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Neoadjuvant Chemotherapy Using Platinum-Based Regimens for Stage Ib2-II Squamous Cell Carcinoma and Non-Squamous Cell Carcinoma of the Cervix

Tadahiro Shoji et al.*
Department of Obstetrics and Gynecology,
Iwate Medical University School of Medicine
Japan

1. Introduction

The methods used for treating stage Ib2-IIb cervical cancers, with a bulky mass, differ between Japan and Western countries. In Western countries, concurrent chemoradiation (CCRT) has been recommended as a standard therapy for such tumors based on the results of multiple large-scale randomized trials and meta-analyses (Morris et al., 1999; Rose et al., 1999; Whitney et al., 1999; Pearcey et al., 2002; Eifel et al. 2004; Green et al. 2001; Lukka et al., 2002). In Japan, Korea, Italy and some other countries, the neoadjuvant chemotherapy (NAC) approach has been extensively introduced to clinical practice (Sugiyama et al., 1999). NAC is considered to be clinically significant in 2 respects: it is expected to improve the radicality and safety of surgery by reducing tumor size; and it is expected to exert systemic effects, i.e., effects on lymph node occult micrometastases, etc. A disadvantage of NAC is delayed initiation of the primary treatment, suggesting the necessity of completing NAC as an auxiliary therapy within a short period of time. Therefore, we may find that NAC is valuable if it can exert efficacy rapidly with high platinum dose intensity (DI), assuring that subsequent primary surgical therapy can be performed as soon as possible. At our facility, a platinum-based regimen has been used for NAC in patients with cervical cancer. Herein, we review the efficacy and safety data on NAC for squamous cell carcinoma of the uterine cervix. We previously reported our interim data and now present the results of an ongoing pilot study on the efficacy and safety of NAC for non-squamous cell carcinoma of the uterine cervix.

2. Subjects and methods

2.1 Subjects

We studied 43 patients with locally advanced cancer of the uterine cervix (clinical stage Ib2 to IIb) who gave informed consent to participate in this study between January 2002 and

*Eriko Takatori, Hideo Omi, Masahiro Kagabu, Tastuya Honda, Yuichi Morohara, Seisuke Kumagai, Fumiharu Miura, Satoshi Takeuchi, Akira Yoshizaki and Toru Sugiyama
Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, Japan

September 2010. All 43 were scheduled to undergo a radical hysterectomy, including 23 with squamous cell carcinoma and 20 with non-squamous cell carcinoma.

2.2 Inclusion criteria

The following set of inclusion criteria was employed for selection of study subjects. (1) Histologically verified squamous cell carcinoma or non-squamous cell carcinoma of the uterine cervix; (2) locally advanced stage Ib2 to IIb; (3) age: 20 years upward and less than 70 years; (4) Eastern Cooperative Oncology Group (ECOG) performance status (PS): 0-2; (5) initially treated case; (6) the presence of an MRI-measurable bulky mass in the uterine cervix; (7) hematologic and blood biochemical findings meeting the following criteria [WBC count ≥ 4,000/mm^3 ; neutrophil count ≥ 2,000/mm^3 ; platelet count ≥ 100,000/mm^3 ; hemoglobin ≥10.0 g/dl ; AST and ALT levels ≤ 2 times the upper limit of normal reference range at study site ; serum total bilirubin level ≤1.5 mg/dl ; serum creatinine ≤1.5 mg/dl ; and creatinine clearance ≥60 ml/min]; (8)life expectancy ≥6 months; and (9) written informed consent personally given by the subject.

2.3 Exclusion criteria

Exclusion criteria were prescribed as follows. (1) Patients with overt infection; (2) patients with a serious complication(s) (e.g., cardiac disease, poorly controlled diabetes mellitus, malignant hypertension, bleeding tendency); (3) patients with active multiple cancer; (4) patients with interstitial pneumonia or pulmonary fibrosis; (5) patients with effusions; (6) patients with a history of unstable angina or myocardial infarction within 6 months after registration, or with a concurrent serious arrhythmia requiring treatment; (7) patients in whom treatment with cisplatin (CDDP), irinotecan (CPT-11), paclitaxel (PTX), docetaxel (DTX) and carboplatin (CBDCA) is contraindicated; (8) patients with (watery) diarrhea; (9) patients with intestinal paralysis or ileus; (10) pregnant women, nursing mothers or women wishing to become pregnant; (11) patients with a history of serious drug hypersensitivity or drug allergy; and (12) patients who were inadequate for safe conduct of this study as judged by the attending physician.

2.4 Administration method and criteria for modification

2.4.1 NAC for squamous cell carcinoma

One course of NAC consisted of 21 days, with a CDDP dose of 70 mg/m^2 on Day 1 and intravenous CPT-11 doses of 70 mg/m^2 on Days 1 and 8. As a rule, 2 courses of NAC were administered to each patient (Fig.1).

2.4.1.1 Criteria for skipping CPT-11

In cases in which hematological data within 2 days before Day 8 did not satisfy the following criteria, CPT-11 was skipped on Day 8: 1) neutrophil count ≥ 1,000/mm^3, 2) platelet count ≥ 75,000/mm^3.

2.4.1.2 Criteria for starting the next course of NAC

In cases in which hematological data within 2 days before the planned start of the next course of treatment did not satisfy the following criteria, starting the second course was

postponed by 2 weeks at a maximum: 1) neutrophil count ≥ 1,500/mm^3, 2) platelet count ≥ 75,000/mm^3, 3) serum creatinine ≤ 1.5 mg/dl.

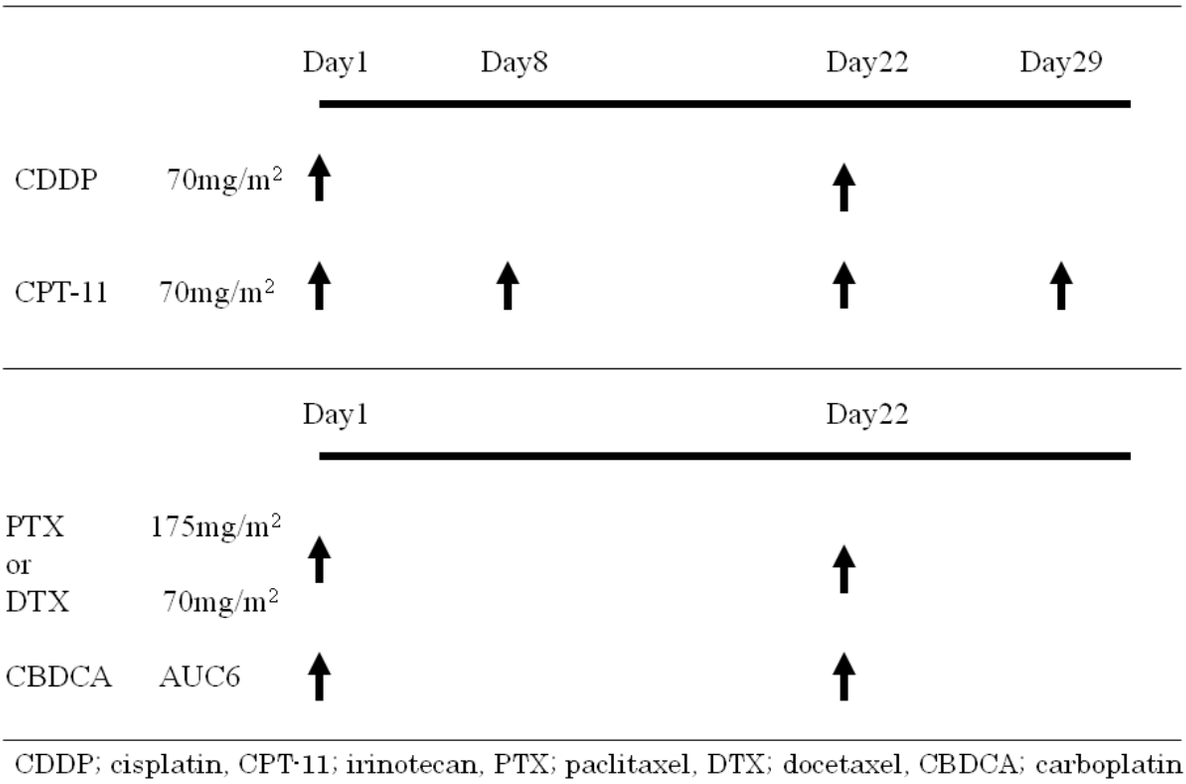

Fig. 1. Treatment protocol of NAC for cervical cancer

2.4.1.3 Dose reduction criteria

In cases exhibiting the following signs of toxicity during the first course of treatment, the CPT-11 and CDDP doses for the second course were reduced from 70 mg/m^2 to 60 mg/m^2: Grade 4 neutropenia lasting 7 days or more; febrile neutropenia lasting 4 days or more; Grade 4 thrombocytopenia; Grade 3 thrombocytopenia accompanied by bleeding; and Grade 3 or more severe non-hematological signs of toxicity other than nausea and vomiting.

2.4.2 NAC for non-squamous cell carcinoma

One course of treatment was 21 days, with a PTX dose of 175 mg/m^2 or DTX dose of 70 mg/m^2 on Day 1 and intravenous CBDCA AUC 6 on Day 1. As a rule, 2 courses of treatment were administered to each patient (Fig.1) .

2.4.2.1 Criteria for starting the next course of treatment

In cases in which hematological data within 2 days before the planned start of the second course of treatment did not satisfy the following criteria, starting the second course was postponed by 2 weeks at a maximum: 1) neutrophil count ≥ 1,000/mm^3, 2) platelet count ≥ 75,000/mm^3.

2.4.2.2 CBDCA dose reduction criteria

In cases exhibiting the following signs of toxicity during the first course of treatment, the CBDCA dose for the second course was reduced from AUC 6 to 5. If signs of toxicity remained after this dose reduction, that for the third course of treatment was reduced from AUC 5 to 4: Grade 4 thrombocytopenia; and Grade 3 thrombocytopenia accompanied by bleeding.

2.4.2.3 PTX dose reduction criteria

In cases exhibiting signs of Grade 2 or more severe peripheral nerve toxicity during the first course, the PTX dose for the second course was reduced from 175 mg/m^2 to 135 mg/m^2. If Grade 2 or more severe peripheral nerve toxicity remained after dose reduction, the PTX dose for the third course was reduced from 135 mg/m^2 to 110 mg/m^2.

2.4.2.4 DTX dose reduction criteria

In cases exhibiting the following signs of toxicity during the first course, the DTX dose for the second course was reduced from 70 mg/m^2 to 60 mg/m^2. If signs of toxicity remained after this dose reduction, the DTX dose for the third course was reduced from 60 mg/m^2 to 50 mg/m^2: Grade 4 neutropenia lasting 7 days or more; and febrile neutropenia lasting 4 days or more.

2.5 Supportive therapy

A granulocyte-colony stimulating factor (G-CSF) preparation was administered in patients developing Grade 4 neutropenia during the first course of NAC. Administration of the G-CSF preparation was permitted for prophylactic purposes during the second and subsequent courses of NAC in cases exhibiting Grade 4 neutropenia during the first course. Anti-emetics were additionally used for prophylactic purposes.

2.6 Observations and tests

The primary endpoint was anti-tumor response. Secondary endpoints were adverse events, surgery completion rate, progression-free survival period, and overall survival period. Hematological tests and urinalysis were carried out before the start of treatment and once weekly, as a rule, after starting treatment. Electrocardiograms and chest X-rays were obtained before the start and at the end of treatment.

2.6.1 Evaluation of anti-tumor response

Anti-tumor response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) by comparing the baseline findings (before the start of treatment) on magnetic resonance imaging (MRI) with the MRI findings at the end of treatment courses. Efficacy evaluation adopted the best rating, without incorporating the response period.

2.6.2 Evaluation of adverse events

Adverse events were evaluated employing the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) version 3.0.

2.7 Primary treatment

Patients with stage Ib2-IIb carcinoma underwent a radical hysterectomy unless the response of the tumor to preoperative treatment was progressive disease (PD) and the tumor was up-staged. In cases in which surgery was not possible, concurrent CCRT was adopted.

2.8 Postoperative therapy

Postoperative radiotherapy or chemotherapy was undertaken additionally in patients with positive vaginal stump, positive lymphadenopathy, positive invasion of the cardinal ligament, or evident invasion of the vasculature.

3. Results

3.1. Results of NAC for squamous cell carcinoma

3.1.1 Background variables

The median age of the 23 patients was 40 (range: 25-63) years. PS was 0 in 20 cases (87.0%) and 1 in 3 (13.0%). The clinical stage of the tumor was Ib5 in 5 cases (21.7%), IIa in 2 (8.7%), and IIb in 16 (69.6%). All patients received 2 courses of NAC (Table 1).

		SCC (N=23)		Non-SCC (N=20)
Age years [Median, Range]		40 [25-63]		52 [32-63]
Performance status at entry	0	19 (82.6%)		15 (75.0%)
	1	4 (17.4%)		5 (25.0%)
	2	0 (0%)		0 (0%)
FIGO Stage at initial diagnosis	Ib	5 (21.7%)		5 (25.0%)
	IIa	2 (8.7%)		0 (0%)
	IIb	16 (69.6%)		15 (75.0%)
Cell type	SCC	23 (100.0%)	Mucinous	9 (45.0%)
			Endometrioid	3 (15.0%)
			Clear cell	1 (5.0%)
			Adenosquamous	7 (35.0%)
Number of Cycles	1	0 (0%)		1 (5.0%)
	2	23 (100%)		16 (80.0%)
	3	0 (0%)		3 (15.0%)

SCC; Squamous cell carcinoma

Table 1. Patient characteristics

3.1.2 Anti-tumor response

The response of the tumor to treatment was assessed in all cases. Five (21.7%) showed a complete response (CR), 15 (65.2%) a partial response (PR), 2 (8.7%) stable disease (SD), and 1 (4.3%) PD. Thus, the response rate was 87.0% (Table 2). Among the cases rated as showing

CR or PR, none showed tumor growth between the end of the first course and the end of the second course of treatment.

	CR	PR	SD	PD	Overall Response
SCC	5 (21.7%)	15 (65.2%)	2 (8.7%)	1 (4.3%)	20 (87.0%)
Non-SCC	4 (20.0%)	11 (55.0%)	5 (25.0%)	0 (0%)	15 (75.0%)

	Surgery completion rate	Median PFS (range)	Median OS (range)
SCC	100%	30 (8-93)	34 (8-93)
Non-SCC	75%	10.5 (3-70)	20 (6-70)

CR,; complete response; PR; pertial response; SD; stable disease; PD; progressive disease
PFS; Progression-free survival, OS; Overall survival

Table 2. Response and clinical outcome

3.1.3 Adverse events

Grade 3 or more severe leukopenia and neutropenia were seen in 6 cases (26.1%) and 14 cases (60.9%), respectively. Grade 3 febrile neutropenia was seen in 1 case (4.3%). The G-CSF preparation was used in 11 (55.0%) of the 23 cases; during 17 (42.5%) of the 46 treatment cycles in total. The mean duration of G-CSF treatment during each course was 3.1 days. Grade 3 or more severe anemia was noted in 3 cases (15.0%), including one patient with Grade 1 anemia requiring blood transfusion. None of the patients developed Grade 3 or more severe thrombocytopenia. Signs of Grade 3 or more severe non-hematological toxicity included nausea in 2 cases (8.7%) and vomiting in 1 (4.3%) (Table 3). No treatment-associated deaths occurred. Chemotherapy was completed as scheduled in 21 (91.3%) of the 23 cases. In the remaining 2 cases, the CPT-11 dose on Day 2 of the second course was skipped. In these 2 cases, the dose was skipped at the discretion of the attending physician because of persistent Grade 3 nausea. There were 2 cases (8.7%) in which the start of the second course was postponed because the neutrophil count criterion was not satisfied. In both cases, the second course was started within 7 days. In one case (4.3%) showing febrile neutropenia lasting at least 4 days, the CDDP and CPT-11 doses for the second course were reduced from 70 mg/m^2 to 60 mg/m^2.

3.1.4 Surgery completion rate and survival period

The completion rate of radical hysterectomy after NAC was 100%. The median follow-up period was 35 months (range: 8-93 months). The median progression-free survival period was 30 months (8-93 months). The median overall survival period was 34 months (8-93 months) (Table 2).

	Grade				
	1	2	3	4	≥3 (%)
Leukopenia	2	15	5	1	6 (26.1)
Neutropenia	1	8	7	7	14 (60.9)
Thrombocytopenia	5	2	0	0	0
Anemia	9	12	1	1	2 (8.7)
Nausea	15	6	2	0	2 (8.7)
Vomiting	12	7	1	0	1 (4.3)
Diarrhea	1	0	0	0	0
Neurotoxicity	0	0	0	0	0
Renaltoxicity	0	0	0	0	0
Fibrile neutropenia	0	0	1	0	1 (4.3)

CDDP; cisplatin, CPT-11; irinotecan

Table 3. Toxicity of CPT-11+CDDP therapy (n=23)

3.2 Results of NAC for non-squamous cell carcinoma

3.2.1 Background variables

The median age of the 20 patients was 51 (range: 30-63) years. PS was 0 in 15 cases (75.0%) and 1 in 5 (15.0%). The clinical stage was Ib2 in 5 cases (25.0%) and IIb in 15 (75.0%). The histological type was mucinous adenocarcinoma in 9 cases (45.0%), endometrioid adenocarcinoma in 3 (15.0%), clear cell adenocarcinoma in 1 (5.0%), and adenosquamous carcinoma in 7 (35.0%). One course of NAC was administered to 1 case (5.0%), 2 courses to 16 (80.0%), and 3 courses to 3 (15.0%) (Table 1).

3.2.2 Anti-tumor response

The response was rated as CR in 4 cases (20.0%), PR in 11 (55.0%), SD in 5 (10.0%), and PD in 1 (4.3%), with the response rate being 75.0% (Table 2).

3.2.3 Adverse events

Grade 3 or more severe leukopenia and neutropenia were seen in 10 (50.0%) and 19 (95.0%) cases, respectively. Grade 3 febrile neutropenia was noted in 2 cases (10.0%). The G-CSF preparation was used for 13 (65.0%) of the 20 cases; it was administered during 19 (45.2%) of the 42 cycles in total. The mean duration of G-CSF preparation treatment during each course was 3.0 days. None of the cases showed Grade 3 or more severe anemia or thrombocytopenia. The only sign of Grade 3 or more severe non-hematological toxicity was nausea, seen in one case (5.0%). None of the cases had signs of Grade 2 or more severe neurotoxicity (Table 4).

In 3 cases (15.0%), the start of the second course of treatment was postponed because the neutrophil count criterion was not satisfied. In all 3 of these cases, the second course was started within 7 days. Both cases (10.0%) with Grade 3 febrile neutropenia for 4 days or more had received DTX/CBDCA therapy prior to the development of neutropenia. In these 2 cases, DTX (from 70 mg/m2 to 60 mg/m2) and CBDCA (from AUC 6 to 5) doses were reduced for the second course of treatment.

3.2.4 Surgery completion rate and survival period

A radical hysterectomy after NAC was completed in 15 of the 20 cases, i.e., the surgery completion rate was 75.0%. The median follow-up period was 20 months (6-70 months). The median progression-free survival period was 10.5 months (3-70 months) and the median overall survival period was 20 months (6-70 months) (Table2).

	Grade				
	1	2	3	4	≥3 (%)
Leukopenia	2	8	9	1	10(50.0)
Neutropenia	1	0	6	13	19(95.0)
Thrombocytopenia	10	0	0	0	0
Anemia	10	10	0	0	0
Nausea	9	2	1	0	1 (5.0)
Vomiting	5	2	0	0	0
Diarrhea	2	0	0	0	0
Neurotoxicity	18	0	0	0	0
Renaltoxicity	0	0	0	0	0
Dyspnea	2	0	0	0	0
Fibrile neutropenia	0	0	2	0	2 (10.0)

TC; Paclitaxel+Carboplatin, DC; Docetaxel+Carboplatin

Table 4. Toxicity of TC or DC therapy (n=20)

4. Discussion

A meta-analysis of the results of NAC for squamous cell carcinoma of the uterine cervix ruled out the effectiveness of radiotherapy applied as the primary treatment but suggested the effectiveness of surgery employed as primary therapy. This analysis suggested the effectiveness of NAC, if: one cycle of treatment lasted no more than 14 days; and the DI of CDDP exceeded 25 mg/m²/week (Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration., 2003). Sugiyama et al reported a CDDP/CPT-11 therapy schedule involving CPT-11 doses on Days 1, 8, and 15 (one course = 28 days) (Sugiyama et al., 1999). We evaluated the efficacy and safety of CDDP/CPT-11 therapy, reportedly an effective NAC regimen, using modified doses and administration schedules. In our study, a single

dose was set at 70 mg/m² for both CDDP and CPT-11, and the therapy was administered for 2 cycles at an interval of 3 weeks, with CDDP administered on Day 1 and CPT-11 on Days 1 and 8. In this way, the DI of CDDP was raised to 23.3 mg/m²/week, and this schedule was expected to reduce the need to skip treatments. Thus, it seems valuable to be able to reduce the time interval from NAC to surgery.

In an analysis of adverse events, Grade 3 or more severe neutropenia developed in 14 (60.9%) of the 23 cases, but subsided in response to short-term treatment with a G-CSF preparation. Severe diarrhea, specific to CPT-11, was not seen in any case when this agent was administered at a dose of 70 mg/m², suggesting that the quality of life (QOL) of patients was maintained during this therapy. The first course of treatment was administered as scheduled in all cases. The start of the second course was delayed, by no more than 7 days, in 3 cases. Furthermore, the CPT-11 dose on Day 8 was skipped in 2 cases. Dose reduction during the second course was necessary in only 2 cases, suggesting that this regimen does not increase the toxicity of these drugs as compared to the dosing regimen with 4-week intervals. Furthermore, the response rate (87.6%) and the surgery completion rate (100%) were satisfactory. Regarding the outcomes of patients treated with this regimen, further follow-up is needed.

Non-squamous cell carcinoma of the uterine cervix has been steadily rising in Japan, currently accounting for approximately 10% to 15% of all cervical cancer cases. Lymph node metastasis is more frequent in cases with invasive non-squamous cell carcinoma than in those with invasive squamous cell carcinoma (Aoki et al., 2002) and sensitivities to radiotherapy and chemotherapy are considered to be lower with non-squamous cell carcinoma (Landoni et al., 1997). Thus, squamous and non-squamous cell carcinomas must be analyzed separately. It is advisable to try new therapeutic strategies for non-squamous cell carcinoma, but the number of published studies involving cases with this type of cervical cancer is small, and the number of cases analyzed is also small. Thus, no high-level evidence has been obtained for this type of cervical cancer. The response rates of adenocarcinoma are reportedly 20% (Thigpen et al., 1986), 15% (Sutton et al., 1993), 14% (Look et al., 1997), and 12% (Rose et al., 2003) to uncombined therapies with CDDP, ifosmide, 5-FU, and oral etoposide, respectively, indicating that the response rates of adenocarcinoma to these therapies tend to be lower than those of squamous cell carcinoma. However, according to the report by Curtin et al, the response rate of adenocarcinoma was as high as 31% even when PTX was used independently (Curtin et al., 2001). DTX has also been attracting considerable interest. Nagao et al evaluated the efficacy of combined chemotherapy using DTX + CBDCA (DTX 60 mg/m² on Day 1, CBDCA AUC 6 on day 1 and then every 21 days) in 17 patients with advanced/recurrent cervical cancer, including 6 with adenocarcinoma and 1 with adenosquamous carcinoma, reporting that a PR was obtained in 6 of the 7 cases with adenocarcinoma (including the one with adenosquamous carcinoma) and that the response rate was thus 86% (Nagao et al., 2005). Following these findings, we conducted a pilot study involving standard regimens of PTX/CBDCA and DTX/CBDCA conventionally used for the treatment of ovarian cancer.

In the analysis of adverse events, Grade 3 or more severe neutropenia developed in 19 (95.0%) of the 20 cases, but subsided in response to short-term treatment with a G-CSF preparation (mean dosing period: 3.0 days/course). During the first course of DTX/CBDCA

therapy, Grade 3 febrile neutropenia developed in 2 cases. In these 2 cases, the dose was reduced during the next course of treatment (DTX, from 70 mg/m^2 to 60 mg/m^2; CBDCA, from AUC 6 to 5). All signs of peripheral neuropathy specific to taxanes, observed during this study, were Grade 1 or less severe, allowing continuation of treatment while preserving the QOL of individual patients. No serious adverse events occurred, and the response rate was 75%, but the completion rate of surgery (radical hysterectomy) was 75%. Thus, the outcomes of treatment in this study were not satisfactory. Possible reasons are: rapid progression of non-squamous cell carcinoma, frequent invasion of tissues/organs surrounding the uterus, and frequent lymph node metastasis.

Numerous reports on phase II studies of NAC for cervical cancer have been published, demonstrating effectiveness in 70%-80% of all cases. Table 5 shows the results of the present study in comparison to those of previous reports (Sugiyama et al., 1999; Hwang et al., 2001; Dueñas-Gonzalez et al., 2001; D'Agostino et al., 2002; Di Vagno et al., 2003; Dueñas-Gonzalez et al., 2003; Umesaki et al., 2004; Shoji et al., 2010; Shoji et al., 2010) and this study.

Author	Year	N.P.	Stage	Histlogical type	Regimens	R.R.(%)
Sugiyama T, et al	1999	23	Ib2, IIb, IIIb	SCC	CDDP + CPT-11	78
Hwang YY, et al	2001	80	Ib2-IIb	SCC, Non-SCC	CDDP + VLB + BLM	94
Gonzalez DA, et al	2001	41	Ib2-IIIb	SCC, Non-SCC	CDDP + GEM	95
Agostino G, et al	2002	42	Ib2-IVa	SCC, Non-SCC	CDDP + EPI + PTX	79
Vagno G, et al	2003	58	Ib2-IIIb	SCC, Non-SCC	CDDP + VNR	85
Gonzalez DA, et al	2003	43	Ib2-IIIb	SCC, Non-SCC	CBDCA + PTX	95
Umesaki N, et al	2004	25	Ib2, IIb, IIIb	SCC	CPT-11 + MMC	76
Shoji T, et al	2010	15	Ib2-IIb	SCC	CDDP + CPT-11	87
Shoji T, et al	2010	66	Ib2-IIb	SCC	NDP + CPT-11	76
Shoji T, et al	-	*23*	*Ib2-IIb*	*SCC*	*CDDP + CPT-11*	*87*
Shoji T, et al	-	*20*	*Ib2-IIb*	*Non-SCC*	*CBDCA + PTX or DTX*	*75*

N.P.: number of patients
R.R.: response rate
CDDP: cisplatin, CPT-11: irinotecan, VLB: vinblastine, BLM: bleomycin, GEM: gemcitabine, PTX: paclitaxel, EPI: epirubicin, VNR: vinorelbine, CBDCA: carboplatin, MMC: mitomycinC, NDP: nedaplatin, DTX: docetaxel

Table 5. Phase II study of NAC for cervical cancer

Most of the reports shown pertain to evaluation of both squamous cell carcinoma and non-squamous cell carcinoma. There is an urgent need to conduct clinical studies on each histological type of cervical cancer and to establish new methods of treatment specific to each type. Only a limited number of reports have demonstrated a high response rate to correlate with a better outcome. Thus, randomized controlled trials (RCT) designed to assess improvement of long-term outcomes are essential. As an RCT evaluating outcomes after NAC, Sardi et al reported a study involving comparisons among 4 groups (NAC + surgery + radiotherapy, surgery + radiotherapy, uncombined radiotherapy, NAC + radiotherapy). They found that the survival rate improved significantly with NAC + surgery +

radiotherapy (7-year survival rate: 41%) as compared to surgery + radiotherapy (41%) (Sardi et al., 1997). Serur et al retrospectively compared the outcomes of treating stage Ib cases between a NAC + surgery group and a surgery alone group, demonstrating a higher 5-year survival rate in the NAC + surgery group although the difference was not statistically significant (80% vs 69%) (Serur et al., 1997). Tierney et al reported the results of a meta-analysis, stating that there was no prognostic improvement (Neoadjuvant Chemotherapy for Cervical Cancer Metaanalysis Colloaboration, 2003). Thus, there is no consensus on this issue.

The JCOG0102 was a representative randomized study of NAC conducted in Japan, designed as an RCT comparing the outcomes of treatment for stage Ib2-IIb cases with bulky tumors between radical hysterectomy (+RT) and NAC + radical hysterectomy (+RT). The JCOG0102 used bleomycin/vincristine/mitomycinC/cisplatin (BOMP) as the NAC regimen. In that study, the response rate to BOMP therapy was low as 61%, and the interim results did not endorse the usefulness of this therapy, forcing the study to be discontinued prematurely (Katsumata et al., 2006). The JGOG1065 was a phase II clinical study on NAC + radical hysterectomy, using nedaplatin and CPT-11 for NAC, carried out in 66 patients with stage Ib2-IIb cervical cancer with a bulky tumor. In that study, the response rate was 75.8% and the 2-year recurrence-free survival period was 73.8% (Shoji et al., 2010). This therapy is expected to reduce nephrotoxicity and adverse events such as nausea and vomiting and appears to be a useful regimen for patients with renal dysfunction and elderly patients from the viewpoint of QOL. However, the response rate to this therapy has not exceeded that to CDDP + CPT-11. At present, there is no plan to launch a phase III clinical study on NAC (NDP/CPT-11) + radical hysterectomy vs. CCRT. There is no evidence supporting the view that NAC improves the outcomes of patients with cervical cancer, and NAC has not been recommended in any set of guidelines. Further studies on the indications for and efficacy of NAC are clearly needed.

5. Conclusions

Irinotecan/cisplatin therapy for squamous carcinoma of the uterine cervix and PTX/CBDCA and DTX/CBDCA therapies for non-squamous cell carcinoma of the uterine cervix showed high anti-tumor efficacy, and the adverse reactions to these therapies could be dealt with satisfactorily, thus allowing safe treatment. In cases with squamous cell carcinoma, outcomes are expected to be improved by NAC, but further evaluation of the outcomes of patients with non-squamous cell carcinoma is awaited.

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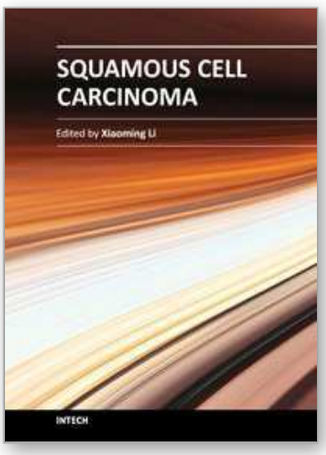

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This book points to some new areas for investigation on squamous cell carcinoma (SCC). Firstly, the features and management of some specific SCC is discussed to give the readers the general principles in dealing with these uncommon and sophisticated conditions. Some new concepts in adjuvant therapy including neoadjuvant therapy and gold nanoparticle-based photo dynamic therapy are introduced. Secondly, a detailed discussion of molecular aspects of tumor invasion and progression in SCC is provided with the emphasis on the roles of some important factors. The role of tumor microenvironment in head and neck SCC is specifically discussed. Thirdly, the roles of cancer stem cells (CSC) in cancer therapy of SCC are described. Molecular mechanisms involving therapeutic resistance and new therapeutic strategies targeting CSC are discussed in detail. Finally, other aspects concerning SCC are included, which involve the assessment, genetic manipulation and its possible clinical implications for the treatment of SCC.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821