Thai Journal of Obstetrics and Gynaecology
September 2002, Vol. 14, pp. 193-200

GYNAECOLOGY

Concurrent Cisplatin-Based Chemoradiation and Adjuvant Hysterectomy for Bulky Stage IB-IIA Cervical Cancer: A Preliminary Report

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ABSTRACT

Objective To evaluate the adverse effects and outcomes of concurrent cisplatinbased chemoradiation and adjuvant hysterectomy for bulky stage IB-IIA cervical cancer.

Design Prospective descriptive study.

Setting Department of Obstetrics and Gynecology, Faculty of Medicine, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University.

Subjects Thirty-four patients with bulky stage IB-IIA cervical cancer attending gynecologic oncology clinic during August 1999 – September 2001.

Intervention All eligible patients were given weekly cisplatin 40 mg/m^2 for 6 cycles concurrently with radiation followed by extrafascial hysterectomy 6 weeks after completion of radiation.

Results Two year progression-free and disease-free survival rates of 79.3% and 68.6% respectively were observed after a median follow-up of 12.0 months. The overall recurrent rate was 15.2%. Local and distant recurrent rates were 6.0% and 3.0%, respectively. Grade 3 neutropenia and anemia were noted in only 5.9% and 2.9% respectively. All acute toxicities were transient and were manageable. There were no treatment-related deaths.

Conclusion For selected patients with bulky stage IB-IIA cervical cancer, concurrent cisplatin-based chemoradiation followed by adjuvant hysterectomy offers an effective treatment option with acceptable toxicity.

Key words: concurrent chemoradiation, adjuvant hysterectomy, stage IB-IIA cervical cancer

Cervical cancer is the second most common type of female cancer worldwide, after breast cancer.[1] It remains the most common cancer and a major health problem in Thai women.[2] Failure to obtain

local-regional control for patients with locally advanced stage disease usually results in death. Stage IB and IIA cervical cancer patients are appropriately treated by either radical hysterectomy with pelvic lymphadenectomy or radiation therapy, with equivalent results.[3] However, larger tumor volumes are associated with a higher incidence of pelvic node recurrence, pelvic failure, and decreased survival.[4,5] Theoretically, chemotherapy and radiotherapy could have a synergistic effect.[6] Since the late 1960s, the optimal treatment for bulky stage IB cervical cancer has been controversial. Several phase II studies have reported that concomitant treatment with cisplatin during radiotherapy results in faster and more complete responses and better survival than expected with radiotherapy alone.[7-14] The recognition, in some centers that patients with bulky stage IB cancers had higher rate of recurrent disease within the cervical area led to the inclusion of adjuvant extrafascial hysterectomy in the treatment regimen for these women. The GOG randomized trial of patients with bulky stage IB cervical cancer treated with concurrent weekly cisplatin, radiation and adjuvant hysterectomy is noteworthy from a histological point of view. A review of the pathology supports an interpretation of the biological benefit from synchronous chemotherapy given with radiation rather than radiation alone.[15] The objective of this study is to evaluate the outcomes of concurrent cisplatinbased chemoradiation and adjuvant hysterectomy for bulky stage IB-IIA cervical cancer in term of progression-free survival, local or distant recurrent rate, and adverse effects.

Materials and Methods

From August 1999 to September 2001, 34 consecutive and previously untreated FIGO bulky stage IB-IIA (primary tumor 4 cm or more, non-neuroendocrine) cervical cancer patients were entered for this study in the Department of Obstetrics and Gynecology, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University. Other eligibility criteria included: age ≤ 70 years, Zubrod performance status score of ≤ 2, no evidence of pelvic or paraaortic lymphadenopathy on computed tomography (CT) scanning and no evidence of cancer on fine-needle aspiration and histologic evaluation in those with clinical enlarged or suspicious-appearing lymph nodes, adequate bone marrow, renal, and hepatic function (WBC ≥ 3000/mm^3, platelet count ≥100,000/mm^3, serum creatinine level 2.0 mg/dL (177 µmol/L), serum bilirubin level ≤ 1.5 times the normal upper limit and serum aspartate aminotransferase level ≤ 3 times the upper of limit), negative anti HIV antibody, no history of other cancers and medically suitable for extrafascial hysterectomy. All eligible patients underwent a complete physical and pelvic examination, chest radiography and abdominal/ pelvic CT scanning. All patients were scheduled to undergo external radiation and intracavitary brachytherapy. Pelvic radiation was delivered with the four-field technique with cobalt-60 or linear accelerator of 4-6 MV. The treatment field was set to extend 3 cm beyond the known extent of disease and to encompass iliac and lower common iliac lymph nodes. Fractions of 2.0 Gy were delivered 5 days a week over a period of 4.5 to 5 weeks, for a total dose of 46- 50 Gy and external irradiation was withheld if the WBC < 3000/mm^3 or platelet count < 100,000/mm^3. High-dose brachytherapy was performed in four intracavitary applications after the completion of external pelvic radiotherapy using Henschke's applicators. The dose to point A (a reference location 2 cm lateral and 2 cm superior to the cervical os) was 30 Gy, for a cumulative dose of 75 Gy, and the cumulative dose to point B (the pelvic wall) was 55 Gy. Patients received cisplatin 40 mg/m^2 intravenously once a week (the total dose not to exceed 70 mg per week) for 6 consecutive weeks concomitantly with radiotherapy. Weekly check up of CBC, urinalysis, AST, ALT, BUN, serum creatinine level and keep up hemoglobin level of at least 10 g/dL. Adverse effects were recorded in accordance with the WHO criteria. Treatment with cisplatin was withheld if the total WBC < 3000/mm^3 or the platelet count < 50,000/mm^3 or if creatinine clearance by the Cockcroft-Gault formula less than 30-50 ml per minute. Extrafascial hysterectomy was performed six weeks

after the completion of radiotherapy. All hysterectomy specimens were evaluated for residual tumor. All patients were evaluated during the courses of treatment and before the surgery. Clinical examination was performed every 3 months during the first year, every 4 months the second year, and every 6 months thereafter. Progression-free survival was calculated from the date of study entry to the date of disease recurrence or the last follow-up visit. Disease-free survival was calculated from the date of completion of treatment to the date of recurrence or the last follow-up visit. Recurrences were classified as local if they were detected in the pelvis, or vagina and as distant if they were detected in extrapelvic locations. Statistical calculations were performed using SPSS software version 10.0 for Windows (SPSS Inc.,Chicago, IL). Two year progression-free survival and disease-free survival were calculated using Kaplan-Meier method. Factors that may be related with recurrence of disease were analyzed using Fisher's exact test or Mann-Whitney U test. All tests were considered significant if p was less than 0.05.

Results

From August 1999 to September 2001, a total of 34 cases of bulky stage IB and IIA cervical cancer underwent extrafascial hysterectomy after receiving concurrent cisplatin-based chemoradiation. The mean age of the patients was 44.18 ± 7.32 years (30-66 years). Approximately 50 percent of cases were between 41-50 years of age. All patients in this study had a good performance status (Zubrod performance status score of 0). Twenty-nine patients were FIGO stage IB and 5 patients were stage IIA. Twenty-two tumors were classified as squamous cell carcinoma, 11 as adenocarcinoma, and 1 as adenosquamous cell carcinoma. Nine carcinomas were graded as well differentiated (G1), 16 as moderately differentiated (G2), and 6 as poorly differentiated (G3). The most common gross appearance of the tumor was exophytic type (73.5%). The tumor size ranged from 4.0 – 8.0 cms, mean 5.35 ± 1.07 cms. The clinicopathological features of the 34 tumors are shown in Table 1. Upon obtaining a surgical specimen and pathologic examination, 18 patients (52.9%) had no residual lesion, 11 patients (32.4%) had microscopic residual lesion and 5 patients (14.7%) showed some macroscopic residual tumor. There were no treatment-related deaths. The frequencies of adverse effects are shown in Table 2. The most common adverse effect was hematologic toxicity. Grade 3 and 2 neutropenia were observed in 2/34 (5.9%) and 8/34 (23.5%). These reactions consisted almost exclusively of transient hematologic effects. Grade 3 and 2 anemia were also observed in 1/34 (2.9%) and 7/34 (20.6%), respectively. Only 1 patient had grade 1 neurotoxicity with spontaneous recovery after finishing treatment. Other adverse reactions such as nausea and vomiting or diarrhea were also found and were manageable. After completion of therapy, 1 patient was subsequently lost to follow-up. The remaining 33 cases have been followed. The mean duration of follow-up was 12.64 ± 6.78 months and the median follow-up was 12.0 months. The 2 year progression-free survival rate was 79.3 % (95 % confidence interval, 60% to 99%) (Fig. 1). The 2-year disease-free survival rate was 68.6 % (95 % confidence interval, 42% to 95%) (Fig. 2). Five patients (15.2%) developed recurrence and 3 of them died. Of these 5 recurrences, 3 recurred within 12 months and the remaining 2 recurred between 1 and 2 years. Concerning the site of recurrence, 1 (3.0%) had distant metastases; another 2 (6.0%) had pelvic recurrences and the remaining 2 (6.0%) had combined distant and pelvic recurrences. The recurrences were analyzed in relation to initial tumor size, histopathologic subtypes, tumor grade and residual tumor. All of these factors were not statistically significant (Table 3).

Table. 1. Characteristics of the Patients

Characteristics	No. of patients (%) (N = 34)
Age (yr)	
≤ 30	1 (2.9)
31-40	9 (26.5)
41-50	18 (53.0)
51-60	5 (14.7)
61-70	1 (2.9)
FIGO stage	
IB	29 (85.3)
IB1 (lesion = 4 cm)	4 (11.8)
IB2 (lesion > 4 cm)	25 (73.5)
IIA	5 (14.7)
Gross appearance	
Exophytic	25 (73.5)
Endophytic	7 (20.6)
Ulcerative	2 (5.9)
Tumor size (cm)	
4.0-5.0	22 (64.7)
5.1-6.0	7 (20.6)
6.1-7.0	3 (8.8)
7.1-8.0	2 (5.9)
Histologic diagnosis	
Squamous cell carcinoma	22 (64.7)
Adenocarcinoma	11 (32.4)
Adenosquamous cell carcinoma	1 (2.9)
Tumor grade	
1 (well differentiated)	9 (26.5)
2 (moderate differentiated)	16 (47.1)
3 (poorly differentiated)	6 (17.6)
Unknown	3 (8.8)

Table 2. Averse Effects

	N = 34				
Adverse Effects	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	percentage of patients				
Neutropenia	44.1	26.5	23.5	5.9	0
Thrombocytopenia	100.0	0	0	0	0
Anemia	35.3	41.2	20.6	2.9	0
Nausea or vomiting	50.0	29.4	17.6	3.0	0
Diarrhea	73.5	26.5	0	0	0
Neurologic effects	97.1	2.9	0	0	0
Cutaneous effects	100.0	0	0	0	0
Pulmonary effects	100.0	0	0	0	0
Cardiovascular effects	100.0	0	0	0	0

Table 3. Analysis of factors affecting recurrence after concurrent cisplatin-based chemoradiation and adjuvant hysterectomy for bulky stage IB-IIA cervical cancer

	Patients with recurrence (%) (n = 5)	Patients without recurrence (%) (n = 28)	*P* value
Tumor size (cm)			0.231
4.0-5.0	2(9.5)	19(90.5)	
5.1-6.0	1(14.3)	6(85.7)	
6.1-7.0	2(66.7)	1(33.3)	
7.1-8.0	0(0.0)	2(100.0)	
Histopathologic subtypes			0.905
Squamous cell carcinoma	3(14.3)	18(85.7)	
Adenocarcinoma	2(18.2)	9(81.8)	
Adenosquamous cell carcinoma	0(0.0)	1(100.0)	
Tumor grade [a]			0.716
1 (well differentiated)	2(22.2)	7(77.8)	
2 (moderate differentiated)	2(13.3)	13(86.7)	
3 (poorly differentiated)	1(16.7)	5(83.3)	
Residual tumor			0.152
No	1(5.6)	17(94.4)	
Microscopic	3(30.0)	7(70.0)	
Macroscopic	1(20.0)	4(80.0)	

[a] Samples where grading was not known were not included in the analysis.

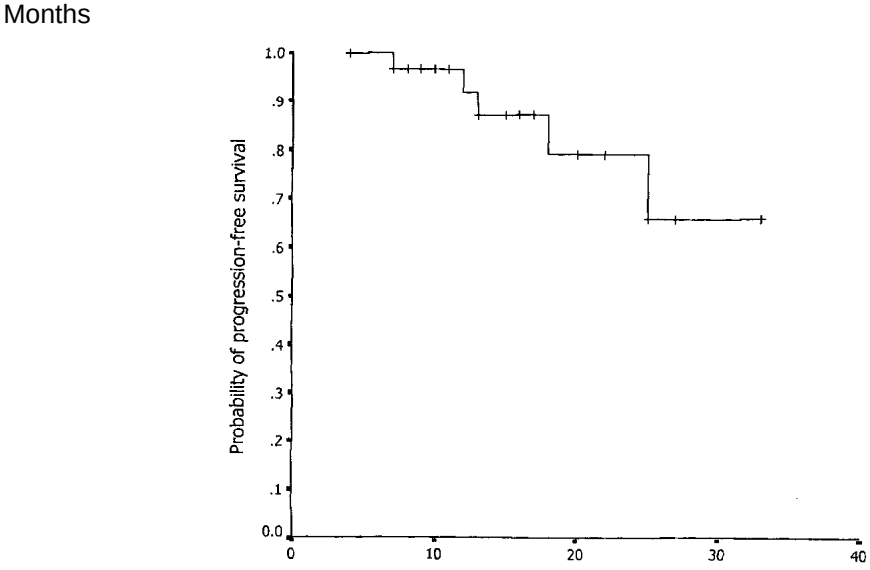

Fig. 1. Kaplan-Meier estimates of progression-free survival in patients with bulky stage IB-IIA given concurrent chemoradiation followed by adjuvant hysterectomy.

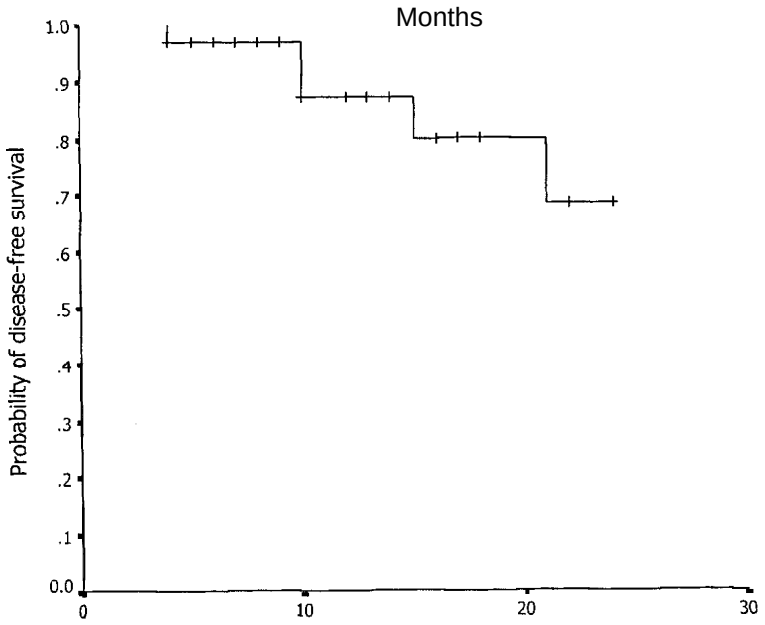

Fig. 2. Kaplan-Meier estimates of disease-free survival in patients with bulky stage IB-IIA given concurrent chemoradiation followed by adjuvant hysterectomy.

Discussion

Recently, five large cooperative randomized clinical trials comparing cisplatin-based chemoradiation with radiation alone or radiation with hydroxyurea have been performed in advanced stage or high-risk cervical cancer patients.[15-19] Based on the results of these five trials, the National Cancer Institute (USA) released a clinical alert declaring the use of chemotherapy concurrently with radiation in women who require radiotherapy as a new standard of treatment for patients with cervical cancer.[20] The optimal treatment for patients with bulky stage IB or IIA lesions is controversial. Because of the increased risk of nodal metastasis and recurrent disease, many treatments and combinations of therapy have been evaluated. Primary radiotherapy is advocated by some authorities owing to the increased need for adjuvant therapy because of poor prognostic factors after radical surgery in these patients.[21] There were also evidences that patients who had planned adjuvant extrafascial hysterectomy after radiation therapy had few central failures, although overall survival rates were only slightly affected.[22] Gallion and associates reported on 75 patients with stage I disease greater than 5 cm in size or barrel-shaped treated with either radiation therapy alone or combined with extrafascial hysterectomy. Recurrent cancer was noted in 47% of patients treated with irradiation alone compared to 16% of those treated with combined therapy ($p<0.01$) The incidence of pelvic recurrence was reduced from 19% to 2% and of extrapelvic recurrence from 16% to 7%.[23] From the GOG study, Keys and colleagues reported that adding weekly infusions of cisplatin to pelvic radiotherapy followed by hysterectomy significantly reduced the risk of disease recurrence and death in women with bulky stage IB cervical cancer.[15] Green and colleagues performed a systematic review of all known randomized controlled trials done between 1981 and 2000 (17 published, two unpublished) of chemoradiation for cervical cancer that included 4580 randomized patients. Cisplatin was the most common agent used. The findings suggest that chemoradiation improves overall survival (hazard ratio 0.71, $p<0.0001$), whether platinum was used (0.70, $p<0.0001$) or not (0.81, $p=0.20$), especially in stage I and II patients. An improvement in

progression-free survival was also seen.[24]

In our institution, concurrent cisplatin-based chemoradiation and adjuvant extrafascial hysterectomy has been used for the treatment of bulky stage IB-IIA cervical cancer since 1999. With a median follow-up of 12.0 months, 15.2% of patients developed recurrence which was lower than that of 21% reported by Keys et al.[15] This may result from shorter period of follow-up while treatment regimen was similar. Many investigators have shown that tumor size is an important prognostic factor, in particular, for stage Ib cervical carcinoma.[25-28] This relation was not found in our study. A larger number of cases may be required to demonstrate this relation. Rate of tumor regression or persistence found at the time of intracavitary insertion might be useful as an indication to substitute operation for a second implant.[22] Perez and colleagues found that tumors that do not regress promptly are more likely to recur.[29] Morphologically persistent cancer in the surgical specimen at adjunctive hysterectomy was found to be a prognostically ominous sign by Russell and coworkers.[30] Maruyama and associates found a small, not significant difference in tumor-free survival between patients with and without persistence at the time of hysterectomy.[31] There was no statistically significant difference between residual tumor, tumor grade or tumor pathology and recurrence of disease at the time of this analysis in our study. In a systematic review and meta-analysis on concomitant chemotherapy and radiotherapy for cervical cancer, grade 3 or 4 hematological and gastrointestinal toxicities were significantly greater in the concomitant chemoradiation group.[24] In our study, severe adverse effects were infrequent. The most common adverse effect was hematologic toxicity with grade 3 neutropenia and grade 3 anemia accounting for 5.9% and 2.9%, respectively. No grade 4 hematologic toxicity was found in this study. Other toxicities (i.e., gastrointestinal and neurological) were transient, minimal, and manageable. As a preliminary report we present in this study, any late toxicity has not been found. A 2-year progression-free and disease-free survival rates were 79.3% and 68.6% after a median 12.0 months of follow-up. In conclusion, concurrent cisplatin-based chemoradiation and adjuvant hysterectomy could be one of the potentially effective treatment options for selected patients with bulky stage IB-IIA cervical cancer, with minimal and manageable toxicity. However, a longer follow-up period is needed to compare survival with other treatment modalities.

Acknowledgments

We are very grateful to Dr. Sumalee Siriaunkgul and Dr. Surapan Khunamornpong, Gynecologic Pathology Division for providing us with all pathology reports; staffs of Therapeutic Radiology and Oncology Division for their sincerely contributions to this study; Mrs. Aree Pantusart and Ms. Sirisopin Teptanee for their assistance on data collecting; Ms. Kittika Kanjanaratanakorn, Clinical Epidemiology Unit, for her advice on statistics.

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