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Concurrent chemoradiotherapy combined with immunotherapy is superior to traditional concurrent chemoradiotherapy in the treatment of advanced cervical cancer

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Summary

Purpose of investigation: In advanced cervical cancer, traditional therapy included concurrent chemoradiotherapy (CCRT), pelvic radiotherapy, and brachytherapy. In the last few years, the development of using of immunotherapy (IMT), targeted therapy, angiogenesis inhibitors, and tyrosine kinase inhibitors encourage us to provide better treatment choices in advanced cervical cancer patients. In this study, the authors propose CCRT combined with immunotherapy (ICRT) as a better treatment option for advanced cervical cancer. *Materials and Methods:* The authors retrospectively reviewed the medical records of 23 patients with advanced cervical who were treated by CCRT or ICRT between 2000 and 2016 at Chang Gung Memorial Hospital. In CCRT group (total 15 cases), patients were treated with traditional platinum-based chemotherapy and radiotherapy. In ICRT group (total eight cases), patients were treated with CCRT and adjuvant IMT. The authors chose Picibanil (OK-432) plus interleukin-2 (IL-2) for adjuvant IMT. Between CCRT and ICRT groups, they analyzed the difference of age, histological type of cervical cancer, follow-up period, recurrence rate, and diagnosis-to-recurrence period between them. They also analyzed the difference of complete blood cell counts and its differentiating counts after one month of treatment. *Results:* Within these parameters, the recurrence rate between ICRT and CCRT group showed significant difference (37.5% *vs.* 86.67%, $p = 0.0257$). The authors observed that diagnosis-to-recurrence duration was longer in ICRT group than CCRT group (67.32 months *vs.* 11.92 months, $p = 0.1464$), although there was no statistical significance found. The laboratory findings one month after treatment showed significant difference in absolute lymphocyte counts (ALC), which showed 1,554.23/μL *vs.* 577.38 /μL (mean value, $p = 0.0011$) in ICRT and CCRT group respectively. *Conclusions:* This study indicated that CCRT combined with immunotherapy is superior to traditional CCRT in treatment of advanced cervical cancer.

Key words: Cervical cancer; Concurrent chemoradiotherapy; Immunotherapy.

Introduction

In developed countries, cervical cancer is the leading cause of malignancy in gynecologic cancer. Due to the Papanicolaou-smear (Pap smear) and human papillomavirus (HPV) cervical cancer screening, pre-cancer lesion was earlier diagnosed. Recent studies showed that the incidence of cervical cancer has dropped to about 5-15 per 100,000 women [1-3]. Despite the fact that the incidence of cervical cancer has dropped dramatically [1, 4-6], the recurrence rate still remained between 8-26% [7-9]. In advanced cervical cancer, recurrence rate was even reported up to 30-50% or more [10-12]. Since high recurrence rate could be a burden to patients and subsequent treatment for recurrent cervical cancer, it was an issue deserving our alert.

According to the guidelines of National Comprehensive Cancer Network (NCCN version 1. 2016) for advanced cervical cancer, traditional treatments were limited to concurrent chemoradiotherapy (CCRT), pelvic radiotherapy, and brachytherapy. In recent years, immunotherapy (IMT) showed promising outcome in a number of cancers [13-20]. Case reports of durable remission of gynecologic cancer after IMT were also published [21-25]. However, retrospective studies were only reported in a few numbers. In the present retrospective study, the authors proposed CCRT combined with immunotherapy (ICRT) as a new treatment option for advanced cervical cancer. The authors retrospectively reviewed the medical records of 23 patients with advanced cervical who were treated by CCRT or ICRT between 2000 and 2016 at Chang Gung Memorial Hospital, aiming to discover whether there was any difference in the

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Table 1. — *Basic information of CCRT (15 cases) and ICRT group (eight cases).*

	CCRT group (mean±SD)	ICRT group (mean±SD)	*p*-value
Age (years)	56.6±18.98	59.88±5.96	0.3827
Histological type			
Adenocarcinoma	2	2	
Squamous cell carcinoma	13	6	
Follow-up period (months)	64.71±57.37	98.44±70.79	0.1901
Diagnosis-to-recurrence duration (months)	11.92±8.27	67.32±70.35	0.1464
Recurrence cases	13	3	0.0257*

*SD: standard deviation. * p-value <0.05.*

Table 2. — *Laboratory findings after one month of therapy between CCRT and ICRT group.*

	CCRT group (mean±SD)	ICRT group (mean±SD)	*p*-value
WBC	4526.67±2477.30/μL	6137.5±2450.62/μL	0.1315
RBC	3872666.67±768072.42/μL	4170000±733134.17/μL	0.4375
Hb	10.57±1.42g/dL	11.66±1.72g/dL	0.2315
MCV	85.52±13.02fl	86.59±10.60fl	0.7135
PLT	183714.29±67403.98 /μL	271875±115239.42/μL	0.1100
ANC	3500.99±2148.72/μL	4048.85±2511.24/μL	0.5063
ALC	577.38±412.35/μL	1554.23±745.55/μL	0.0011*

*ANC: absolute neutrophil count, ALC: absolute lymphocyte count, * p-value <0.05*

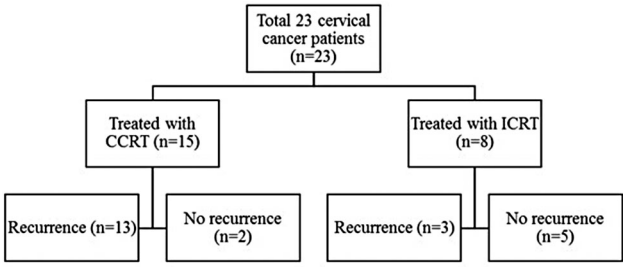

Figure 1. — Flow diagram of CCRT and ICRT groups.

outcomes between treatment by CCRT or ICRT.

Materials and Methods

The authors retrospectively reviewed the medical records of 23 patients with advanced cervical who were treated by CCRT or ICRT (CCRT combined with cytokine-based IMT) between 2000 and 2016 at Chang Gung Memorial Hospital. This study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital, Taoyuan, Taiwan (100- 3902A3).

Inclusion criteria were as follows: (1) International Federation of Gynecology and Obstetrics (FIGO) Stage 2B to 4B, (2) definite pathology report showing squamous cell carcinoma (SCC) or adenocarcinoma (ADC) of the cervix, and (3) follow-up period longer than at least one year. Cancer recurrence was confirmed by positron emission tomography-computed tomography (PET-CT) or tissue biopsy. All these examinations were performed and confirmed by specialists in radiology and pathology.

In CCRT group, patients were treated with traditional platinum-based chemotherapy and radiotherapy. In ICRT group, patients were treated with CCRT and adjuvant IMT. The authors chose Picibanil (OK-432) plus interleukin-2 (IL-2) for adjuvant IMT. OK-432 was administered on day 1 by subcutaneous injection. IL-2 was administered on day 2 by subcutaneous injection.

The authors used the Mann-Whitney U test and Fisher's exact test, and set *p*-value less than 0.05 as statistical significance.

Results

Of all the 23 patients, 15 were treated with CCRT while the remaining eight patients were treated with ICRT. Basic information such as age, histological type of cervical cancer, follow-up period, recurrence, and diagnosis-to-recurrence period were analyzed (Table 1).

Within these parameters, only recurrence between ICRT and CCRT group showed significant difference (37.5% *vs.* 86.67%, $p = 0.0257$). In CCRT group, 13 cases of recurrence were noted. In ICRT group, only three cases of recurrence were observed (Figure 1). That is, patients treated with ICRT had fewer chance of recurrence.

The authors observed that even in recurrence cases, diagnosis-to-recurrence duration was longer in ICRT group than CCRT group (67.32 months *vs.* 11.92 months, $p = 0.1464$); although there was no statistical significance found. They also analyzed the difference of complete blood cell counts and its differentiating counts after one month of treatment (Table 2). Significant difference was only found in absolute lymphocyte counts (ALC) which showed 1,554.23/μL *vs.* 577.38/μL (mean value, $p = 0.0011$) in ICRT and CCRT group respectively.

Absolute neutrophil counts (ANC) in ICRT group were higher than control group (4,048.85/μL *vs.* 3,500.99/μL), although there was no statistical significance. The mean value of white blood cells (WBC) and platelets (PLT) were also all higher in ICRT group; unfortunately, there were no statistical significances noted.

Discussion

CCRT and/or brachytherapy were considered standard treatment choices for advanced cervical cancer. Research has shown that the recurrence rate [10-12] was about 30-50% or more and the five-year survival rate was around 15-50% [26-28]. Several brand-new treatments for cervical cancer such as immunotherapy and thermotherapy were emerging. These therapies all showed promising results [13, 18-20, 29, 30]. In the present study, the authors proposed ICRT as a better treatment choice for advanced cervical cancer. The present data showed that the recurrence rate was significantly lower in ICRT group compared to CCRT group (37.5% *vs.* 86.67%, $p = 0.0257$).

A previous study concluded that ALC after one month of therapy > 1,242/μL had a better outcome in refractory ovarian cancer [31]. The present authors thought that a similar

result would be observed in advanced cervical cancer, and ultimately they found that ALC in ICRT group was higher than the CCRT group (1,554.23/μL *vs*. 577.38/μL, p = 0.0011). Thus, they concluded that ALC after one month of therapy >1,554/μL would show a better outcome in advanced cervical cancer.

OK-432 was an extract from *Streptococcus pyogenes* Su strain which showed anti-tumor properties [32-34]. Its anti-tumor activities were first proved in 1973[35]. Since then, cases of successful outcome after adjuvant OK-432 treatment in some cancer were reported [36, 37]. Previous studies showed that adjuvant OK-432 therapy could lead to a better outcome in cervical cancer [38, 39]. A similar result was noted in the present study as well. Patients underwent ICRT indeed showed a less recurrence rate.

Conclusion

In conclusion, the present results indicated that ICRT could be a better treatment choice than CCRT for advanced cervical cancer. The recurrence rate in ICRT group was significant lower than in the CCRT group. On the other hand, ALC after one month of therapy, >1,554/μL showed better outcome in advanced cervical cancer.

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