 liver disfunction during cycles 1 or 2. Although their clinical responses were stable disease, they completed surgery and received CCRT after surgery. All four patients were alive, without recurrence, at the time of this writing.

For the median follow-up period of 39.0 months, the 2- and 3-year PFS rates were 88.0% (95% CI: 75.2–94.4%) and 83.8% (95% CI: 70.6%–91.6%), respectively (Fig. 2), and the 2- and 3-year OS rates were 98.0% (95% CI: 86.4–99.7%) and 95.4% (95% CI: 82.9–98.9%), respectively (Fig. 3).

Table 4 displays the pathological and clinical information of the eight patients who experienced recurrence. Seven patients were stage IIB, and four patients had adenocarcinoma. The effectiveness of chemotherapy in the eight patients with recurrence was evaluated; they displayed non-pathological complete response, and two displayed clinical complete response. The patients with high-risk factors were not necessarily the same patients who experienced recurrence. The site of recurrence was the lungs in four patients, the pelvic cavity in three patients, and the retroperitoneal lymph nodes in three patients. Four patients who recurred at the pelvic cavity and/or the retroperitoneal lymph nodes received RT as a secondary treatment. Among these four patients, one patient with high-risk factors (lymph vascular invasion and parametrial invasion), who received adjuvant chemotherapy, experienced recurrence at the bladder wall and pelvic lymph node. The recurrent tumors were responded to secondary RT; however, she eventually died with the disease progression after 10 months. The other 3 low-risk patients are alive without recurrence now.

Patient treatment flow

Figure 4 shows the patient treatment flow. Six women could not complete the three planned cycles of chemotherapy before surgery. The specific reasons for the

Table 4 Patients with recurrence ($N=8$)

FIGO stage*	Histology	Response clinical (pathological)	High-risk factors				Adjuvant therapy	Recurrence		Survival (months)
			LVI	Paramet	Stump	LN		Site	Period (months)	
IB2	Adeno	CR (non-pCR)	−	−	−	−	Not done	Lung	11	34 DOD
IIB	SCC	PR (non-pCR)	+	+	−	−	Chemo	Bladder wall/PLN	9	19 DOD
IIB	SCC	CR (non-pCR)	−	−	−	−	Not done	Lung	29	44 NED
IIB	SCC	PR (non-pCR)	−	−	−	−	Not done	Vaginal stump	4	43 NED
IIB	SCC	PR (non-pCR)	−	−	−	−	Not done	Bladder wall	13	33 NED
IIB	Adeno	PR (non-pCR)	−	−	−	−	Not done	Pln / pan	15	42 NED
IIB	Adeno	PR (non-pCR)	+	−	−	+	Chemo	Lung / pancreas	28	29 AWD
IIB	Adeno	PR (non-pCR)	+	+	−	+	Chemo	Lung / PAN	15	39 AWD

REC recurrence, *LVI* lymph vascular invasion, *Paramet* parametrial invasion, *Stump* stump positive, *LN* lymph-node metastasis, *Adeno* adenocarcinoma, *CR* complete response, *pCR* pathological complete response, *SCC* squamous cell carcinoma, *PR* partial response, *PLN* pelvic lymph node, *PAN* para-aortic lymph node, *DOD* dead of disease, *NED* no evidence of disease, *AWD* alive with disease

*FIGO staging system revised in 2008

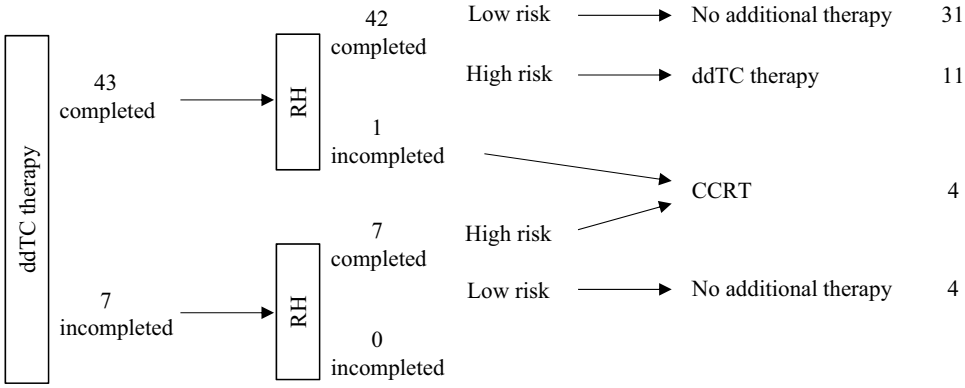

Fig. 4 Patient treatment flow. *ddTC therapy* dose-dense TC therapy, *RH* radical hysterectomy

discontinuation of pre-operative chemotherapy included anaphylactic reactions to carboplatin, in two patients, prolongation of grade 4 neutropenia, in two patients, and the prolongation of grade 3 or 4 liver dysfunction, in two patients. Forty-nine women (98%), including the six patients described above, completed the planned radical hysterectomy, with retroperitoneal pelvic lymph-node resection. No patient received extended surgery, including pelvic exenteration. As described above, one patient with stage IIA2 adenocarcinoma, whose clinical response to chemotherapy was stable disease, could not complete radical hysterectomy due to the adhesion of the uterine cervix to the bladder wall. No severe surgical morbidity and mortality was observed. Eleven patients (22%) with one or more high-risk factors received three additional cycles of dose-dense TC therapy after hysterectomy. All 11 patients who received adjuvant chemotherapy begun chemotherapy within 45 days of surgery. Another 35 patients (70%), without any high-risk factors, received no additional therapy. Only four women (8%), including one patient who could not complete radical hysterectomy and three patients with one or more high-risk factors, received CCRT after surgery.

Toxicity

Table 5 shows the hematological and non-hematological toxicities associated with treatment. Grade 3/4 neutropenia, anemia, and thrombocytopenia were observed in 58%, 24%, and 2% of patients, respectively. Although the predominant toxicity manifestation was neutropenia, only one patient (2%) experienced febrile neutropenia. Two patients (4%) received a red blood cell transfusion during chemotherapy, and no patients received a platelet transfusion. Grade 3/4 non-hematologic toxicities were rare. No treatment-related deaths were observed.

Table 5 Toxicity ($N=50$)

Hematologic	Grade			
	3	4	3/4	
Leucopenia	11	0	11 (22%)	
Anemia	11	1	12 (24%)	
Thrombocytopenia	1	0	1 (2%)	
Neutropenia	27	2	29 (58%)	
Febrile neutropenia	1	0	1 (2%)	
Non-hematologic	Grade			
	1	2	3	4
Vomiting	7	2	0	0
Nausea	24	8	1	0
Anorexia	25	8	0	0
Stomatitis	13	0	0	0
Peripheral neuropathy				
Motor	2	0	0	0
Sensory	26	2	0	0
Myalgia/arthritis	34	0	0	0
Rash	8	3	0	0
Fatigue	33	10	0	0
Allergic reaction	0	2	0	0
Liver dysfunction	19	2	1	0

(CTCAE ver. 4.0)

Discussion

Our new, multidisciplinary therapy, which consists of dose-dense TC therapy, both before and after radical hysterectomy, showed a favorable efficacy, with an acceptable toxicity, among women with locally advanced cervical cancer. The 2- and 3-year PFS rates were 88.0% and 83.8%, and the 2- and 3-year OS rates were 98.0% and 95.4%, respectively. These extremely positive survival rates were obtained without extensive adjuvant RT/CCRT. These results were comparable to the data obtained during the SGSG-013 study, in terms of efficacy, whereas severe non-hematologic toxicities were extremely rare in the present study [3]. Consequently, 46/50 (92%) patients completed the planned protocol therapy. Only four women (8%), including one woman who could not complete radical hysterectomy, received adjuvant CCRT (Fig. 4). Thus, the replacement of cisplatin with carboplatin was considered reasonable.

The dose-dense TC therapy showed an extremely high overall response rate of 92%, including clinical and pathological complete response rates of 36% and 22%, respectively. In contrast, the previous studies showed that the clinical and pathological complete response rates of various NACT regimens used to treat locally advanced cervical cancer ranged from 7.5% to 39% and 11% to 20%, respectively [9]. Consequently, although 14% (7/50) of the women were unable to complete all three planned NACT cycles, a remarkable 98% (49/50) of women completed radical hysterectomy in this study. Employing a highly effective chemotherapy regimen is extremely important for increasing the completion rate of radical hysterectomy and reducing the need for adjuvant RT/CCRT. The triweekly administration of paclitaxel and cisplatin has been considered to be the most effective regimen for metastatic cervical cancer [10]. However, dose-dense, weekly paclitaxel administration was superior, in terms of OS, when compared with triweekly paclitaxel administration, in phase III trials for breast and ovarian cancer [11, 12].

Although 14 patients (28%) with high-risk factors potentially required adjuvant CCRT, we were able to replace the role of adjuvant CCRT with adjuvant chemotherapy in 11 of 14 patients. Thus, we could reduce the number of patients who required adjuvant CCRT from 15 to 4, including one patient who could not complete radical hysterectomy. Among 11 high-risk patients, who had received adjuvant chemotherapy, only one patient experienced recurrence at the bladder wall and pelvic lymph node, and received secondary RT (Table 4). On the other hand, 3 of 35 patients without high-risk factor, who had regarded as out of indication for adjuvant therapy, encountered pelvic and/or retroperitoneal lymph nodes recurrence, and received RT.

A Japanese, single-institutional survey demonstrated that the combination of chemotherapy, using irinotecan and cisplatin, followed by radical hysterectomy and postoperative chemotherapy, without RT, achieved excellent survival among stage IB2 to IIB cervical cancer patients [13]. The 2- and 3-year PFS rates were 91.2% and 86.1%, respectively. This single-institutional retrospective study supports the efficacy and safety of the new treatment strategy that has been introduced by our study group.

Unfortunately, our study did not evaluate the quality of life (QOL) or long-term toxicity. Therefore, we could not make comparisons between CCRT and radical hysterectomy followed by RT/CCRT in terms of QOL or long-term toxicity. The use of RT/CCRT following radical pelvic surgery may even further compound the risks of treatment-related toxicities [14]. The avoidance of RT/CCRT is expected to reduce RT-related toxicity. Conversely, surgical treatment with radical hysterectomy may cause significantly increased perioperative morbidity, compared with definitive radical hysterectomy [15]. To strengthen the assurance of this new strategy, without RT, QOL and long-term RT-related toxicity assessments are essential in future studies. In addition, the continuous administration of dose-dense TC therapy to patients with stable disease or positive margin is controversial. All four patients with stable or progressive disease received CCRT after surgery, because they had high-risk factors (Table 3). At the time of this writing, all of these patients were alive, without recurrence. Although no patient with stable disease received adjuvant dose-dense TC therapy

in this study, patients with stable disease or positive margins may need to receive adjuvant CCRT instead of dose-dense TC therapy.

Recently, two large randomized-controlled trials (RCTs) demonstrated the inferiority, in terms of disease-free survival or PFS, of NACT followed by radical hysterectomy compared with CCRT, among patients with locally advanced cervical cancer [16, 17]. A single-institutional, RCT conducted in India, which compared the efficacy and toxicity of NACT followed by radical hysterectomy with those of CCRT, in 635 patients with IB2 to IIB squamous cervical cancer, revealed that NACT followed by radical hysterectomy was associated with an inferior 5-year disease-free survival (DFS) rate compared with CCRT [69.3% vs. 76.7% (hazard ratio, 1.38; 95% CI, 1.02–1.87; $p = 0.038$)] [16]. Similarly, the EORTC55994 trial also revealed the inferiority of NACT followed by radical hysterectomy in terms of the 5-year DFS [56.9% vs. 65.6% ($p = 0.021$)] in 626 women with stage IB2 to IIB cervical cancer [17]. Because the 2-year and 3-year DFS and OS rates were not reported in these two large RCTs, direct comparisons between these and the current study are impossible to perform. However, the 2-year PFS rate [88.0% (95% CI: 75.2–94.4%)] in the current study does not appear to be less than the 2-year DFS that can be extrapolated from the Kaplan–Meier curve among patients assigned to the CCRT arm of these two RCTs (approximately 85–90%). Characteristics of patients who were allocated to CCRT arm in Indian or EORTC55994 trial and patients who registered to the present study were almost similar, (e.g., median age: 48 vs. 47 vs. 46 years old, PS = 1: 7.6% vs. 12% vs. 8%, stage IIB: 57.7% vs. 57% vs. 64%, non-SCC: 0% vs. 15% vs. 26%, enlarged lymph nodes: 14.2% vs. not recorded vs. 16%, respectively).

Our treatment strategy represents a multidisciplinary therapy, using chemotherapy and radical hysterectomy, without RT/CCRT. This strategy differs from the traditional concept of NACT, which includes adjuvant RT/CCRT. In the current study, 92% of patients completed the scheduled therapy, consisting of chemotherapy and radical hysterectomy, without RT/CCRT. In contrast, in the Indian trial, among the 316 patients who assigned to the NACT arm, only 248 patients (78.5%) completed the scheduled NACT followed by radical hysterectomy therapy. Among these patients, 73 patients (29.4%) received adjuvant RT/CCRT. In the EORTC55994 trial, among 314 patients allocated to the NACT arm, only 240 patients (76.4%) completed NACT followed by radical hysterectomy. Among these patients, 60 patients (25.0%) received adjuvant RT/CCRT. Thus, only 55.3% and 57.3% of the participants in the Indian trial and the EORTC55994 trial, respectively, completed NACT followed by radical hysterectomy, without RT/CCRT.

According to the National Comprehensive Cancer Network clinical guidelines, CCRT is the primary treatment recommendation (category 1), followed by radical hysterectomy with pelvic lymphadenectomy (category 2b), for stage IB3 and IIA2 cervical cancer (FIGO 2018) [2]. For stage IIB cervical cancer, CCRT is exclusively recommended. Our treatment strategy may not exceed the standard therapy, in terms of efficacy. However, this strategy may be applicable among young women who desire the avoidance of RT-induced ovarian dysfunction, vaginal stenosis, or secondary carcinogenesis in the irradiated field. This treatment might be suitable for patients with non-SCC cervical carcinoma, which tends to resistant RT. Additionally, in the future, it may be applied to a strategy using NACT, followed by fertility-sparing surgery.

In conclusion, our newer multidisciplinary strategy using dose-dense TC therapy demonstrated equivalent efficacy and fewer toxicity events compared with dose-dense TP therapy, among women with locally advanced cervical cancers. This strategy could considerably diminish the applications of RT/CCRT, without reducing survival. A study should be performed to identify those patients who will benefit from our multidisciplinary strategy.

Author contributions SN designed and conducted the study, contributed to the analysis of data, and wrote the initial draft of the manuscript. SY, MS, TK, and JK contributed to the design and conducted the study. All authors have contributed to data collection and interpretation, and critically reviewed and revised the manuscript. All authors read and approved the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest None of the authors report a conflict of interest.

Ethical approval The protocol was approved by the local ethics committee of each participating center before initiating clinical trial recruitment. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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