Cisplatin vs. Mitomycin in Concurrent with Radiotherapy for Locally Advanced Cervical Cancer

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Purpose

The primary objective of this study was to compare the time to progression and overall survival of the 2 concurrent radiochemotherapy regimens (radiation + mitomycin vs. radiation + cisplatin) for locally advanced cervical cancer.

The secondary objective was to estimate the response rates and toxicities of the 2 treatment arms.

Introduction

Invasive cervical cancer is the fifth most common cancer disease worldwide and the second most common tumor dependent cause of death in women (1). Since introduction of cervical cancer screening the risk of dying from cervical cancer has been reduced to approximately 70% in industrial countries due to early diagnosis. Screening has not helped to improve stage-related prognosis, and despite the dramatic advances in diagnosis in recent years, a considerable number of patients are still presenting with advanced cervical cancer(2).

The cervical cancer was the most common female cancer in the northern part of Thailand, accounted for 19.6% of all newly diagnosed cases. It was the most common malignancy in the age-group 30-59 and the second most common cancer death for females with the mortality rate 11.0 per 100,000 population, accounted for 13.2 % of all cancer death (3). Recently the treatment of choice for advanced cervical cancer (FIGO stages IIB-IVA) was radiotherapy, where patients receive a combination of external beam radiation and intracavitary brachytherapy (4-7). Since 1984 a num-

ber of small phase II studies have been published, indicating that the combination of radiotherapy with platinum-containing chemotherapy could prove advantageous for these patients (8-21). These data have been extended and confirmed in large, prospective phase III studies, which clearly show that this combined modality therapy, especially with platinum-containing regimens, can lead to a prolonged time to disease recurrence and an increase in overall survival (22-26). Therefore combined modality therapy with radiotherapy and simultaneous application of platinum-containing agents is set to rapidly become the standard of care in this patient population. However our own study using Mitomycin C current with radiotherapy (27) also showed similar result as the reports using Cisplatin concurrent with radiotherapy.

Material and Methods

We enrolled women of under 65 years of age who had stages IIB through IVA squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the cervix according to the staging system of the International Federation of Gynecology and Obstetrics from May 2004 and December 2006. All cancers were confirmed histologically by the pathologist. Women with a Karnofsky performance status of 70-100% and complete blood count, renal, and hepatic functions that were within normal ranges were eligible for the study. Patients with disease outside the pelvic cavity and distant metastases were excluded. Each patient was required to undergo a complete physical examination, a pelvic examination, chest radiography, cystoscopy, proctoscopy, and intravenous pyelography or abdominal computed tomography to determine the clinical stage of the cancer. Patients were required to understand the trial and provide written informed consent.

Radiotherapy:

All patients were scheduled to undergo external beam irradiation, and intracavitary brachytherapy, and they randomly assigned to receive 1 of the 2 chemotherapy regimens during the period of radiotherapy. The prescribed regimen of radiotherapy was identical in both groups. External-beam radiation was delivered with anteroposterior and posteroanterior opposed beams or the use of 4-field box technique. The fields could be modified to include areas of known tumor. When cancer extends to the lower third of the vagina, it is prudent to cover the full length of the vaginal canal and to electively treat the inguinal lymph nodes. The total dose of external beam radiotherapy was 50-60 Gy given in fractions of 1.8-2.0 Gy five times a week for 5-6 consecutive weeks. Central shielding was performed by a 4-cm wide midline bar after the dose of 40-44 Gy has been delivered. The radioisotope used for high dose rate (HDR) intracavitary radiotherapy was Iridium-192 (Ir-192) The first

intracavitary treatment was performed after the additional external-beam therapy was delivered with a central shielding. We gave 4-6 sessions of HDR brachytherapy using Fletcher's type applicator to each patient. The rectal dose was limited to less than 60 % of point A. The brachytherapy was performed within 2 weeks after the completion of pelvic irradiation, with the goal of keeping the total treatment time under 8 weeks when possible. The aim is that all patients receive a total cumulative dose to point A (a reference location 2 cm lateral and 2 cm superior to the cervical os) of at least 75 Gy. The suggested maximal doses to bladder and the rectum were 70 and 65 Gy, respectively. Within 24 hours after the first radiation fraction was administered, patients in both groups received the first dose of chemotherapy.

Chemotherapy :

The patients were randomly assigned to receive one of the two chemotherapy regimens; which were given concomitantly with external beam radiotherapy.

Arm1: Cisplatin 40 mg/m^2/day on weekly schedule for 6 cycles

Arm2: Mitomycin C 10 mg/m^2 on day 1 and 29

Results:

Between May 2004 and December 2006, 343 patients with locally advanced carcinoma of the cervix, FIGO Stage IIB-IVA, were entered into this study. The patients were randomized into 2 arms. Table 1 shows the patient characteristics of both groups. They were balanced in number and median age. However, Arm 1 had more stage IIIB-IVA and more squamous cell histology compared to Arm 2.

Table 1. Patients Characteristics

	Arm 1: Cisplatin	Arm 2: MMC
Number of Pts.	170 (49.9%)	172 (50.1%)
Stage IIB	110	96
IIIA	2	2
IIIB	59	72
IVA	0	2
Complete Rx.	168	167
Incomplete Rx.	3	5
Median age	49	50
Histology		
Squa. Cell CA	137	152
Adeno CA	29	19
Adeno Scc CA	5	1

The median follow-up time was 17.5 months(2.1 - 42.0 mos.). The 3-year actuarial disease-free survival (DFS) was 76.2%, and 66.3%, for arms 1, 2 respectively(Table 2). The local recurrence was 7.0%, and 17.4%, for arms 1, 2 respectively. The metastatic rates were 13.4%, and 15.7%, for arms 1, 2 respectively. At the time of analysis, there were minimal late side effects, especially in gastrointestinal and genitourinary systems (Table3). Figure 1 and 2 shows the disease-free survival curve and overall survival curve, repectively.

Table 2. Pattern of failure

	Arm 1 : Cisplatin	Arm 2 : MMC
Total patients	171	172
Relapsed and Progressive disease	30 (17.5%)	46 (26.7%)
No evidence of disease	130 (76.2%)	114 (66.3%)

Late complications were evaluated for all patients who received the radiochemotherapy. Acute adverse effects occurred during or within 3 months from the end of radiation therapy. Thereafter, the late effect were utilized, according to the RTOG criteria . Acute side effects were generally tolerable in both arms, and most of the patients completed the treatment. Bone marrow toxicity was comparable in both treatment arms. The types and frequencies of late complications are shown in Table 3.

Table 3. Late complications

Bladder complication	Grade 1	Grade 2	Grade 3	Grade 4
Arm 1: Cisplatin	6	1	1	0
Arm 2: MMC	7	2	0	0
Rectal complication	Grade 1	Grade 2	Grade 3	Grade 4
Arm 1: Cisplatin	10	0	0	2
Arm 2: MMC	10	3	5	1

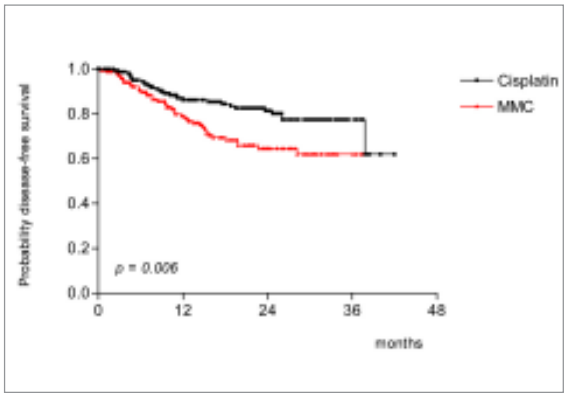

Figure 1 : Disease-free survival curve

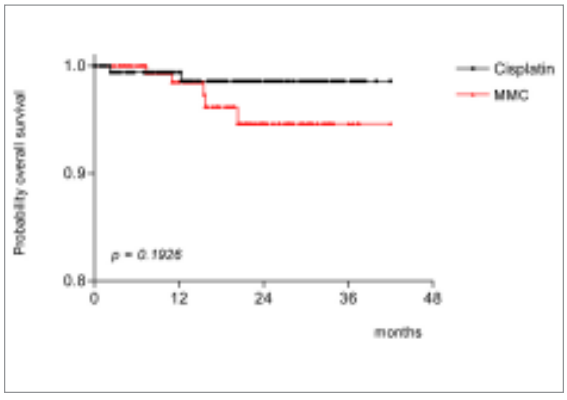

Figure 2 : Overall survival curve

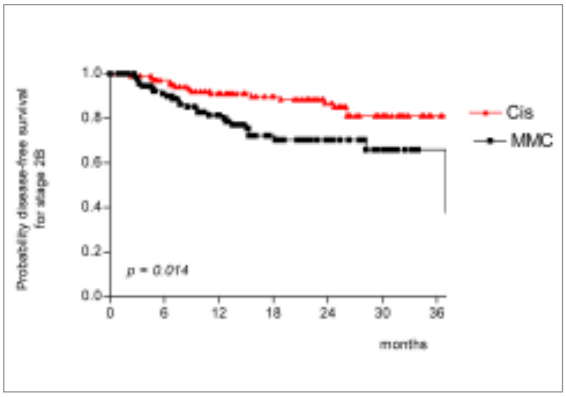

Figure 3 : Disease-free survival of Stage IIB patients

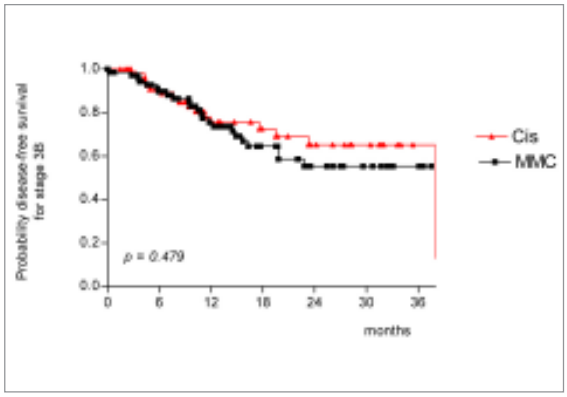

Figure 4 : Disease-free survival of Stage IIIB patients

Discussion:

From May 2004 and December 2006, there were 343 locally advanced cervical cancer patients entered onto the study. All patients received concurrent radiochemotherapy as a primary treatment. There were 170 patients in Arm 1 (RT + cisplatin), 172 patients in Arm 2 (RT+ Mitomycin). From the analysis, we found that the 3-year disease-free survival rates were significantly different favoring Cisplatin Arm (Arm 1). The disease-free survival curves (Figure 1) showed the difference, favoring Arm1 (p=0.006). However, the 3-year overall survival rates were not significantly different among the 2 regimens. The overall survival curves(Figure 2) showed the trend of the inferiority of the Mitomycin Arm (p=0.19) when compared with the Cisplatin Arm. Regarding the imbalance of stage distribution, we analyzed the disease-free survival by stage. The disease-free survival were significantly difference (p=0.01) in only stage IIB disease group (Figure 3). While the disease-free survival were not significantly difference (p=0.479) between the 2 treatments groups in stage IIIB patients (Figure 4).

Conclusions:

The overall survival of these concurrent non-platinum chemoradiation were not inferior to the standard cisplatin-based regimen. This study demonstrates the results of a large randomized clinical study. It requires the longer follow-up for the late complications.

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