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The role of raltitrexed/cisplatin with concurrent radiation therapy in treating advanced cervical cancer

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Abstract. – OBJECTIVE: To explore the effectiveness and safety of raltitrexed/cisplatin with concurrent radiotherapy in treating of patients with advanced cervical cancer.

PATIENTS AND METHODS: Sixty-five patients with stage IIB-IVA cervical cancer enrolled in this study, received raltitrexed/cisplatin with concurrent radiotherapy. The treatment consisted of raltitrexed 3 mg/m² iv 15 min, d1; cisplatin 60 mg/m² iv 60 min, d1, and pelvic radiotherapy, using three-dimensional conformal radiotherapy. The radiotherapy was implemented over Elekta accelerator (Model Type Precise), with 2.0 Gy per fraction for the whole pelvic or pelvic extension field. Central lead shield was used if the dose reached 30 Gy to produce a total dosage of 50 Gy. Following radiation therapies of full pelvic field or extended-field, additional radiation with the dose of 56-60 Gy was administrated to the lymph node metastases. Brachytherapy of iridium 192 was completed in our hospital, with the dose of 7Gy per fraction for point A, once a week, with six fractions for internal radiations during the full treatment course of eight weeks.

RESULTS: A total of 65 patients completed radiotherapy with two cycles of concurrent chemotherapy. Amongst them, chemotherapy was delayed for a week due to hypoleukocytosis for seven of the patients. Total response rate, three-year disease-free survival, and three-year overall survival OS were 95.4%, 75.4%, and 90.7%. High-grade (≥ 3) acute toxicities were hypoleukocytosis (23.1%) and thrombocytopenia (6.2%) with a prevalence of high-grade (≥ 3) late toxicities at 1.5%. One patient received surgical resection because of a partial intestinal obstruction after 8 months of radiotherapy.

CONCLUSIONS: Raltitrexed/cisplatin combined with concurrent radiotherapy is effective in treating advanced cervical cancer.

Key Words:
Phase II trial, Cervical cancer, Raltitrexed, Radiotherapy.

Introduction

Cervical carcinoma is one of the most common gynecologic cancers worldwide[1]. The prognosis of cervical cancer is favorable,with an approximately 80-90% 5-year survival rate in early-stage disease. However, advanced disease carries a poor prognosis. Current standard treatment for locally advanced cervical cancer, which is not eligible for surgical treatment, is cisplatin-based concurrent chemoradiation. On the basis of the results of five randomized clinical trials,which consistently showed improved survival in patients treated with cisplatin-based chemoradiation, the U.S. National Cancer Institute (NCI) recommends concurrent chemoradiotherapy as the standard treatment for high-risk and above IIB stage cervical cancer[2-6].

Although recently reported meta-analyses[7] also demonstrated improved local control rates and survival with cisplatin-based chemotherapy concurrent with radiation, combined chemotherapy and radiotherapy cannot increase the benefits compared with cisplatin alone,and was associated with a significant increase in grade 3 and 4 toxic reactions. However, due to toxic reactions from the combined chemotherapies, most oncologists prefer to use cisplatin with radiotherapy[8-12]. Increased local control and improved survival probility can be achieved throuth double combined agents; however, It is vital to decrease the toxic effect of treatment[13]. Therefore, the aim of our study is to find a high effective and low toxic drug combined with cisplatin used in concurrent chemoradiotherapy in the treatment in cervical caner.

With the continuous introduction of 5-FU analogs, raltitrexed is a concern due to its unique acting mechanism and ease of use. As a selective antimetabolite, raltitrexed, a quinazoline folate analogue, is an aqueous soluble thymidylate syn-

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thase inhibitor of a new generation, which could undergo cellular uptake *in vivo* and metabolized to a series of polyglutamic acid derivatives by folypolyglutamate synthetase. These metabolites have even more potent inhibitory activities against thymidylate synthase interfering with cellular DNA synthesis, and their intra-cellular retention behaviors are associated with long-term cytotoxic activities. The use of raltitrexed in the treatment of multiple solid tumors, such as advanced colorectal cancer, malignant pleural mesothelioma, pancreatic cancer, head and neck cancer, are now ongoing. In clinical practice, raltitrexed is characterized by well-established efficacy, limited side effects, convenience of administration and favorable acceptability[14,15], so in the present study, the addition of raltitrexed to cisplatin chemotherapy and radiotherapy was investigated for effect and toxic reactions.

Patients and Methods

Inclusion Criteria and Clinical Examinations

Subjects in this study included chemotherapy-naive patients with confirmed stage IIb-IVa cervical squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma, aged 25-70 years (median: 51 years), with a KPS score of ≥70 points. Patients with six months life expectancies who could tolerate concurrent chemoradiation therapies were eligible. Their neutrophils were ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin ≥ 90 g/L, and the liver and kidney functions were normal. All patients underwent pre-treatment examinations of blood routine and hepatorenal functions, as well as radiological examinations including pelvic MRI, abdominal CT/ultrasound, and chest X-ray. All patients signed an informed consent.

Phase-II Clinical Trial

Subjects included 65 patients aged 25-70 years, admitted to our hospital from January to December 2010. The KPS score was 70-80 points in 23 patients and ≥ 80 points in 42 patients. Forty-nine patients had cervical lesions of 2-4 cm in the maximal diameter and ≥ 4 cm in 16 patients. For pathological classification, patients had squamous cell carcinoma (n=47), adenocarcinoma (n=12) and adenosquamous carcinoma (n=6). According to the International Federation of Gynecology and Obstetrics classification system, patients were classified as Stage-IIb (n=47), -IIIa (n= 10), -IIIb (n=7), and –Iva (n=1) (Table I).

Radiotherapy Procedure

Pelvic radiotherapy was performed using the three-dimensional conformal radiotherapy. CT-based simulation localization was performed prior to the intervention. Patients were asked to lie in the prone position with the position maintained with thermoplastic film. Patients were trained to hold their urine, and a CT simulator was used for localization, with the scanning ranging from the third lumbar vertebrae to the site of 2 cm inferior to ischial tuberosity, with 5 mm in slice thickness and 5 mm in inter-slice distance. The gross tumor volume (GTV) was determined based on the CT images. Primary tumor areas of the uterus, cervix and vagina, and areas adjacent to the common, external, and internal iliac; obturator, anterior sacral lymph nodes were considered as part of the clinical target volume (CTV). The upper bound of the CTV was defined as the region of abdominal aortic bifurcation, while the lower bound was defined as the area at the lower edge of the obturator, with possible invasions to lower vaginal segments or the lower edge of ischial tuberosity. With solid tumors in the uterus, cervix or lymph nodes or common, internal and external iliac artery as the reference, lateral extensions of 7 cm were established as the posterior, anterior, left and right bounds. A 10-cm extension outside the CTV was assigned to be the planned target volume. Pinnacle treatment planning system was used during the design and operation. Four-field box radiation of 15MV-X ray was implemented over the anterior area with central lead shield. Two-field radiation was imple-

Table I. Patient characteristics (n = 65).

Characteristics	Column	Number
Age	≥ 40	57
	< 40	8
KPS Score	> 70~< 80	23
	≥ 80	42
Pathology	Squamous cell carcinoma	47
	Adenocarcinoma	12
	Adeno-squamous carcinoma	6
FIGO Stage	IIb	47
	IIIa	10
	IIIb	7
	IVa	1
Tumor size	≤ 4 cm	49
	> 4 cm	16

mented over the anterior and posterior areas with central lead shield. The radiotherapy was implemented over Elekta accelerator (Model Type Precise), with 2.0 Gy per fraction for the whole pelvic or pelvic extension field. Central lead shield was used if the dose reached 30 Gy to produce a total dosage of 50 Gy. Pelvic extended-field radiation therapy was used for three patients with para-aortic lymph node metastases, while full pelvic field radiation therapy was used for seven patients with pelvic lymph node metastases. Following radiation therapies of full pelvic field or extended-field, additional radiation with the dose of 56-60 Gy was administrated to the lymph node metastases. Brachytherapy of iridium 192 was completed in our hospital, with the dose of 7Gy per fraction for point A, once a week, with six fractions for internal radiations during the full treatment course of eight weeks. Volume restrictions of critical organs were evaluated based on the D2 cm^3 (minimal radiation dose per 2 cm^3 volume) criteria, with D2 $cm^3 \leq 5$ Gy for rectum and sigmoid, ≤ 5.5 Gy for bladder, and ≤ 4.5 Gy for small intestine. Concurrent chemotherapies was started 3-7 days after radiotherapy, which include raltitrexed 3 mg/m^2, continuous intravenous infusion within 15 minutes and cisplatin 60 mg/m^2, continuous intravenous infusion within 60 minutes, with 21 days for one cycle and two circles for this regimen.

Supportive Care

During the same day of raltitrexed and cisplatin administration, patients underwent rehydration and diuresis, with intake of 2500-3000 ml liquid. Dexamethasone and azasetron hydrochloride were administered as antiemetic therapies 0.5 hour before chemotherapies. After the chemotherapies, the daily oral administration of metoclopramide was prescribed to treat the delayed emesis induced by cisplatin. For patients with more severe delayed emesis, diazepam, metoclopramide, omeprazole and prednisone were prescribed in combination. Montmorillonite powder and loperamide hydrochloride were prescribed for patients with diarrhea. Intravenous rehydration was given to patients with more severe diarrhea and anorexia. Human G-CSF (human granulocyte colony-stimulating factor) was prescribed if WBC $< 3.5 \times 10^9$/L.

Follow-up

Weekly re-examination of blood routine and monthly re-examination of hepatic and renal functions were performed during the treatment course. These examinations were repeated once in the first month after radiotherapy, and once every three months for the following two years. After two years of ending treatment, these examinations were repeated once every six months.

Evaluation of the Efficacy and Toxicity

Short-term treatment response, which included complete remission (CR), partial response (PR), stable (SD), and progressed disease (PD), was evaluated in accordance with the RECIST (Response Evaluation Criteria In Solid Tumors, 2009). Response rate (RR) was calculated with CR+PR, and the disease control rate was calculated as CR+PR+SD. Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), which divides the toxicities into grades 1-5.

Statistical Analysis

Frequencies of adverse reactions were estimated on a direct approach.

Results

Treatment Completion and Follow-up

A total of 65 patients completed the radiotherapy and two cycles of concurrent chemotherapy. Among them, in seven of the patients, chemotherapy was delayed a week due to hypoleukocytosis. The post-chemotherapy follow-up was persistent to December 31, 2013, with follow-up lasting 36-45 months with a median follow-up of 39 months. No participant lost during follow-up.

Toxicities

The toxicities are summarized in Table I. A total of 21 patients experienced grade 1-2 toxicities, with vaginal stenosis, chronic abdominal pain, rectal tenesmus, occasional melena and gross hematuria. The incidence of high-grade ($\geq$ 3) late toxicities was 1.5%. One patient received surgical resection due to partial intestinal obstruction after 8 months of radiotherapy. No adverse reaction-related to death was reported (Table II).

Preliminary Results

A total of 65 patients completed the radiotherapy and 2 cycles of concurrent chemotherapy, with CR for 46 patients, PR for 16 patients and an OR rate of 95.4%, a DCR of 100%, a 3-

Table II. Distribution of the acute adverse reactions.

Toxicities	Grade of toxicity						Percentage of grade 3-4 toxicities (%)
	0	1	2	3	4	5	
Nausea	15	39	11	0	0	0	0
Vomiting	43	14	8	0	0	0	0
Diarrhoea	31	26	6	1	1	1	3.1
Anorexia	27	25	13	0	0	0	0
Fatigue	25	35	5	0	0	0	0
Leukocytes	3	25	22	11	4	1	23.1
Hemoglobin	15	30	17	3	0	0	4.6
Platelets	43	11	7	4	0	0	6.2
Hepatic dysfunction	61	4	0	0	0	0	0
Rash	62	3	1	0	0	0	0
Fever	57	5	3	0	0	0	0

year DFS of 75.4%, and a 3-year OS of 90.7%. According to the relapse criteria defined as local recurrence of radiation field, there were two cases of local relapse and five cases of parametrial recurrence. In addition, there were patients confirmed with para-aortic lymph node metastasis (n=1), left supraclavicular lymph node metastasis (n=2), pulmonary metastasis (n=3), and liver metastasis (n=1). Four patients died of tumor progression and distant metastasis. One patient died of chemoradiotherapy-induced diarrhea and leukopenia, and another patient died of major vagina and abdominal hemorrhage (Figure 1).

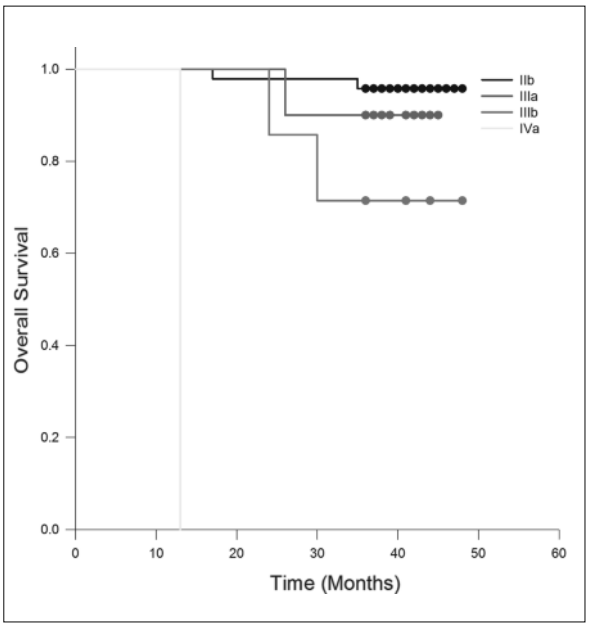

Figure 1.

Discussion

The regimens, commonly known as concurrent chemoradiation using cisplatin at 40 mg/m^2 weekly for 6 weeks in locally advanced cervical cancer, became the standard of care and was rapidly adopted by most oncologists.In this treatment option, patients have good tolerance and favorable efficacy, however, therapeutic results are far from optimal and novel therapies need to be investigated[16]. A promising studies focused on improving the drug component of the strategy and molecularly targeted. A recent, randomized, phase III trial has shown for the first time that combination chemotherapy with cisplatin and gemcitabine concurrently with radiation improves parameters of survival over cisplatin alone and establishes a new standard for the management of locally advanced cervical cancer[17]. We think that the improvement seen in arm gemcitabine plus cisplatin chemoradiotherapy partly contribute to adjuvant gemcitabine and cisplatin. Moreover, significantly difference side effects of hematologic toxicities and gastrointestinal toxicity had been observed in combined group than that of single cisplatin group. Tewari's report is the first randomized phase III trial showing increasing survival with bevacizumab in the treatment of recurrent and metastatic cervical cancer[18]. As knowledge accumulates on the molecular mechanisms underlying carcinogenesis in the cervix, the anticipated development and assessment of molecularly targeted agents may offer a promising perspective for cervical cancer.

In this work, patients with advanced cervical cancer were selected to receive raltitrexed/cisplatin and concurrent radiation in combination. All

patients enrolled to this Phase-II trial completed the concurrent regimen of raltitrexed 3 mg/m^2 plus cisplatin 60 mg/m^2 for two circles, but 7 patients had their chemotherapies delayed for one week due to leukopenia. All patients continued to complete the radiotherapies. The total response rate was 95.4%, with a disease control rate of 100%, a 3-year disease free survival of 75.4% and a 3-year overall survival of 90.7%. In comparing the efficacy of radiation monotherapy in the treatment of advanced cervical cancer described by Pu et al[19], with our regimen, there was an increase in three-year survival with reduced recurrence and distant metastasis. This may be associated with combination chemotherapies, resulting in improved survival rate. Moreover, the fact of a higher proportion of patients with stage-IIb disease and a lower proportion of patients with stage-IIIa and IIIb diseases, might contribute to the significant difference in efficacy.

The major adverse reactions of raltitrexed include nausea, vomiting, neutropenia and elevated transaminase, most of which are mild or moderate in intensity. The major acute adverse reactions were gastrointestinal reactions. As shown by our studies, the frequencies of grade-3, -4 leukopenia and thrombocytopenia was 23.1% and 6.2% in 65 patients. As Goel et al[20] described, the frequencies of grade-3, -4 leukopenia and thrombocytopenia was 22.6% and 5.7% in patients with advanced cervical cancer who underwent the regimen of 3-week cisplatin concomitant with radiation therapy. This is consistent with our results, which suggests that the concurrent use of raltitrexed is not associated with increased blood toxicity. The frequencies of acute gastrointestinal reactions such as Grade I/II nausea and vomiting were lower in comparison to those described by Goel et al, suggesting the possible roles of ethnic differences in drug induced reactions. Moreover, the use of gastrointestinal symptom based subjective evaluations might also be involved. The frequency of Grade-III advanced adverse reactions was 1.5 in this study, which was similar to the frequency of 1.7% in patients receiving cisplatin-containing therapies[21]. Long-term follow-up was needed in assessment of late effects[22] when the raltitrexed/ cisplatin combined with concurrent radiotherapy is used in clinical application

Conclusions

The combination of raltitrexed/cisplatin with radiotherapy is characterized by favorable efficacy, acceptable adverse reaction and good tolerance. However, due to the restrictions of limited patient numbers and short observation period, further studies are warranted to address the efficacy and safety of this regimen compared with cisplatin monotherapy in combination with radiotherapy.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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