

ORIGINAL RESEARCH

# A phase III randomized, controlled trial of nedaplatin versus cisplatin concurrent chemoradiotherapy in patients with cervical cancer

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**Background:** We evaluated the non-inferiority of nedaplatin-based and cisplatin-based concurrent chemoradiotherapy in cervical cancer patients.

**Design:** Patients aged 28-82 years with pathologically diagnosed cervical cancer (stage IB-IVA) were randomly chosen for the study. Patients in both the cisplatin and nedaplatin groups received radiotherapy and weekly intravenous nedaplatin 30 mg/m<sup>2</sup> or cisplatin 40 mg/m<sup>2</sup> concurrently.

**Results:** One hundred and sixty patients who received treatment between 10 May 2018 and 31 August 2020 were included. The 3-year overall survival in the nedaplatin group (median 30.5 months) was not significantly different from that in the cisplatin group (28.5 months; hazard ratio 0.131, 95% confidence interval 0.016-1.068; *P* = 0.058). No significant differences in hematological toxicity were observed between the two groups. Vomiting (40 versus 61), nausea (44 versus 67), and anorexia (52 versus 71) were more common in the cisplatin group whereas effects on liver function, including total bilirubin (7 versus 3), alanine aminotransferase (7 versus 2), and aspartate aminotransferase (6 versus 2), were more common in the nedaplatin group. Four patients in the cisplatin group had grade I creatinine elevation, whereas none in the nedaplatin group had abnormal creatinine levels. Two patients in the nedaplatin group discontinued concurrent chemotherapy because of infusion, and one patient in the cisplatin group discontinued treatment because of infusion-induced dizziness.

**Conclusions:** Our findings suggest that nedaplatin has a milder gastrointestinal reaction but a more significant effect on liver function than cisplatin. In patients with cervical cancer, nedaplatin-based concurrent chemoradiotherapy could serve as an alternative treatment to cisplatin.

**Key words:** cervical cancer, concurrent chemoradiotherapy, nedaplatin, cisplatin

## INTRODUCTION

Cervical cancer is a common malignant tumor located in the female genital tract, resulting in the third highest mortality rate in developing countries.<sup>1</sup> According to the available data in 2018, there were nearly 570 000 new cervical cancer cases and ~310 000 deaths around the world.<sup>2</sup> China is one of the developing countries with the highest cervical cancer incidence and mortality, of which ~110 000 new cases and almost 50 000 deaths occurred in 2018.<sup>3</sup> In recent years, the morbidity and mortality of cervical cancer have shown an upward trend, severely threatening women's lives and health.<sup>4</sup> Cervical

cancer in different stages has different treatment options. Surgery is often the primary treatment of early-stage cervical cancer, whereas concurrent chemoradiotherapy (CCRT) is the major treatment of advanced cervical cancer.<sup>5</sup>

According to the National Comprehensive Cancer Network (NCCN) guidelines, treating advanced cervical cancer patients with cisplatin-based CCRT every week is a uniform consensus (Category 1).<sup>6</sup> Some patients, however, cannot tolerate severe gastrointestinal reactions and nephrotoxicity caused by cisplatin. Nedaplatin is a new platinum agent with a molecular structure similar to that of cisplatin. It also has mild nephrotoxicity and gastrointestinal reactions compared with cisplatin.<sup>7,8</sup> Moreover, nedaplatin does not require hydration for renal protection. Studies have shown that nedaplatin has ~10 times higher water solubility than cisplatin and milder gastrointestinal reactions and renal toxicity. Some studies, however, have reported a more significant bone marrow suppression with nedaplatin, especially thrombocytopenia.<sup>9</sup>

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Compared with cisplatin, nedaplatin has less toxicity and fewer side-effects in some tumor treatments, such as non-small-cell lung cancer and esophageal cancer.<sup>10-12</sup> Li et al.<sup>13</sup> retrospectively analyzed 155 cervical cancer patients who received nedaplatin or cisplatin-based CCRT during radiotherapy. They concluded that patients who received nedaplatin had a higher recurrence rate than those who received cisplatin. They did not support the use of nedaplatin in CCRT for cervical cancer.<sup>13</sup> Japanese researchers Kagabu et al.<sup>14</sup> found no significant difference in toxicity between cisplatin- or nedaplatin-based postoperative CCRT for cervical cancer. A meta-analysis concluded that nedaplatin could be used as an alternative for patients who cannot tolerate the side-effects of cisplatin in cervical cancer.<sup>15</sup> This analysis demonstrated that CCRT with nedaplatin had an advantage in clinical outcomes compared with cisplatin, showing better efficacy in reducing chemotherapy toxicity. Fujiwara et al.<sup>16</sup> also reported that nedaplatin-based CCRT in cervical cancer is effective and safe. Furthermore, in combination chemotherapy regimens for cervical cancer, nedaplatin showed better safety and effectiveness than cisplatin.<sup>17</sup>

The efficacy of nedaplatin and cisplatin in the treatment of cervical cancer, however, remains controversial. Current comparative studies of cisplatin and nedaplatin in cervical cancer are all retrospective and lack prospective randomized, controlled studies. Therefore, we conducted a phase III randomized, controlled trial to investigate the clinical efficacy and adverse reactions of nedaplatin- and cisplatin-based CCRT in advanced cervical cancer.

## METHODS

### Study design and participants

This was an open-label, non-inferiority, randomized, controlled trial for cervical cancer treatment. Eligible patients were between the ages of 18 and 85 years with histologically confirmed cervical cancer (including squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and small-cell carcinoma); stage IB2-IVA [according to the 2014 cervical cancer staging revised by the Federation International of Gynecology and Obstetrics (FIGO); clinical stage defined by gynecological oncologists and radiation oncologists] by imaging [thoracic computed tomography (CT) or abdominal ultrasound, CT, magnetic resonance imaging (MRI), or bone scan]. All included patients had no evidence of distant metastasis, normal blood function (white blood cell count  $\geq 3500/\mu\text{l}$ , platelet count  $\geq 100\,000/\mu\text{l}$ , and hemoglobin  $\geq 90\text{ g/l}$ ), adequate renal function (creatinine clearance  $\geq 60\text{ ml/min}$ ), normal liver function (serum bilirubin, alanine aminotransferase, aspartate aminotransferase  $\leq 1.5 \times 5n$ ), normal liver function (serum b Eastern Cooperative Oncology Group (ECOG) performance score of 0-2. Exclusion criteria included severe uncontrollable infection; factors affecting drug administration, distribution, metabolism, and excretion, such as chronic diarrhea, ascites, pleural effusion, etc.; concurrent receiving experimental treatments in other clinical studies; long-term use of immune system inhibitors or concomitant use of immunostimulants after organ transplantation; and

pregnancy or lactation. Other key exclusion criteria were psychiatric disorders and medical comorbidities. The ethics committee approved the study protocol at our center, and all patients provided written informed consent.

### Randomization and masking

Eligible patients were randomly assigned (1 : 1) to receive nedaplatin- or cisplatin-based CCRT. Randomization was carried out using computer-generated random number code. Details of the random assignment were contained in sequentially numbered opaque sealed envelopes prepared by the statistician. After obtaining informed consent from eligible patients, the researchers sequentially opened the envelopes and assigned patients to the appropriate intervention. This was an open-label study in which all patients and clinicians were aware of the treatment regimen.

### Procedures

Both the groups received CCRT. Radiation therapy was carried out using 6MV photons in a linear accelerator (1.8 Gy/fraction/day, 5 days/week, a total of 25-28 fractions). Of these, three FIGO stage III and six stage II patients received brachytherapy in other hospitals after external beam irradiation. Both the groups received chemotherapy and radiotherapy within the same week. Patients in the nedaplatin group were intravenously administered 30 mg/m<sup>2</sup> infusion of nedaplatin. Meanwhile, patients in the cisplatin group simultaneously received a 40 mg/m<sup>2</sup> intravenous infusion of cisplatin associated with hydration. The two regimens were repeated weekly (with a maximum interval of 10 days depending on the patient's condition) and continued until the end of radiotherapy, unacceptable toxicity, or the patient's request for treatment discontinuation. If the patient's white blood cell count, absolute neutrophil count, platelet count, liver function, and renal function continued to meet the inclusion criteria, treatment was carried out after the first cycle. Patients with grade II or higher leukemia during the chemotherapy cycle should be treated symptomatically with granulocyte colony-stimulating factor. Before enrollment, each patient was required to provide a complete medical history and undergo a physical examination, complete blood count, biochemical laboratory tests, chest and abdominal CT, whole-brain CT or MRI, and isotopic bone scan or [<sup>18</sup>F]2-fluoro-2-deoxy-D-glucose positron emission tomography. During treatment, a complete blood count and differential white blood cell count were carried out before and after each cycle of chemotherapy, and other biochemical laboratory data, such as creatinine levels, were measured. Treatment efficacy was assessed every 3 months for the first 2 years and every 6 months for the third year. After the completion or discontinuation of this treatment, patients who relapsed or progressed were permitted to receive other treatments.

### Outcomes

The primary endpoint was progression-free survival at 3 years, and the secondary endpoint was the overall survival

and toxicity grade. Progression-free survival was defined as the time from randomization to documented local or regional recurrence, distant metastasis, or death from any cause, whichever occurred first. Overall survival was defined as the time from randomization to death from any cause or censoring at the date of the last follow-up.

### Statistical analysis

In this study, a non-inferiority trial was conducted to assess the efficacy and safety of nedaplatin versus cisplatin in CCRT for cervical cancer. According to our previous experience, we assumed that the safety of the experimental group after completing five cycles of nedaplatin chemotherapy would increase by 20%. The experimental parameters were as follows:  $\alpha = 0.05$  (bilateral),  $\beta = 80\%$ ; the enrollment ratio of the experimental group and the control group was 1 : 1; and the estimated sample size was 73 cases in both the experimental and control groups. All analyses were carried out using SPSS version 22, according to the sample size calculation formula for the comparison of the two rates.

Considering the dropout factor during the clinical trial with an estimated dropout rate of 10%, 160 patients were enrolled in the clinical plan and randomly assigned (1 : 1) to the experimental and control groups. Efficacy analyses were carried out among the intention-to-treat population of randomly assigned patients and the per-protocol population of patients who received at least one chemotherapy cycle. For safety analysis, all randomly assigned participants were included, except those who did not receive chemotherapy. We used the  $\chi^2$  test and Fisher's exact test for categorical variables and the Mann–Whitney  $U$  test for continuous variables to assess differences between groups. We calculated the progression-free

and overall survival using the Kaplan–Meier method and 95% confidence intervals (CIs) using the Greenwood formula. Hazard ratios (HR) were calculated using a Cox proportional hazards model. Multivariate analyses were carried out using Cox proportional hazards models and sub-distribution hazard function models to test for the independent significance of treatment interventions. The potentially important prognostic factors considered during modeling were patient age ( $>50$ ,  $\leq 50$  years), performance status (0, 1, 2), FIGO stage (I, II, III, IV), and chemotherapy intervention (nedaplatin, cisplatin). Adverse events were compared using the  $\chi^2$  test.

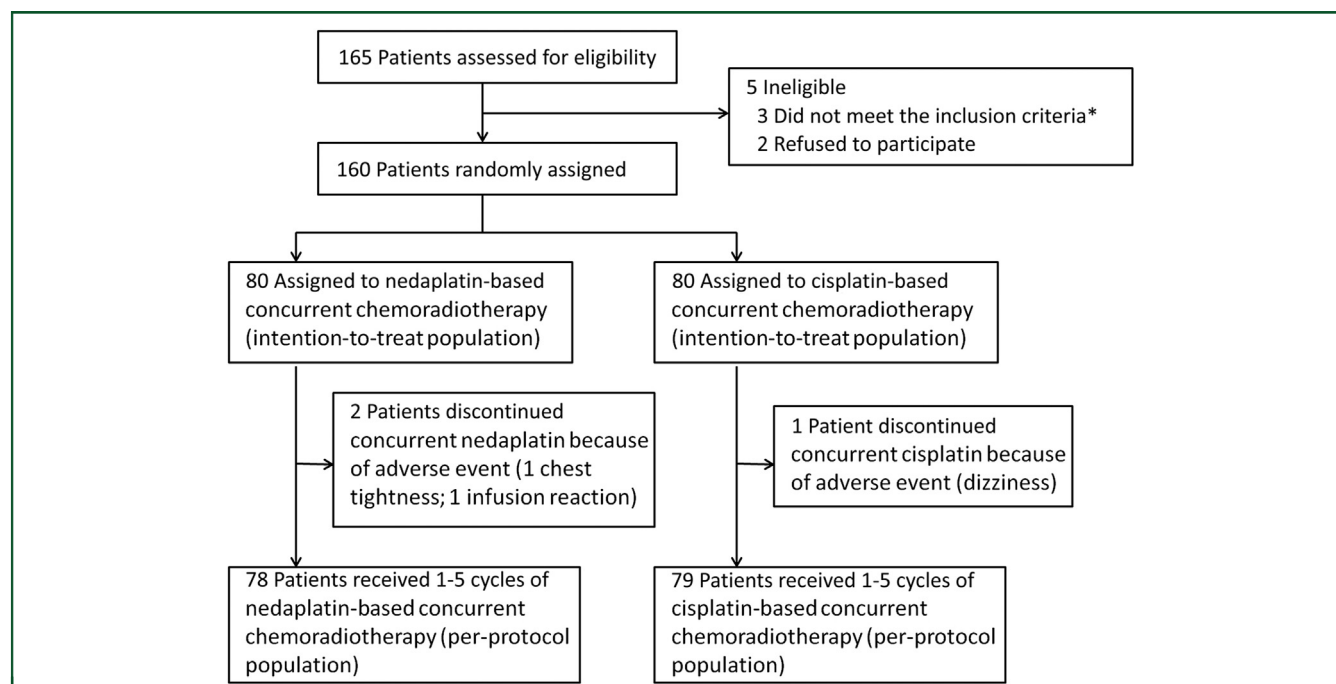
Statistical tests for the primary endpoint were one-sided, with  $P < 0.025$  considered significant; all other statistical tests were two-sided, with  $P < 0.05$  considered significant. This trial was registered in the Chinese Clinical Trial Registry (ChiCTR1800017108).

### Role of the funding source

Shanghai Jiao Tong University Affiliated Sixth People's Hospital participated in the management and audit work. The sponsors had no role in the study design, data collection, analysis, interpretation, or writing of the report. The corresponding authors have access to all data and are ultimately responsible for the decision to submit the publication.

### RESULTS

We evaluated 165 cervical cancer patients treated in our department between 10 May 2018 and 31 August 2020. Five patients were excluded on the basis of the inclusion and exclusion criteria. The remaining 160 patients were randomly assigned to receive nedaplatin-based ( $n = 80$ ) or cisplatin-based ( $n = 80$ ) CCRT (Figure 1). The baseline



**Figure 1. Trial profile.** We enrolled 165 patients according to the inclusion and exclusion criteria. Ultimately, 78 patients in the nedaplatin group and 79 patients in the cisplatin group completed treatment.

\*Two patients without adequate haematological function, one without adequate hepatic function.

demographic and clinical characteristics were similar between the two treatment groups (Table 1). No differences were observed in parameters other than the patients' FIGO stage. Considering the different stages among patients in the two groups, we carried out a stratified analysis by stage in the follow-up analysis. The cut-off date was 7 March 2022. The median follow-up for progression-free survival in the intention-to-treat and per-protocol population analyses was 30 months.

Eight patients died later in the follow-up: one (1.25%) in the nedaplatin group and seven (8.75%) in the cisplatin group. There was no difference in overall survival between the two groups (HR 0.131, 95% CI 0.016-1.068; one-sided stratified log-rank  $P = 0.058$ ; Figure 2A). In the nedaplatin group, the median overall survival was 30.5 months; 1-year overall survival was 100%; 2-year and 3-year overall survival was 98.75%. In the cisplatin group, the median overall survival was 28.5 months; 1-year overall survival was 97.5%, 2-year overall survival was 93.75%, and 3-year overall survival was 91.25%. Progression-free survival was longer in the nedaplatin group than in the cisplatin group (HR 3.963, 95% CI 1.303-12.053; one-sided stratified log-rank  $P = 0.015$ ; Figure 2F). The median progression-free survival was 30 months in the nedaplatin group and 28 months in the cisplatin group. Although our study was randomized, there were still significant differences in the FIGO staging between the two groups. Subgroup analyses

were carried out according to different FIGO stages. The stage-specific survival analysis (stage I, stage II, stage III, and stage IVA) by intention-to-treat showed no difference in overall survival (Figure 2B-D) and progression-free survival (Figure 2G-I) between the two treatment groups. Among the multivariate analyses by prognostic factors, the FIGO stage was an independent prognostic factor for overall survival (Table 2).

After a median follow-up time of 30.5 months [interquartile range (IQR), 13-46 months] for the nedaplatin group and 28.5 months (IQR, 2-46 months) for the cisplatin group, two local recurrences [0 of 80 (0%) in the nedaplatin group versus 2 of 80 (2.5%) in the cisplatin group], three lymph node metastases [1 (1.25%) versus 2 (2.5%)], 15 distant failures [3 (3.74%) versus 12 (15%)], and 18 patients with progression [4 (5%) versus 14 (17.5%)] were observed at the last follow-up. Eight patients died [1 of 80 (1.25%) in the nedaplatin group versus 7 of 80 (8.75%) in the cisplatin group].

Table 3 shows all the adverse events. Leukopenia was less frequent in the nedaplatin group than in the cisplatin group. Three patients in the cisplatin group had grade IV lymphopenia, whereas none of the patients in the cisplatin group had lymphopenia above grade III. The majority of anemia and thrombocytopenia that occurred in both groups were grade I, and all the above-mentioned adverse reactions were below grade III. Gastrointestinal reactions, such as vomiting, nausea, and anorexia, were significantly reduced in the nedaplatin group compared with those in the cisplatin group. The reduction in gastrointestinal symptoms resulted in less weight loss in the nedaplatin group than that in the cisplatin group. Regarding the effects on liver function, including the increase in total bilirubin, aspartate aminotransferase, and alanine aminotransferase levels, the incidence rate of the nedaplatin group was higher than that of the cisplatin group. The side-effects on liver function were grade I adverse reactions, however, with an incidence rate of <10%. Four patients in the cisplatin group had grade I creatinine elevation (5.06%) versus zero in the nedaplatin group. Two patients had noticeable infusion reactions in the nedaplatin group at the beginning of concurrent chemotherapy, and concurrent chemotherapy was terminated immediately. One patient in the cisplatin group developed dizziness during concurrent chemotherapy and chemotherapy was terminated. No other adverse reactions were observed during the treatment. None of the patients died during treatment.

## DISCUSSION

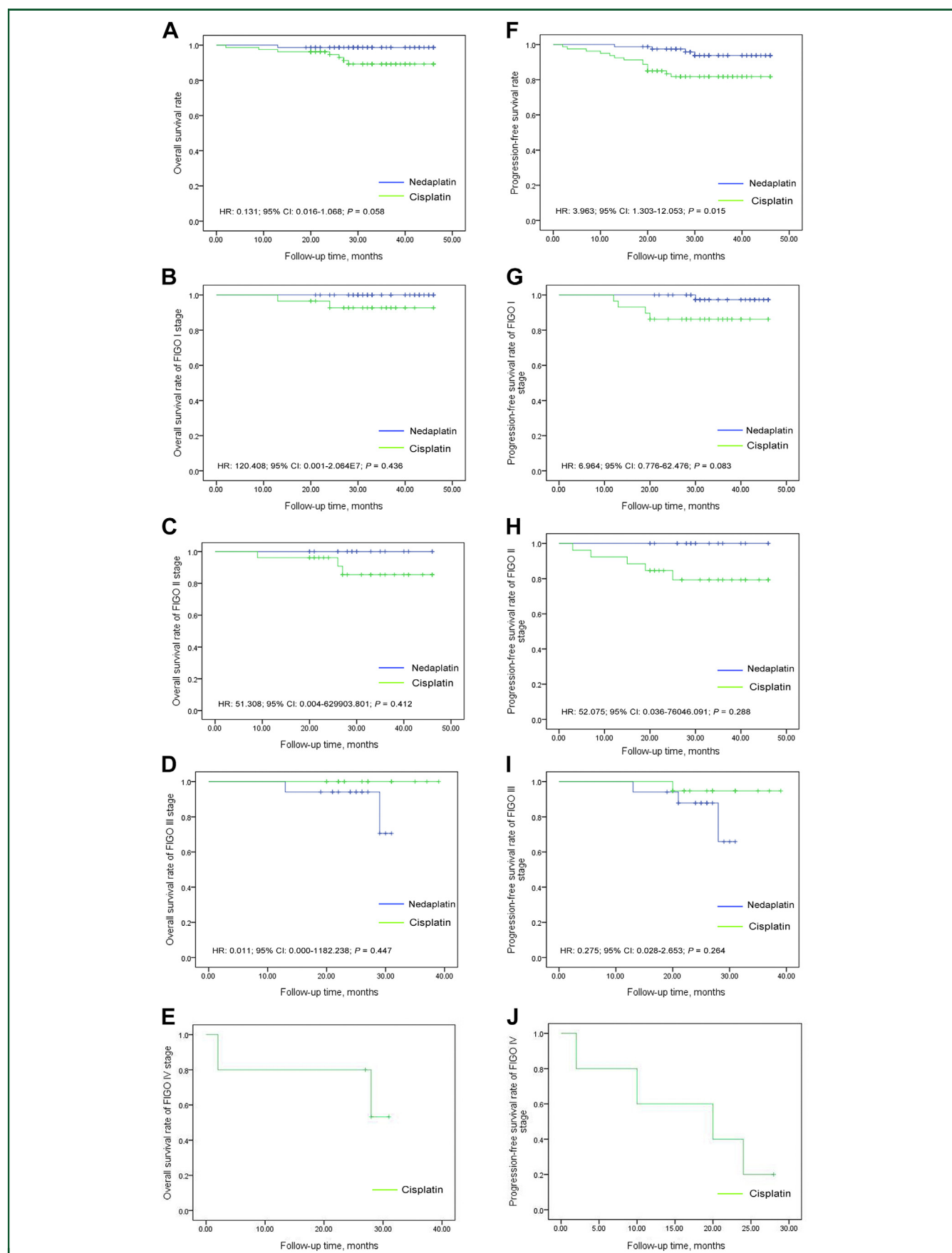
This is the first randomized trial in China to evaluate the non-inferiority of nedaplatin-based CCRT and standard cisplatin-based CCRT in terms of overall survival and progression-free survival in early-stage cervical cancer patients. In addition, compared with patients in the cisplatin group, those in the nedaplatin group had significantly fewer gastrointestinal side-effects, no renal impairment, and no need for hydration during administration. Our results are inconsistent with a study reported by Chinese scholars for

**Table 1. Patient characteristics**

	NDP group (N = 80)	DDP group (N = 80)
Age		
Median years	52.9	49.9
Range (years)	30-82	28-72
≤50	35 (43.7)	38 (47.5)
>50	45 (56.3)	42 (52.5)
Histological pattern		
Squamous cell carcinoma	66 (82.5)	62 (77.5)
Adenocarcinoma	11 (13.7)	10 (12.5)
Adenosquamous carcinoma	2 (2.5)	6 (7.5)
Small-cell carcinoma	1 (1.3)	2 (2.5)
ECOG score		
0	55 (68.8)	60 (75.0)
1	19 (23.7)	15 (18.7)
2	6 (7.5)	5 (6.3)
FIGO stage		
IB	45 (56.3)	29 (36.3)
IIA	17 (21.3)	20 (25.0)
IIB	1 (1.2)	7 (8.7)
IIIA	0 (0)	1 (1.2)
IIIB	1 (1.2)	1 (1.2)
IIIC	16 (20.0)	17 (21.3)
IVA	0 (0)	5 (6.3)
Cycles received		
0	2 (2.5)	1 (1.3)
1	6 (7.5)	9 (11.2)
2	13 (16.2)	19 (23.7)
3	23 (28.8)	30 (37.5)
4	24 (30.0)	16 (20.0)
5	12 (15.0)	5 (6.3)

Data are n (%), unless otherwise specified.

DDP, cisplatin; NDP, nedaplatin; ECOG, Eastern Cooperative Oncology Group; FIGO, Federation International of Gynecology and Obstetrics.



**Figure 2. Kaplan–Meier plots for overall survival and progression-free survival in patients.** Overall survival in (A) the intention-to-treat, (B) FIGO I stage, (C) FIGO II stage, (D) FIGO III stage, and (E) FIGO IV stage; progression-free survival in (F) the intention-to-treat, (G) FIGO I stage, (H) FIGO II stage, (I) FIGO III stage, and (J) FIGO IV stage.

CI, confidence interval; FIGO, Federation International of Gynecology and Obstetrics; HR, hazard ratio.

**Table 2. Multivariable analyses of prognostic factors by overall survival**

Subject characteristics	Events, n/N (%)	Hazard ratio (95% CI)	P value
Age			
≤50	2/70 (2.86)	1 (ref)	
>50	6/90 (6.67)	2.429 (0.475-12.419)	0.287
ECOG score			
0	5/115 (4.35)	1 (ref)	
1	2/34 (5.89)	1.375 (0.255-7.425)	0.711
2	1/11 (9.09)	2.200 (0.234-20.717)	0.491
FIGO stage			
IB	2/74 (2.70)	1 (ref)	
IIA	2/37 (5.41)	2.057 (0.278-15.218)	0.480
IIB	1/8 (12.50)	5.143 (0.413-64.095)	0.203
IIIA	0/1 (0)	0.000	1
IIIB	0/2 (0)	0.000	1
IIIC	1/33 (3.03)	1.125 (0.098-12.860)	0.925
IVA	2/5 (40.00)	24.000 (2.467-233.453)	0.006 <sup>a</sup>
Treatment group			
NDP	1/80 (1.25)	1 (ref)	
DDP	7/80 (8.75)	7.575 (0.910-63.068)	0.061
Cycles received			
0	1/3 (33.33)	1 (ref)	
1	3/15 (20.00)	0.500 (0.033-7.541)	0.617
2	1/32 (31.25)	0.065 (0.003-1.459)	0.085
3	1/53 (1.89)	0.038 (0.002-0.863)	0.040 <sup>a</sup>
4	0/40 (0)	0.000	0.997
5	2/17 (11.76)	0.267 (0.016-4.463)	0.358

<sup>a</sup>P value calculated with an adjusted Cox proportional hazards model.

locally advanced cervical cancer,<sup>9</sup> but in accordance with multiple studies in Japan, which supported the use of nedaplatin as an alternative for CCRT in cervical cancer.<sup>14,15,18-20</sup> Our trial showed that patients undergoing nedaplatin-based CCRT had similar overall survival and progression-free survival with cisplatin-based CCRT.

Treatment options were selected based on various factors including drug effectiveness and patient and physician preferences. Our study not only provides scientific evidence to support concurrent nedaplatin-based chemoradiation as an effective treatment alternative, but also opens up possibilities for more treatment options.

**Table 3. Adverse events during treatment**

	NDP group (n = 78)				DDP group (n = 79)				P value
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	
<b>Hematological</b>									
Leukopenia	30 (38.46)	18 (23.08)	4 (5.13)	0	31 (39.24)	26 (32.91)	6 (7.59)	0	0.247
Neutropenia	13 (16.67)	10 (12.82)	3 (3.85)	1 (1.28)	22 (27.84)	6 (7.59)	2 (2.53)	1 (1.27)	0.463
Anemia	35 (44.87)	4 (5.13)	0	0	34 (43.04)	1 (1.27)	0	0	0.350
Thrombocytopenia	3 (3.85)	1 (1.28)	0	0	4 (5.06)	1 (1.27)	0	0	0.934
Lymphopenia	7 (8.97)	27 (34.62)	41 (52.56)	0	4 (5.06)	25 (31.65)	47 (59.49)	3	0.192
<b>Non-hematological</b>									
Vomiting	20 (25.64)	16 (20.51)	4 (5.13)	0	30 (37.97)	22 (27.84)	9 (11.39)	0	0.021*
Nausea	21 (26.92)	18 (23.08)	5 (6.41)	0	32 (40.51)	24 (30.38)	11 (13.92)	0	0.009*
Anorexia	23 (29.49)	22 (28.21)	7 (8.97)	0	33 (41.77)	25 (31.65)	13 (16.46)	0	0.011*
Constipation	10 (12.82)	5 (6.41)	0	0	12 (15.19)	7 (8.87)	0	0	0.473
Diarrhea	22 (28.21)	8 (10.26)	0	0	23 (29.11)	9 (11.39)	0	0	0.387
Hiccups	2 (2.56)	0	0	0	2 (2.53)	0	0	0	0.942
Weight loss	30 (38.46)	12 (15.38)	1 (1.28)	0	34 (43.04)	14 (17.72)	3	0	0.041*
Fatigue	7 (8.97)	6 (7.69)	0	0	7 (8.86)	7 (8.86)	0	0	0.849
Fever	2 (2.56)	1 (1.28)	0	0	3 (3.80)	0	0	0	0.904
Total bilirubin	6 (7.69)	1 (1.28)	0	0	2 (2.53)	1 (1.27)	0	0	0.034*
ALT increase	6 (7.69)	1 (1.28)	0	0	1 (1.27)	1 (1.27)	0	0	0.044*
AST increase	5 (6.41)	1 (1.28)	0	0	1 (1.27)	1 (1.27)	0	0	0.046*
Creatinine increase	0	0	0	0	4 (5.06)	0	0	0	<0.001*

Data are n (%). No grade 5 adverse events occurred during treatment. As prespecified by protocol, differences in adverse events were analyzed using  $\chi^2$  test.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DDP, cisplatin; NDP, nedaplatin.

\*  $P < 0.05$  is considered significant.

In a randomized, non-inferiority, phase III controlled trial, He et al.<sup>9</sup> of Sun Yat-sen University in China showed that concurrent nedaplatin-based chemoradiotherapy is more prone to serious hematologic toxicity than cisplatin in locally advanced cervical cancer. More severe hematologic toxicity of nedaplatin than cisplatin was also shown in a study in head and neck tumors.<sup>21</sup> The clinical outcomes in a retrospective study from Wuhan University did not support the use of nedaplatin as an alternative to cisplatin in CCRT for locally advanced cervical cancer patients. Their results did not demonstrate the substitutability between cisplatin and nedaplatin.<sup>13</sup> These results, however, contradict multiple previous researches indicating that nedaplatin-based CCRT is safe and effective for cervical cancer patients.<sup>14,15,18-20</sup>

We set a 10% non-inferiority margin in this trial because a previous study reported that concurrent nedaplatin-based chemoradiation has a 5-year overall survival compared with radiotherapy alone. The benefit of overall survival was >20%.<sup>22</sup> This cut-off was set considering the expected reduction in toxicity and a more convenient dosing schedule for nedaplatin. The dose of nedaplatin (30 mg/m<sup>2</sup>) was based on a phase II study by Niibe et al.<sup>23</sup> Their results suggested that nedaplatin-based CCRT was a safe and effective treatment of cervical cancer. Our findings are also consistent with multiple studies reported by Japanese scholars.<sup>14,18-20</sup> Compared with cisplatin-treated patients, patients treated with nedaplatin-based concurrent chemotherapy had similar overall survival and improved gastrointestinal and renal toxicity. The 3-year overall survival rate in the nedaplatin-based CCRT group in our trial (98.75%) was higher than that in the trial (92%) reported by Kagabu et al.<sup>14</sup> This increase could be explained by the fact that in our trial, 56.3% of patients in the nedaplatin group were early stage IB patients. Another interesting observation is that all patients in our trial received fewer cycles of concurrent chemotherapy than in the trial reported by Kagabu et al.<sup>14</sup> In Kagabu's study, the median number of chemotherapy cycles for patients in the nedaplatin group was 5.5 (range, 2-6) and for patients in the cisplatin group was 5 (range, 2-5).<sup>14</sup> Although our patients received fewer chemotherapy cycles, our patients had a higher overall survival. One reason for this could be the use of more precise intensity-modulated radiotherapy (IMRT) technology in recent years. From another point of view, the current results also call for deeper consideration: Does modern medical treatment technology still require high-intensity concurrent chemotherapy? This question deserves further investigation.

Compliance, defined as patients who received three or more chemotherapy cycles, was 73.8% in the nedaplatin group and 63.8% in the cisplatin group. The compliance in our trial was not as good as in previous experiments, in which most patients completed five concurrent chemotherapy cycles.<sup>23-25</sup> One cause of the low patient compliance was the limited number of hospital beds, resulting in some patients failing to undergo concurrent chemotherapy every seven days as required. Some patients refused to continue chemotherapy because of treatment-induced discomfort. Factors that contributed to the high patient rejection rate can

be listed as follows: leukocytes declined dramatically after each cycle of chemoradiotherapy, requesting symptomatic treatment with colony-stimulating factor therapy; the recovery time for a hemogram extends the predetermined time for concurrent chemotherapy. These events increase patients' anxiety about acute toxicity and greatly reduce their willingness to undergo subsequent treatment. Furthermore, frequent and persistent gastrointestinal reactions prevented the patient from continuing the concurrent chemotherapy. There were fewer patients in the cisplatin group who received more than three cycles of concurrent chemotherapy than those in the nedaplatin group, because ~20% more patients in the cisplatin group experienced gastrointestinal symptoms than those in the nedaplatin group. This discrepancy is also in agreement with previous studies.<sup>7,10</sup> The liver damage in the nedaplatin group was grade I and was therefore relatively tolerable. A possible reason for this could be the large number of hepatitis B virus (HBV) carriers in China. We speculate that nedaplatin has a more significant effect on liver function in HBV carriers. This hypothesis, however, requires further research in future study.

This study has several limitations. First, this was a single-center study with a single dataset. We hope that a multi-center clinical study will be carried out in the future. Second, although our study was strictly randomized, the clinical stages of the two groups of patients were statistically different. This could be explained by the small sample size and patient bias of our department. The patients admitted in a certain period were mainly patients in the early post-operative stage, whereas those in another period were mainly locally advanced patients without surgery. Although we carried out data stratification in this research, we hope that future studies will focus on patients in certain specific clinical stages. Third, due to the relatively short follow-up time in this analysis, the value of the overall survival endpoint is limited, and longer follow-up is required to fully assess overall survival and long-term toxic effects. Fourth, the completed chemotherapy cycles in our study were not as expected, for various reasons. Nonetheless, our overall survival rate was not worse than that reported in other studies. Does this result imply a possible treatment option of five-cycle concurrent chemotherapy in some patients? Fifth, the coronavirus epidemic in early 2020 was a significant contributory factor interfering with the treatment process because patients were forced to prolong their treatment time. Sixth, given the different toxicity reactions between the two groups, patient adherence to three or more cycles of chemotherapy was reduced by 10% in the cisplatin group compared with the nedaplatin group, which may have been a confounding factor. Seventh, the unit price of nedaplatin is more expensive than that of cisplatin. In our study, nedaplatin was on average RMB 80 (about \$11) more expensive per cycle than cisplatin for the same patient. This does increase the financial burden for some patients. This is also a problem that we need to pay attention to in clinical practice. Eighth, for locally advanced patients, we should consider immunotherapy and targeted therapy. Due to the clinical advantages of the abscopal effect currently being

investigated in clinical trials,<sup>26</sup> the potential role of immunotherapy in relation to radiation therapy, platinum salts, and other targeted agents [poly (ADP-ribose) polymerase (PARP) inhibitors] should be further explored.<sup>27</sup> Finally, whether these results can be applied to non-Asian patient populations remains to be determined in future studies.

### Conclusions

Our findings suggest that nedaplatin-based CCRT could be used as an alternative to cisplatin-based CCRT for cervical cancer treatment. Due to the distinct toxicity of the two platinum salts, nedaplatin and radiotherapy, could play essential role in the combined therapy for cervical cancer and other malignancies in future.

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### DISCLOSURE

The authors have declared no conflicts of interest.

### ROLE OF THE FUNDER/SPONSOR

The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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