Original Articles

Phase II study of radiation therapy combined with weekly nedaplatin in locally advanced uterine cervical carcinoma (LAUCC): Kitasato Gynecologic Radiation Oncology Group (KGROG 0501) - initial analysis

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Summary

Objective: Locally advanced uterine cervical carcinoma (LAUCC) treated with chemoradiotherapy is considered to be the standard treatment regimen. However, no evidence of its efficacy and safety has been obtained from the Japanese population. Furthermore, the total dose of Japanese radiation therapy protocol is less than that of the USA which indicated that chemoradiotherapy for LAUCC is better than radiation therapy alone by phase III clinical trials. Thus, the current phase II study was designed to evaluate chemoradiotherapy with a lower radiation dose for LAUCC using weekly nedaplatin effectively and safely in the Japanese population. Nedaplatin is a platinum drug and no hydration is required to infuse patients because it is less toxic on renal function. If this phase II trial is successful, chemoradiotherapy for LAUCC in out-patient clinics could be possible. *Patients and Methods:* Patients registered in the current study were found to have LAUCC based on the following criteria i) pathologically proven squamous cell carcinoma or adenocarcinoma, ii) FIGO clinical Stage Ib, IIa, IIb with bulky tumor (diameter > 40 mm assessed by pelvic magnetic resonance imaging) or pelvic lymph node swelling (diameter > 10 mm assessed by pelvic computed tomography); iii) FIGO clinical Stage IIIa, IIIb and IVa with no paraaortic lymph node swelling (diameter > 10 mm) observed by abdominal computed tomography; iv) age: 20-75 years; v) performance status: 0-2. The treatment protocol was as follows: Radiation therapy in a combination of external beam radiation therapy (total dose: 50 Gy-52 Gy/25-27 fractions with central shielding after 30-32 Gy) with high-dose rate intracavitary irradiation (24-30 Gy/4-6 fractions to point A). Chemotherapy applied in the current study was weekly nedaplatin infused intravenously (30 mg/mm^2/time, once a week, total 150 mg/mm^2/5 weeks). Sample size in the current study was 45 LAUCC patients recruited for three years at a single institution. This protocol was permitted by the ethics committee of Kitasato University Hospital. *Results:* Ten patients were registered in this study between June 2005 and March 2006. The median age was 57.5 years (range 36-73). PS0 was five and PS1 was five. As for clinical stage, nine were IIIb and only one was IIb. Nine patients were proven to have squamous cell carcinoma and one adenocarcinoma. The median maximum tumor diameter was 62.5 mm (range 30-100 mm). As for initial response, eight had CR and two had PR (100% response rate). As for hematological acute morbidity, three were grade 2, six were grade 3, and one was grade 4. *Conclusions:* This initial analysis of the phase II study confirmed that concurrent chemoradiotherapy using nedaplatin is safe and efficacious, thus we decided to undergo further studies.

Key words: Concurrent chemoradiotherapy; High-dose rate intracavitary brachytherapy (HDR-ICBT); Nedaplatin; Locally advanced uterine cervical carcinoma.

Introduction

Locally advanced uterine cervical carcinoma (LAUCC) treated with chemoradiotherapy is considered to be the standard treatment regimen. However, no evidence of its efficacy and safety has been obtained from the Japanese population. Futhermore, the total dose of the Japanese radiation therapy protocol is less than that of the US which indicated that concurrent chemoradiotherapy achieved better treatment outcomes than radiaton therapy alone by phase III trials [1-3]. Nakano *et al*. reported a more than 20-year retrospective analysis of LAUCC of the Japanese population treated with radiation therapy alone using the standard Japanese radiation therapy protocol [4]. The method is the combination of external beam radiation therapy with concomitant use of high-dose-rate intracavitary brachytherapy (HDR-ICBT). The external beam radiation therapy protocol was the following: the fractionation was 1.8-2 Gy per fraction, 5 fractions per week, totaling 20-40 Gy using the entire pelvic irradiation field without central shielding, followed by 2 Gy per fraction, 5 fractions per week totaling 15-30 Gy using the entire pelvic field with central shielding. Thus, the total dose was 45-60Gy. The HDR-ICBT protocol

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was the following: fractionation was 5-6 Gy per fraction to point A, once per week totaling 15-24 Gy per 3-4 fractions, which was performed concomitantly with entire pelvic irradiation using central shielding. Then, the total BED was about 62-86 Gy10 [4]. These are less than the ABS guideline dose of 100-108 Gy10 [5, 6].

Thus, the current phase II study was designed to evaluate chemoradiotherapy with this lower radiation dose of the Japanese HDR-ICBT protocol for LAUCC using weekly nedaplatin effectively and safely in the Japanese population. Nedaplatin is a platinum drug produced by Shionogi Pharmaceutical Co., Japan and requires no hydration to infuse patients because it is less toxic for renal function. If this phase II trial is successful, chemoradiotherapy for LAUCC in out-patient clinics could be possible.

The purpose of the current initial analysis was to evaluate the safety and efficacy by evaluating acute toxicities and initial response.

Patients and Methods

Patients registered in the current study were found to have LAUCC based on the following criteria (Table 1): i) pathologically proven squamous cell carcinoma or adenocarcinoma; ii) FIGO clinical Stage Ib, IIa, IIb with bulky tumor (diameter > 40 mm assessed by pelvic magnetic resonance imaging) or pelvic lymph node swelling (diameter > 10 mm assessed by pelvic computed tomography); iii) FIGO clinical Stage IIIa, IIIb and IVa with no paraaortic lymph node swelling (diameter > 10 mm) observed by abdominal computed tomography; iv) age 20-75 years; v) performance status 0-2. The treatment protocol was the following: radiation therapy with a combination of external beam radiation therapy (total dose 50 Gy-52 Gy/25-27 fractions with central shielding after 30-32 Gy) with high-dose rate intracavitary irradiation (24-30 Gy/4-6 fractions to point A). The chemotherapy applied in the current study was weekly nedaplatin infused intravenously (30 mg/mm^2/time, once a week, total 150 mg/mm^2/5 weeks). The sample size was 45 LAUCC patients recruited for three years at a single institution. The protocol was permitted by the ethics committee of Kitasato University Hospital.

Table 1. — *Eligibility criteria*.

i)	Pathologically proven squamous cell carcinoma or adenocarcinoma
ii)	No paraaortic lymph node swelling (≥ 10 mm) by abdominal CT
iii)	Clinical FIGO Stage Ib, IIa, IIb with bulky tumor (≥ 40 mm assessed by pelvic MRI or pelvic CT)
iv)	Clinical FIGO Stage IIIa, IIIb and IVa
v)	Age: 20-75 years
vi)	Performance status (Eastern Cooperative Oncology Group): 0-2
vii)	No prior radiation therapy for abdomen or pelvis
viii)	Adequate function of bone marrow, kidney and liver
	white blood cell count ≥ 2500 mm^3
	neutrophils ≥ 1000 mm^3
	hemoglobin ≥ 8.0g/dl
	platelet count ≥ 75000 mm^3
	creatinin ≤ 2.0 mg/dl
	24 h-Ccr ≥ 60 ml/min
	GOT and GPT ≤ 2 times of upper limit of normal at our institution
	T.Bil ≤ 2 times or the upper limit of normal at our institution
ix)	Written informed consent

MRI: magnetic resonance imaging; CT: computed tomography; GOT: glutamic-oxalacetic transaminase; GPT: glutamic-pyruvate transaminase; T.Bil: T. billirubin.

Results

Ten patients were registered in the study between June 2005 and March 2006. Patient characteristics are listed in Table 2. Median age was 57.5 years (range 36-73). PS0 was 5 and PS1 was 5. As for clinical stage, nine were IIIb and only one was IIb. Nine patients were proven to be squamous cell carcinoma and one adenocarcinoma. Median maximum tumor diameter was 62.5 mm (range 30-100 mm). As for initial response, eight were CR and two were PR (100% response rate) (Table 3). Hematological acute morbidity in white blood cells resulted in four grade 3 and one grade 4, in neutrophils there were five grade 3, in hemoglobin there was one grade 3 and in platelet cells one grade 3 (Table 4). No patient experienced grade 3 or greater acute non-hematological morbidity.

Table 2. — *Patient characteristics*.

Age	36-73 years (median: 57.5 years)
Performance status:	
0	5
1	5
2	0
Clinical FIGO stage:	
IIb	1
IIIb	9
Histopathology:	
squamous cell carcinoma	9
adenocarcinoma	1
Maximum tumor diameter	30-100 mm (median: 62.5 mm)

Table 3. — *Initial Response*.

CR	8
PR	2

CR: complete response - PR: partial response - Response rate (RR): 100%

Table 4. — *Hematological acute morbidity*.

	G0	G1	G2	G3	G4
White blood cell	0	2	3	4	1
Neutrophils	2	2	1	5	0
Hemoglobin	4	4	1	1	0
Platelet cells	5	3	1	1	0

Discussion

Concurrent chemoradiotherapy treatment (CCRT) for LAUCC has been established as the standard treatment since three large phase III trials and one meta-analysis comparing RT with CCRT for LAUCC revealed its superiority to RT alone [1-3, 7]. The standard regimens of chemotherapy contain cisplatin (CDDP). CDDP is a widely used chemotherapeutic platinum drug for various malignancies [8-11]. However, CDDP has severe renal toxicity, and then heavy hydration is required to undergo treatment using CDDP. Thus, CCRT using CDDP in outpatient clinics is difficult. On the other hand, nedaplatin is also a platinum drug which lessens renal toxicity and requires no hydration. Kodaira *et al*. reported that a phase I/II study of a combination of nedaplatin and 5-FU for locally advanced esophageal cancer with radiation therapy achieved better outcomes of 45.9% for 2-year

survival [9]. Nemoto *et al*. also reported that a retrospective analysis of a combination of nedaplatin and 5-FU for recurrent esophageal cancer with radiation therapy achieved better outcomes of 69.0% for 2-year survival [10]. A phase I trial of CCRT for LAUCC using nedaplatin has been completed in a Japanese protocol of the HDR-ICBT schedule [11]. Thus, we conducted the current phase II trial. The details of the current trial have been previously reported [12]. CCRT for LAUCC in outpatient clinics could be possible if the current phase II study is successful.

In the current study, all ten patients had CR or PR. Thus, the response rate was 100% and CR rate was 80% (Table 3).

There is a weak point of nedaplatin use which is more severe hematological toxicities than CDDP [8]. In the current study, only one patient experienced grade 4 hematological toxicity (neutropenia). G-CSF has been found to overcome neutropenia in recent years. Thus, this hematological toxicity is acceptable. Grade 3 or greater hematological toxicity occurred in five patients (Table 4). This rate is also acceptable.

Ohno *et al*. reported that their retrospective analysis of 43 LAUCC patients treated with CCRT using CDDP in a Japanese protocol radiation treatment schedule achieved 14 grade ≥ 3 leucopenia (58%), and two grade ≥ 3 anorexia (8%) [13]. These results including the current phase II study suggest that CCRT using nedaplatin is not more severely toxic for hematological events than CDDP. Moreover, no grade 3 or greater anorexia occurred in the current phase II study, which suggests that CCRT using nedaplatin could be less toxic than CDDP.

Toita *et al*. also reported a retrospective analysis of CCRT for LAUCC using CDDP in a Japanese-style radiation therapy protocol [14]. There were 33 out of 40 grade ≥ 3 leukopenia (83%), which indicated more toxicity than the current phase II study.

In conclusion, the initial analysis of the current phase II study suggests that CCRT using nedaplatin for LAUCC in a Japanese protocol of radiation therapy schedule (HDR-ICBT, lower dose of BED10) could be effective and safe. Further studies on a mature population are strongly recommended.

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