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ORIGINAL ARTICLE

A randomized phase III clinical trial of weekly versus tri-weekly cisplatin-based chemoradiotherapy for locally advanced cervical cancer: results of the TACO (GCIG/KGOG 1027/THAI 2012) study

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Background: The standard treatment for locally advanced cervical cancer is cisplatin-based chemoradiotherapy; however, the optimal dose and dosing schedule of cisplatin remain debated. The aim of this study was to compare the clinical outcomes of weekly cisplatin at 40 mg/m^2 versus those of tri-weekly cisplatin at 75 mg/m^2 during radiation in patients with locally advanced cervical cancer.

Patients and methods: In this prospective, randomized clinical trial, we enrolled 314 patients with stage IIB-IVA cervical cancer, randomly assigning them in a 1 : 1 ratio into two arms. The weekly arm received a weekly dose of 40 mg/m^2 cisplatin for six cycles, whereas the tri-weekly arm received a tri-weekly dose of 75 mg/m^2 cisplatin for three cycles, both concurrently with radiotherapy. The primary endpoints included 3-year recurrence-free survival according to a superiority design, with $P < 0.05$ indicative of statistical significance. Overall survival, toxicity profiles, and quality of life (QOL) were also analyzed.

Results: Chemotherapy delay was more frequent in the weekly arm than in the tri-weekly arm ($P = 0.008$). However, the 3-year recurrence-free survival rate between the two arms did not significantly differ (78.7% in the weekly arm, 84.1% in the tri-weekly arm; hazard ratio 0.71, 95% confidence interval 0.39-1.32, $P = 0.28$). The pattern of recurrence did not differ significantly between the two arms. Grade 3 and 4 hematological toxicities occurred less frequently in the tri-weekly arm ($P < 0.001$). Furthermore, the tri-weekly arm had better QOL scores across several domains compared with the weekly arm.

Conclusion: In this study, tri-weekly cisplatin-based chemoradiotherapy was not statistically superior to a weekly schedule in terms of survival outcomes for patients with locally advanced cervical cancer. However, the tri-weekly

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regimen exhibited a more favorable toxicity profile and improved QOL compared with the weekly regimen. These results suggest tri-weekly cisplatin administration as a feasible alternative for chemoradiotherapy in cervical cancer.
Key words: cervical cancer, chemoradiotherapy, cisplatin, weekly, tri-weekly, quality of life

INTRODUCTION

Cervical cancer poses a substantial global health burden, with over 650 000 new cases diagnosed annually.[1] For patients presenting with locally advanced cervical cancer not amenable to surgical resection, concurrent chemoradiotherapy is the established standard of care. In the 1990s, a series of pivotal randomized clinical trials consistently demonstrated a survival advantage for concurrent chemoradiotherapy compared with radiotherapy alone despite heterogeneity in the cisplatin dose and dosing schedules.[2-6] The survival benefit of chemoradiotherapy led to an alert by the National Cancer Institute in 1999, recommending chemoradiotherapy for invasive cervical cancer.[7] In the aforementioned trials, two different cisplatin administration schedules were adopted: weekly cisplatin at 40 mg/m^2[2,4] and tri-weekly cisplatin at a dose range of 50-75 mg/m^2 combined with 5-fluorouracil (5-FU).[3-5] Because a subsequent study revealed that the addition of 5-FU to cisplatin did not confer a survival benefit but increased toxicity,[8] 5-FU was excluded from the standard chemoradiotherapy regimen. Therefore, two cisplatin regimens remained prominent: weekly cisplatin at a dose of 40 mg/m^2 and tri-weekly cisplatin at a dose of 75 mg/m^2. However, despite the absence of comparative phase III trials, weekly cisplatin-based concurrent chemoradiotherapy gradually gained acceptance as a standard in cervical cancer owing to its favorable toxicity profile.[9,10]

The tumor response to cisplatin is known to be increased as its peak concentration increases, suggesting a potential survival benefit with a higher cisplatin concentration during radiation compared with a lower cisplatin concentration.[11] However, a higher dose of cisplatin-based chemoradiotherapy (100 mg/m^2 every 3 weeks) yields a significantly increased occurrence of severe adverse events.[12,13] Consequently, comparative studies of weekly versus tri-weekly cisplatin during radiation were conducted to verify whether the weekly cisplatin can mitigate the high toxicity of the tri-weekly cisplatin for human cancers such as head and neck cancer (HNC).[12-15] Although the weekly regimen has several hypothetical advantages, such as ease of administration and enhanced radiosensitization, its survival benefit compared with the tri-weekly regimen remains unclear.[12,15] Extrapolation of the results of the comparative studies for other cancers directly to cervical cancer has at least two limitations: (i) the cisplatin dose of 100 mg/m^2 in tri-weekly regimens was higher than the usual dose of 50-75 mg/m^2 for cervical cancer, and (ii) the radiation field and depth of the target lesion in cervical cancer differ fundamentally from those in other cancers, leading to distinct toxicity profiles.

Currently, a couple of clinical trials in which weekly and tri-weekly regimens are being compared in cervical cancer are under way.[16,17] A meta-analysis revealed better survival outcomes and lower toxicity with tri-weekly cisplatin-based chemoradiotherapy compared with the weekly regimen.[16] However, the survival benefit of chemoradiotherapy stems from a complex interplay of various factors, including the toxicity profile, treatment compliance, and quality of life (QOL). Therefore, selection of the optimal cisplatin dose and dosing schedule should be determined based on a comprehensive evaluation of all these parameters in a well-controlled, randomized, phase III clinical trial.

In this study, we aimed to investigate whether differences in survival outcomes, toxicity profiles, and QOL exist between a weekly cisplatin regimen of 40 mg/m^2 (six cycles) and a tri-weekly regimen of 75 mg/m^2 (three cycles) administered concurrently with radiotherapy in patients with locally advanced cervical cancer.

PATIENTS AND METHODS

Eligibility criteria

From January 2012 to December 2019, a total of 314 patients with histologically confirmed stage IIB-IVA cervical cancer were enrolled in this trial. Patients were allocated in a 1 : 1 ratio to either the weekly arm (weekly cisplatin, 40 mg/m^2, six cycles) or the tri-weekly arm (cisplatin, 75 mg/m^2 every 3 weeks, three cycles), both administered concurrently with radiotherapy. Inclusion criteria were Eastern Cooperative Oncology Group performance status of 0-2 and adequate hematological function (absolute neutrophil count $>$1500/μl, platelet count $>$100 000/μl), kidney function [serum creatinine concentration $<$ upper limit of normal (ULN) or calculated creatinine clearance $>$60 ml/min], and hepatic function [total bilirubin concentration $<$1.5 $\times$ ULN, alkaline phosphatase and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $<$3 $\times$ ULN]. Patients were excluded if they had stage IVB disease with distant metastasis, rare tumor histology such as melanoma or metastatic cancers, a history of prior chemotherapy or radiotherapy, a history of other concurrent malignancies, known hypersensitivity to platinum agents, or serious medical comorbidities, or if they were pregnant.

Staging procedures

Disease staging was carried out according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system. Before randomization, the extent of disease was evaluated using chest X-ray radiography, intravenous pyelography, and abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI). Cystoscopy and colonoscopy were conducted as indicated based on clinical suspicion of bladder or rectal involvement. Tumor size was defined via clinical palpation under general anesthesia or as the largest diameter measured on pre-treatment CT or MRI scans. Distant metastasis was confirmed, whenever feasible, via fine needle aspiration biopsy or cytology. If

biopsy was not possible, a clinical diagnosis of distant metastasis was made based on enlarged lymph nodes (exceeding 1 cm in the short axis diameter) on a CT scan or positron emission tomography (PET)/CT scan.

Ethical considerations

This study was registered on ClinicalTrials.gov (NCT01561586) and approved by the institution's review board (K-1112-001-003). All patients were enrolled after providing written informed consent. This study was conducted according to good clinical practice guidelines, applicable laws and regulations, and principles laid down by the World Medical Assembly in the 1964 Declaration of Helsinki and its later amendments.

Treatment protocols

Patients in the weekly arm received cisplatin intravenously at a dose of 40 mg/m^2, diluted in 250 ml of 0.9% sodium chloride, administered over 1-2 h weekly for a total of six cycles, concurrent with radiotherapy. Patients in the tri-weekly arm received cisplatin intravenously at a dose of 75 mg/m^2, diluted in 250 ml of 0.9% sodium chloride, administered over 1-2 h every 3 weeks for a total of three cycles, concurrent with radiotherapy. Pre- and post-hydration were provided with at least 1000 ml of 0.9% sodium chloride administered intravenously before and after each cisplatin infusion in both arms.

External beam radiotherapy (EBRT) was delivered to the whole pelvis via a conformal four-field box technique by using 4-18 megavoltage X-rays. When central shields were utilized during EBRT, they typically measured 4 cm in width at the field isocenter. The planned total dose to the pelvic sidewall was 45.0-50.4 Gy, delivered in daily fractions of 1.8-2.0 Gy. For patients with bulky parametrial tumors or gross lymph node metastases, an additional boost of 5-10 Gy was applied, resulting in a total external dose of 55-60 Gy. Low dose rate intracavitary brachytherapy (ICBT) using a ^{137}Cs source was applied, and the prescribed dose to point A was 30-40 Gy in one to two fractions. For high dose rate (HDR) ICBT using a ^{192}Ir source, 6.5 Gy/fraction for three to five fractions was applied and the prescribed dose to point A was 22.5-26.0 Gy, depending on the EBRT dose and number of HDR insertions. The total equivalent dose in 2 Gy fractions equivalent dose in 2 Gy fractions to point A for HDR ICBT, combining EBRT and ICBT, was 82-85 Gy. The planned radiotherapy period was 56 days (up to 67 days was considered acceptable). Compliance with the treatment protocol (including the target definition, target dose, and organ at risk limits) was assessed via central radiotherapy review. Calibration of external radiotherapy beams was independently verified by the Radiation Quality Assurance Laboratory.

Compliance and toxicity assessment

Treatment compliance was assessed by comparing the percentage of completed chemotherapy cycles and the incidence of radiotherapy delays exceeding 1 week between the two treatment arms. Complete blood count and platelet counts were measured weekly in both weekly and tri-weekly arms; moreover, they were assessed twice weekly if the absolute neutrophil count or the platelet count were $<$500/μl and $<$50 000/μl, respectively. Serum creatinine, electrolyte, alkaline phosphatase, AST/ALT, and bilirubin levels were obtained at baseline before treatment initiation and subsequently assessed weekly in the weekly arm and tri-weekly in the tri-weekly arm during treatment. Hematological, gastrointestinal, kidney, endocrinological, inflammatory, and neurological toxicities were evaluated after each chemotherapy cycle by using the Gynecologic Oncology Group (GOG) Common Terminology Criteria for Adverse Events version 3.0.

Assessment of QOL

QOL assessment was carried out using the European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core questionnaire (QLQ-C30), which contains five functional scales (physical, cognitive, emotional, social, and role functioning), a global health status/QOL scale, three symptom scales (pain, fatigue, and nausea/vomiting), and six single items used to assess additional symptoms and perceived financial impact. The EORTC Cervical Cancer questionnaire (CX24) was used to evaluate specific symptoms occurring after radiotherapy and chemotherapy, and four items of the Functional Assessment of Chemotherapy/GOG—Neurotoxicity subscale (NTx) were used to assess the impact of any peripheral neuropathy.

Baseline measurements were completed before randomization to control for effects influencing patients before treatment. QOL was assessed during radiation, 3 and 7 weeks after the first day of treatment. A QOL assessment for long-term effects was carried out 9 months after the first day of treatment.

Follow-up

Patients underwent follow-up examinations every 3 months for the first 2 years and every 6 months for the subsequent 3 years. Follow-up assessments included a physical examination, tumor marker measurement, and a Pap smear. Chest X-ray, abdominopelvic CT or MRI, and PET or PET/CT scans (optional) were carried out annually. Disease recurrence was determined according to histological or radiological evidence of the presence of a tumor. Any suspicious lesion identified on a CT scan was followed up with repeat CT scans every 3 months until recurrence was clinically confirmed. In the event of recurrence, PET or PET/CT was carried out to identify other sites of disease, and all recurrence sites were meticulously documented.

Statistical considerations

This trial was designed as an open-label, randomized study with a 1 : 1 allocation ratio. Random assignment was computer-generated using a random permutation method with block sizes of 2, 4, and 6. Investigators were masked to the assignment of treatment groups, and sequentially numbered envelopes were used for random allocation. Categorical clinical characteristics at baseline were

Table 1. Clinical characteristics of patients

	Weekly (n = 152)	Tri-weekly (n = 140)	P value
Median follow-up (months)	49.0	50.0	—
Age (years)	55.8	53.9	0.20
Tumor size (mm)	49.9 ± 15.2	49.2 ± 14.0	0.73
Hemoglobin (g/l)	11.8 ± 1.4	11.8 ± 1.7	0.96
ECOG performance scale			0.55
0	129 (84.9%)	124 (88.6%)	—
1	17 (11.2%)	13 (9.3%)	—
2	3 (2.0%)	1 (0.7%)	—
Unknown	3 (2.0%)	2 (1.4%)	—
FIGO stage (2009)			0.84
IB_2	15 (9.8%)	16 (11.4%)	—
IIB	103 (67.8%)	96 (68.6%)	—
IIIB	28 (18.4%)	21 (15.0%)	—
IVA	6 (4.0%)	7 (5.0%)	—
Histology			0.11
Squamous	137 (90.1%)	114 (81.4%)	—
Adenocarcinoma	12 (7.9%)	20 (14.3%)	—
Adenosquamous	1 (0.7%)	2 (1.4%)	—
Others	2 (1.3%)	4 (2.9%)	—
Chemotherapy (cycles)			NA
0	5 (3.3%)	6 (4.3%)	—
1	3 (2.0%)	1 (0.7%)	—
2	0 (0.0%)	13 (9.3%)	—
3	5 (3.3%)	120 (85.7%)	—
4	5 (3.3%)	—	—
5	17 (11.2%)	—	—
6	117 (77.0%)	—	—
Completed chemotherapy	(≥4 cycles)	(≥2 cycles)	0.230
No	13 (8.6%)	7 (5.0%)	—
Yes	139 (91.4%)	133 (95.0%)	—
Delayed chemotherapy (>2 weeks delay)			0.008
No	111 (73.0%)	121 (86.4%)	—
Yes	41 (27.0%)	19 (13.6%)	—
RT major deviation			0.886
Yes	23 (15.1%)	23 (16.4%)	—
No	129 (84.9%)	117 (83.6%)	—
Extended RT			0.303
No	148 (97.4%)	132 (94.3%)	—
Yes	4 (2.6%)	8 (5.7%)	—
Delayed RT			>0.99
No	140 (92.1%)	129 (92.1%)	—
Yes	12 (7.9%)	11 (7.9%)	—

Variables are presented as means ± standard deviations or n (%).
Others, undifferentiated.
ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; NA, not applicable; RT, radiotherapy.

Table 2. Pattern of recurrence in patients with locally advanced cervical cancer treated with weekly or tri-weekly cisplatin-based chemoradiotherapy

	Weekly (n = 152)	Tri-weekly (n = 140)	P value
Recurrence, n (%)			0.647
No	124 (81.6)	118 (84.3)	—
Yes	28 (18.4)	22 (15.7)	—
Recurrence site, n (%)			0.634
Central or regional	12 (35.3)	7 (23.3)	—
Distant	19 (55.9)	19 (63.3)	—
Mixed	3 (8.8)	4 (13.3)	—
Persistent disease, n (%)			0.890
No	135 (88.8)	126 (90.0)	—
Yes	17 (11.2)	14 (10.0)	—

compared between the two treatment arms by using the chi-square test or Fisher's exact test, as appropriate. For continuous variables, mean and median values were compared using the independent-samples t-test and the Wilcoxon rank-sum test, respectively. Survival curves and rates were estimated using the Kaplan–Meier method. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were generated using a Cox proportional hazards model to compare survival outcomes between the groups. Statistical analyses were carried out using SPSS Statistics for Windows (version 13.0; SPSS Inc., Chicago, IL).

RESULTS

Baseline clinical characteristics were well balanced between the weekly and tri-weekly arms with respect to age, tumor size, hemoglobin level, performance status, FIGO stage, and histology (Table 1). The majority of patients in both the weekly (67.8%) and tri-weekly (68.6%) arms presented with FIGO stage IIB disease, and squamous-cell carcinoma was the predominant histology (90.1% in the weekly arm versus 81.4% in the tri-weekly arm; Table 1).

Treatment completion rates for the scheduled chemotherapy cycles were 77.0% in the weekly arm and 85.7% in the tri-weekly arm. Chemotherapy compliance, defined as receipt of at least four cycles in the weekly arm and at least two cycles in the tri-weekly arm, did not differ significantly between groups (91.4% and 95.0% in the weekly and tri-weekly arms, respectively; $P = 0.230$).The incidence of delayed chemotherapy events was significantly lower in the tri-weekly arm (13.6%) than that in the weekly arm (27.0%; $P = 0.008$; Table 1). No statistically significant differences were observed between the two arms regarding the rate of deviation, extended fields, or delays in radiotherapy (Table 1).

Recurrence rates were 18.4% in the weekly arm and 15.7% in the tri-weekly arm, while persistent disease rates were 11.2% and 10.0%, respectively ($P = 0.65$ and 0.89, respectively; Table 2). The patterns of recurrence and the rate of persistent disease did not differ significantly between the two arms. No statistically significant differences were observed between the two arms for either 3-year recurrence-free survival (78.7% in the weekly arm, 84.1% in the tri-weekly arm; HR 0.71, 95% CI 0.39-1.32, $P = 0.28$) or 5-year overall survival (73.9% in the weekly arm, 72.7% in the tri-weekly arm; HR 1.10, 95% CI 0.65-1.86, $P = 0.73$) (Figure 1).

Grade 1 and 2 toxicities, including hematological, endocrinological, hepatic, urological, inflammatory, and neurological adverse events, occurred more frequently in the tri-weekly arm (575 events) than those in the weekly arm (674 events; Table 3). Conversely, grade 3 and 4 toxicities occurred significantly more frequently in the weekly arm (211 events) than those in the tri-weekly arm (181 events), particularly hematological toxicity (49.3% versus 30.4%, $P < 0.001$; Table 3). Grade 3 and 4 gastrointestinal toxicities occurred more frequently in the tri-weekly arm (6.6% versus 16.0%, $P = 0.005$).

Assessment of QOL parameters indicated that several domains, including global health status (66.5 versus 61.9, $P = 0.001$), physical functioning (83.4 versus 80.1,

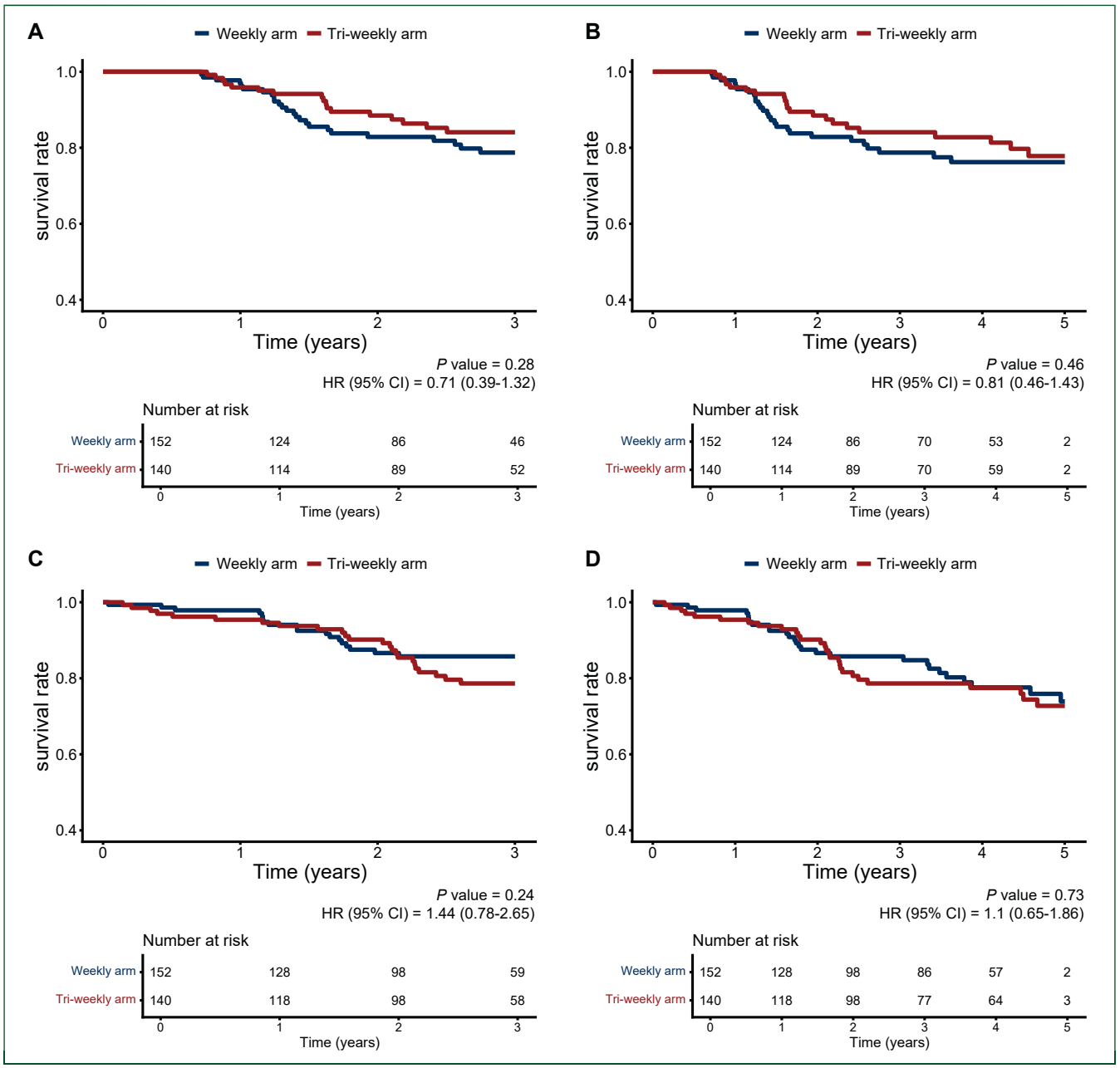

Figure 1. Survival outcomes of patients with locally advanced cervical cancer treated with weekly or tri-weekly cisplatin-based chemoradiotherapy. (A) 3-year recurrence-free survival, (B) 5-year recurrence-free survival, (C) 3-year overall survival, (D) 5-year overall survival.
CI, confidence interval; HR, hazard ratio.

$P = 0.007$), role functioning (88.3 versus 85.5, $P = 0.006$), and dyspnea (15.0 versus 18.1, $P = 0.038$) were significantly more favorable in the tri-weekly arm (Table 4). Appetite loss (66.5 versus 61.9, $P = 0.001$), diarrhea (80.8 versus 77.9, $P = 0.007$), and cognitive function were worse in the tri-weekly arm than those in the weekly arm ($P = 0.003$; Table 4).

DISCUSSION

This prospective, randomized clinical trial demonstrated that the administration of tri-weekly cisplatin at a dose of 75 mg/m^2 concurrently with radiation did not yield a statistically significant survival benefit compared with a weekly cisplatin regimen in terms of 3-year recurrence-free or overall survival. However, grade 3 or 4 hematological toxicities occurred less frequently and the QOL scores were higher in the tri-weekly arm than those in the weekly arm. This results suggest that a higher peak cisplatin concentration or a longer exposure to cisplatin during radiation may not critically impact survival outcomes in patients with cervical cancer, at least within the dose ranges studied. The weak impact of the cisplatin peak concentration on survival outcomes was previously reported in other cancers such as HNC.[12-14] Although the mechanism is not well known, those studies suggested that the survival difference is minimal if the cumulative dose of cisplatin is >200 mg/m^2 in chemoradiotherapy.[13-15,18] Because both the weekly

Table 3. Toxicity profile of patients with locally advanced cervical cancer treated with weekly or tri-weekly cisplatin-based chemoradiotherapy

	Grades[a] 1-2			Grades[a] 3-4		
	Weekly (n = 674)	Tri-weekly (n = 575)	P value	Weekly (n = 211)	Tri-weekly (n = 181)	P value
Hematological, n (%)	270 (40.1)	277 (48.2)	<0.001	104 (49.3)	55 (30.4)	<0.001
Anemia	124 (18.4)	120 (20.9)	—	15 (7.1)	10 (5.5)	—
Neutropenia	104 (15.4)	134 (23.3)	—	75 (35.5)	38 (21.0)	—
Thrombocytopenia	42 (6.2)	23 (4.0)	—	12 (5.7)	4 (2.2)	—
Others	0	0	—	2 (0.9)	3 (1.7)	—
Gastrointestinal, n (%)	200 (29.7)	153 (26.6)	0.285	14 (6.6)	29 (16.0)	0.005
Endocrinological, n (%)	71 (10.5)	36 (6.3)	0.011	55 (26.1)	48 (26.5)	>0.99
Hepatic, n (%)	1 (0.1)	21 (3.7)	<0.001	13 (6.2)	12 (6.6)	>0.99
Urological, n (%)	24 (3.6)	9 (1.6)	0.046	6 (2.8)	9 (5.0)	0.406
Inflammatory, n (%)	18 (2.7)	5 (0.9)	0.033	3 (1.4)	7 (3.9)	0.226
Pulmonological, n (%)	4 (0.6)	3 (0.5)	>0.99	9 (4.3)	6 (3.3)	0.822
Cardiovascular, n (%)	1 (0.1)	0	>0.99	2 (0.9)	6 (3.3)	0.196
Kidney, n (%)	12 (1.8)	29 (5.0)	0.002	4 (1.9)	1 (0.6)	0.465
Dermatological, n (%)	5 (0.7)	9 (1.6)	0.263	1 (0.5)	0	>0.99
Orthopedic, n (%)	0	0	NA	0	1 (0.6)	0.939
Allergic, n (%)	2 (0.3)	2 (0.3)	>0.99	0	0	NA
Ophthalmological, n (%)	2 (0.3)	3 (0.5)	0.853	0	0	NA
Dental, n (%)	1 (0.1)	1 (0.2)	>0.99	0	0	NA
Neurological	46 (6.8)	17 (3.0)	0.003	0	0	NA
Esophagitis	0	1 (0.2)	0.934	0	0	NA
Myalgia	0	1 (0.2)	0.934	0	0	NA
Others	17 (2.5)	8 (1.4)	0.228	0	7 (3.9)	0.048

CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable.
[a]Grade based on CTCAE version 3.0.

Table 4. Comparison of quality of life in patients with locally advanced cervical cancer treated with weekly or tri-weekly cisplatin-based chemoradiotherapy

	Weekly	Tri-weekly	P value
Global health status/QOL	61.9 ± 23.4	66.5 ± 21.5	0.001
QL: global health status	80.4 ± 19.2	82.4 ± 17.3	0.078
Functional scales (higher values signify better functioning)	77.9 ± 25.8	80.8 ± 24.0	0.062
PF: physical functioning	80.1 ± 19.8	83.4 ± 18.6	0.007
RF: role functioning	85.5 ± 17.3	88.3 ± 15.3	0.006
EF: emotional functioning	80.8 ± 24.7	83.3 ± 22.4	0.101
CF: cognitive functioning	31.4 ± 23.8	27.2 ± 22.3	0.003
SF: social functioning	14.9 ± 21.6	14.4 ± 22.2	0.721
Symptom scales (higher values indicate greater symptom severity)	19.1 ± 22.7	16.8 ± 21.2	0.097
FA: fatigue	14.9 ± 22.1	11.8 ± 20.0	0.097
NV: nausea and vomiting	24.4 ± 27.3	22.8 ± 25.1	0.347
PA: pain	29.5 ± 29.9	28.1 ± 28.3	0.466
Single-item symptom scores (higher values indicate greater symptom severity)	18.8 ± 26.1	17.2 ± 23.8	0.296
DY: dyspnea	18.1 ± 25.1	15.0 ± 22.8	0.038
SL: insomnia	19.3 ± 27.5	17.2 ± 25.5	0.219
AP: appetite loss	61.9 ± 23.4	66.5 ± 21.5	0.001
CO: constipation	80.4 ± 19.2	82.4 ± 17.3	0.062
DI: diarrhea	77.9 ± 25.8	80.8 ± 24.0	0.007

Values are indicated as means ± standard deviations.
QOL, quality of life.

(cumulative dose: 40 $mg^2 \times 6 = 240\ mg^2$) and tri-weekly (cumulative dose: 75 $mg^2 \times 3 = 225\ mg/m^2$) regimens have cumulative doses of >200 mg/m^2, this study supports the concept of 'minimal cumulative dose of cisplatin'. Some researchers have suggested another explanation to the effect that human papillomavirus-positive cancers are more sensitive to radiation treatment, potentially mitigating the added effect of high-dose cisplatin-based chemoradiotherapy.[19,20] The exact relationship between survival outcomes and cisplatin concentration during chemoradiotherapy remains unknown and warrants investigation in future studies. None the less, given the comparable efficacy of the two schedules, a tri-weekly chemotherapy schedule may also be administered in combination with radiotherapy, depending on support from pharmacological data and the available evidence from other tumor types.

This study is unique in that the QOL was compared between weekly and tri-weekly cisplatin-based chemoradiotherapy for cervical cancer. Most of the QOL parameters were significantly more favorable in the tri-weekly arm in this study. The several parameters favoring the weekly arm were cognitive functioning, appetite loss, and diarrhea (Table 4). Although the exact mechanisms are not known, these QOL results suggest that the tri-weekly regimen may be associated with a better patient experience and reduced treatment burden in several key areas.

Financial considerations for cancer treatment have been a pertinent issue in low- to middle-income countries, where cervical cancer is prevalent. Although this study did not include a cost—benefit analysis, the weekly cisplatin regimen likely has the advantage because it does not require hospitalization. However, a tri-weekly cisplatin dose of 75 mg/m^2 can also be administered without hospitalization if sufficient pre- and post-hydration are provided, which may give it the cost—benefit advantage. Thorough and formal cost-effectiveness evaluations are necessary, considering the difference in economic status and medical infrastructure across countries.

In conclusion, this prospective randomized trial did not demonstrate a survival advantage for tri-weekly cisplatin administration at a dose of 75 mg/m^2 concurrent with radiotherapy compared with weekly cisplatin administration at a dose of 40 mg/m^2 combined with radiotherapy for patients with locally advanced cervical cancer. Nevertheless, the tri-weekly regimen was associated with a more favorable toxicity profile, particularly with lower rates of grade 3 or 4 neutropenia, fewer instances of delayed chemotherapy, and improved patient-reported QOL across several domains.

Therefore, given the comparable efficacy, the tri-weekly chemotherapy regimen may represent a feasible and better-tolerated alternative for patients with locally advanced cervical cancer and may be delivered in combination with radiotherapy according to available local structural resources as well as patient's wishes and general clinical condition.

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DISCLOSURE

The authors have declared no conflicts of interest.

REFERENCES

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-263.
2. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med*. 1999;340(15):1154-1161.
3. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med*. 1999;340(15):1137-1143.
4. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med*. 1999;340(15):1144-1153.
5. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol*. 1999;17(5):1339-1348.
6. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol*. 2008;26(35):5802-5812.
7. NCI Urges Chemo-RT Combination for Invasive Cervical Cancer. *Oncol NEWS Int*. 1999;8(4).
8. Lanciano R, Calkins A, Bundy BN, et al. Randomized comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation in advanced cervix cancer: a gynecologic oncology group study. *J Clin Oncol*. 2005;23(33):8289-8295.
9. Green JA, Kirwan JM, Tierney JF, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet*. 2001;358(9284):781-786.
10. Lukka H, Hirte H, Fyles A, et al. Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer: a meta-analysis. *Clin Oncol (R Coll Radiol)*. 2002;14(3):203-212.
11. Bonomi P, Blessing JA, Stehman FB, DiSaia PJ, Walton L, Major FJ. Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol*. 1985;3(8):1079-1085.
12. Guan J, Zhang Y, Li Q, et al. A meta-analysis of weekly cisplatin versus three weekly cisplatin chemotherapy plus concurrent radiotherapy (CRT) for advanced head and neck cancer (HNC). *Oncotarget*. 2016;7(43):70185-70193.
13. Szturz P, Wouters K, Kiyota N, et al. Weekly low-dose versus three-weekly high-dose cisplatin for concurrent chemoradiation in locoregionally advanced non-nasopharyngeal head and neck cancer: a systematic review and meta-analysis of aggregate data. *Oncologist*. 2017;22(9):1056-1066.
14. Jacinto JK, Co J, Mejia MB, Regala EE. The evidence on effectiveness of weekly vs triweekly cisplatin concurrent with radiotherapy in locally advanced head and neck squamous cell carcinoma (HNSCC): a systematic review and meta-analysis. *Br J Radiol*. 2017;90(1079):20170442.
15. Noronha V, Joshi A, Patil VM, et al. Once-a-week versus once-every-3-weeks cisplatin chemoradiation for locally advanced head and neck cancer: a phase III randomized noninferiority trial. *J Clin Oncol*. 2018;36(11):1064-1072.
16. Chen X, Zou H, Li H, et al. Weekly versus triweekly cisplatin-based chemotherapy concurrent with radiotherapy in the treatment of cervical cancer: a meta-analysis. *Int J Gynecol Cancer*. 2017;27(2):344-349.
17. Ryu S-Y, Lee W-M, Kim K, et al. Randomized clinical trial of weekly vs. triweekly cisplatin-based chemotherapy concurrent with radiotherapy in the treatment of locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys*. 2011;81(4):e577-e581.
18. Strojan P, Vermorken JB, Beitler JJ, et al. Cumulative cisplatin dose in concurrent chemoradiotherapy for head and neck cancer: a systematic review. *Head Neck*. 2016;38(suppl 1):E2151-E2158.
19. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35.
20. Spreafico A, Huang SH, Xu W, et al. Impact of cisplatin dose intensity on human papillomavirus-related and -unrelated locally advanced head and neck squamous cell carcinoma. *Eur J Cancer*. 2016;67:174-182.