Concurrent Radiation Therapy and Irinotecan in Stage IIIB Cervical Cancer

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Abstract

The present study was to evaluate the efficacy and toxicity of concurrent radiation therapy and irinotecan in patients with stage IIIB cervical cancer. Fifteen patients with no prior radiation therapy and chemotherapy were enrolled in the study. These patients received 50 Gy of external radiation to whole the pelvis, 50 Gy with an additional dose of 6-10 Gy to the parametrium and 1 or 2 sessions of intracavitary Cesium-137. Weekly intravenous infusion of 40 mg/m^2 irinotecan was given for 5 cycles during the course of radiation therapy. Of 14 evaluable patients, 4 (28.6%) achieved complete response and 7 (50.0%) achieved partial response. Treatment-related toxicity included grade 1 & 2 anemia, grade 1 & 2 leucopenia, grade 1 & 2 neutropenia and 7.1 per cent grade 3 diarrhea. No grade 4 toxicity or treatment-related death occurred in the present study.

Conclusion : Irinotecan is a promising new cytotoxic agent in treatment concurrently with radiation therapy in newly diagnosed locally advanced cervical cancer. This modality of treatment appeared to be effective with acceptable toxicity.

Key word : Cervical Cancer, Radiation Therapy, Irinotecan

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Cervical cancer is the most common cancer among women in Siriraj Hospital with an incidence of 14-16 per cent of new patients diagnosed with cancer each year[1]. Approximately 80 per cent of these patients presented with locally advanced diseases (stage II to IV according to International Federation of Gynecology and Obstertrics staging system 1994).

The limitation of radiation therapy (RT) in controlling locally advanced cervical cancer is due to the dose required to control a large tumor exceeding normal tissue tolerance. Combined RT and chemotherapy is one of the several methods used to overcome this problem.

In addition to its cytoreductive effect, concurrent chemotherapy and RT offers a number of advantages including avoidance of delay in the initiation of RT, inhibition of repair of sublethal damage from RT and synchronizing cells to the radiosensitive phase of the cell cycle. Since the early 1980s, several phase III studies investigating the role of various concurrent chemotherapies have been reported. The agents most commonly employed include hydroxyurea, cisplatin, 5-fluorouracil and mitomycin-C. In 1999, the US National Cancer Institute (NCI) issued a clinical alert with regard to positive survival advantages found with platinum-based concurrent chemoradiotherapy in 5 prospective randomized studies [2-6] in women with locally advanced (stage IB to IVA) cervical cancer.

Irinotecan hydrochroride (CPT-11) is a semisynthetic derivative of camptothecin, an alkaloid contained in such plants called Camptotheca acuminata. Irinotecan stabilizes the topoisomerase I–DNA complex which is necessary for DNA replication. Several phase II studies have shown that irinotecan is an active agent against advanced or recurrent cervical cancer.

In view of these favorable outcomes, the authors conducted a phase II study to evaluate the therapeutic activity and toxicity profile of concurrent RT and irinotecan as primary treatment in patients with newly diagnosed stage IIIB cervical cancer.

PATIENTS AND METHOD

Patients were included in this study if they met the following criteria : histologically confirmed stage IIIB squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma, measurable disease by physical examination and/or imaging studies, aged between 30 and 60 years, Karnofsky performance status (KPS) $\geq$ 70, adequate bone marrow function (Hemoglobin $\geq$ 10 g %, white blood cell $\geq$ 4,000/mm^3, absolute neutrophil count $\geq$ 1,500/mm^3, platelet count $\geq$ 100,000/mm^3), adequate renal and hepatic function (creatinine $\leq$ 1.5 mg/ml, bilirubin $\leq$ 2 mg %, SGOT & SGPT $\leq$ 2 x upper normal limit). Eligible patients gave written informed consent.

Patients were excluded for any of the following criteria : involvement of paraaortic lymph node, previous or concurrent malignancy except for adequately treated squamous or basal cell skin cancer, previous pelvic radiation therapy or chemotherapy, concurrent severe medical conditions including psychiatric disorders.

Prior to enrollment, a complete medical history review and physical examination was recorded. The initial evaluations included cystoscopy, proctoscopy, chest radiography and computed tomography of the whole abdomen. Complete blood count (CBC) and blood chemistry were also performed.

External RT was delivered with anterior/posterior opposed beams of cobalt-60 photon. The treatment fields extended from the transverse process of L5 to the inferior border of obturator foramen. The lateral borders of treatment fields were at 2 cm from the pelvic brim. The total dose of 50 Gy, 1.8 Gy per fraction was delivered to whole pelvis with midline shielding at 30 or 36 Gy. The additional dose of 6 to 10 Gy, 2 Gy per fraction was delivered to bilateral parametrium after complete pelvic radiation.

Cesium -137 was used as low-dose-rate intracavitary radiation in 1 or 2 sessions for total Time-dose-fractionation (TDF) 81 or 54 at point A (2 cm lateral to a point 2 cm cephalad to internal os of cervix) respectively. The intracavitary treatment was performed during external beam radiation.

A dose of 40 mg/m^2 irinotecan diluted in 100 ml 0.9 per cent normal saline was given as 60-minute intravenous infusion on day 1,8,15, 22 and 29 of RT. Before the administration of irinotecan, patients received intravenous antiemetics and steroids. Atropine sulphate was administered in patients who developed cholinergic syndrome.

Dose level and treatment schedule of irinotecan were modified based on side effects. Chemotherapy was delayed if patients developed $\geq$ grade 2 on Radiation Therapy Oncology Group (RTOG) radiation morbidity scoring criteria. Patients who did not meet treatment criteria after 2-week delay of chemotherapy were removed from the study. If patients experienced $\geq$ grade 3 toxicity, the dose of a subsequent

cycle of irinotecan was reduced by 5 mg/m^2. Patients who needed dose reduction during the course of treatment continued to receive the same reduced dose unless further dose reduction was required.

For patients with adenocarcinoma who achieved clinical complete response, extrafascial hysterectomy and bilateral salpingooophorectomy were performed at 4 to 6 weeks after completion of treatment.

Tumor response and toxicity criteria

During treatment, patients were evaluated weekly by clinical assessment and CBC was done before each cycle of irinotecan. At the end of treatment, patients were evaluated by physical examination, pelvic examination, CBC and blood chemistry. After completion of treatment, patients were followed monthly for the first 3 months.

Patients were considered evaluable for response if they received at least 3 cycles of irinotecan. Responses were evaluated according to WHO criteria: complete response (CR) was defined as the total disappearance of all evidence of the tumor for at least 4 weeks, partial response (PR) was a $\geq$ 50 per cent reduction in the sum of products of the longest perpendicular diameter of measurable lesion (s) for at least 4 weeks, stable disease (SD) was < 50 per cent reduction or a < 25 per cent increase in the sum of products of the longest perpendicular diameter of measurable lesion (s) for at least 4 weeks, progressive disease (PD) was $\geq$ 25 per cent increase in the sum of products of the longest perpendicular diameter of measurable lesion (s) for at least 4 weeks or the appearance of a new lesion.

Toxicity was assessed according to RTOG radiation morbidity scoring criterias except for cramping abdominal pain at the time of each evaluation.

Statistical analysis

All patients enrolled in the study were monitored for treatment related toxicity and response which were estimated by per cent.

RESULTS

Patient characteristics

A total of 15 patients were enrolled in the study between May 2001 and February 2002. Of all patients registered, one was excluded from analysis due to treatment refusal and she was lost.

The characteristics of 14 evaluable patients are listed in Table 1. The median age was 47 years (range 33 to 56 years). The median Karnofsky Performance Status (KPS) was 90 (range 80 to 90)

Table 1. Patient characteristics.

Characteristics	No. of patients
Total number	14
Age	
Median (range)	47 (33-56) years
Histology	
Squamous cell CA	9
AdenoCA	3
Adenosquamous cell CA	2
KPS	
90	12
80	2

Treatment and compliances

The median total dose of radiation was 86 Gy (range 80.6 to 100 Gy) The median total time of radiation was 7 weeks (range 6 to 11 weeks). RT was interrupted during the course of treatment in 2 patients due to skin toxicity and severe abdominal cramping pain.

A total of 67 cycles of irinotecan were administered. The median number of chemotherapy cycles received was 5 (range 3 to 5). Twelve patients (85.7%) completed full-scheduled administration of chemotherapy. Two patients did not complete 5 cycles of 5 cycles because of severe abdominal cramping pain in one and patient refusal in one.

Treatment responses

Of 14 patients evaluated, CR occured in 4 (28.6%) patients and PR in 7 (50.0%) The overall response rate was 11 (78.6%). Two patients had SD and 1 had PD. Table 2 lists treatment responses by histology. No patient in this study achieved complete clinical response at 1 month after completion of treatment. One patient who developed lung metastasis died 3 months after completion of treatment.

Toxicity

Table 3 lists the toxicity which occurred in the present study. The major side effects were hematotogic and gastrointestinal disturbances. Anemia was the most frequent side effect which occurred in 12 (85.7%) patients with grade 1 and grade 2 in 8 and 4 patients respectively. Leucopenia and neutropenia were observed in 11 (78.6%) patients with grade 1 in

Table 2. Treatment responses.

Characteristics	Treatment response							
	CR		PR		SD		PD	
	N	%	N	%	N	%	N	%
Overall	4	28.6	7	50.0	2	14.3	1	7.1
Histology								
Squamous cell CA	2		2		1		1	
AdenoCA	1		1		1		-	
Adenosquamous cell CA	1		1		-		-	

Table 3. Treatment toxicities.

Characteristics	Treatment toxicity					
	Grade 1		Grade 2		Grade 3	
	N	%	N	%	N	%
Hematologic						
Anemia	8	57.1	4	28.6	-	-
Leucopenia	6	42.9	3	21.4	-	-
Neutropenia	-	-	2	14.3	-	-
Nonhematologic						
Diarrhea	4	28.6	4	28.6	1	7.1
Nauseavomitting	1	7.1	-	-	-	-
Skin	-	-	3	21.4	-	-
Genitourinary	3	21.4	-	-	-	-

6 and grade 2 in 5. All recovered within 1 week without discontinuation of chemotherapy in all 67 cycles of chemotherapy delivered.

Diarrhea was the most severe side effect in the present study but only 1 (7.1%) patient experienced grade 3 toxicity. All recovered within 1 week. No cycle of chemotherapy was discontinued due to this toxicity. Other side effects included skin reaction in 3, nausea or vomitting in 1 and genitourinary symptom in 3 patients. Two patients experienced severe abdominal cramping pain. No grade 4 toxicity or treatment-related death was found during the present study.

DISCUSSION

Based on the results of 5 randomized prospective phase III trials of concurrent chemoradiotherapy in locally advanced cervical cancer, US NCI recommended that strong consideration should be given to the incorporation of concurrent chemotherapy and RT in women who require RT for treatment for cervical cancer. The potential magnitude of those benefits can only be estimated from one trial in which concurrent therapy was compared with optimal RT alone. There remains uncertainty with regard to the optimal choice of chemotherapy (drugs and schedules). The Gynecologic Oncology Group has chosen weekly cisplatin at the dose of 40 mg/m^2 as its standard with which newer regimens will be compared[7].

Irinotecan is an agent that has shown activity against a wide range of human cancers. As a single agent in cervical cancer, several phase II studies have shown 13-21 per cent response rates in advanced or recurrent disease[8-11]. Sugiyama et al reported the outcome of the first study of combined cisplatin and irinotecan in advanced or recurrent cervical cancer with a 59 per cent response rate[12]. For newly diagnosed locally advanced disease, two phase II Japanese studies reported a 78 to 81 per cent response rate with irinotecan and cisplatin as neoadjuvant chemotherapy[13,14].

Irinotecan was selected for concurrent treatment with RT in the present study due to its demonstrated activity in several phase II trials including rectal and non small cell lung cancer[15-17]. No study of concurrent RT and irinotecan in newly diagnosed locally advanced cervical cancer has been reported before. Of 14 evaluable patients, the overall response rate was 78.6 per cent.

In view of toxicity, diarrhea was the most severe side effect in the present study. All patients with diarrhea were controlled with loperamide and recovered within 1 week. Anemia which is also common in patients with cervical cancer occurred most frequently but no grade 3 or 4 toxicity was found. Most recovered with blood transfusion. Leucopenia and neutropenia also recovered within 1 week without omitting irinotecan on a subsequent cycle. Interruption of RT during the course of treatment was needed in 2 patients. No grade 4 toxicity or treatment-related death was found in the present study.

The increase in dose intensity of irinotecan may have improved the response rate in the present study but toxicity may also be increased due to overlapping side effects of this agent and RT to pelvic field. Further study to evaluate the combination of irinotecan and other agents such as cisplatin concurrently with RT is warranted to improve the response rate with acceptable toxicity.

In conclusion, irinotecan is a promising new cytotoxic agent in treatment concurrently with RT in newly diagnosed locally advanced cervical cancer. The major dose-limiting side effects were diarrhea and leucopenia, Interruption of RT and dose reduction of chemotherapy during the course of treatment were needed in a few patients. This modality of treatment appeared to be effective with acceptable toxicity.

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การรักษาด้วยรังสีพร้อมกับยาเคมีบำบัดอิริโนทีแคน ในมะเร็งปากมดลูกระยะ IIIB

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การศึกษาเพื่อประเมินประสิทธิภาพและผลข้างเคียงของการรักษาด้วยรังสีพร้อมกับยาเคมีบำบัด irinotecan ในมะเร็งปากมดลูกระยะ IIIB ผู้ป่วยใหม่จำนวน 15 รายซึ่งไม่เคยได้รับการรักษาด้วยรังสีหรือยาเคมีบำบัดมาก่อนได้รับการรักษาด้วยการฉายรังสีที่อุ้งเชิงกราน 50 เกรย์โดยเพิ่มปริมาณรังสีที่พารามีเตรียม 6–10 เกรย์และใส่แร่ซีเซียม 137 1–2 ครั้ง พร้อมกับการฉีดยา irinotecan 40 มก/ม^2 เข้าหลอดเลือดดำทุกสัปดาห์ระหว่างการฉายรังสีเป็นจำนวน 5 ครั้ง ผลการรักษาในจำนวน 14 รายที่ประเมินได้พบว่า 4 ราย (ร้อยละ 28.6) มีการตอบสนองแบบสมบูรณ์และ 7 ราย (ร้อยละ 50.0) มีการตอบสนองแบบไม่สมบูรณ์ ผลข้างเคียงที่สำคัญ ได้แก่ อุบัติการณ์เม็ดเลือดแดงต่ำเกรด 1 และ 2, เม็ดเลือดแดงขาวต่ำเกรด 1 และ 2, เม็ดเลือดแดงขาวนิวโตรฟิลต่ำเกรด 1 และ 2 และถ่ายเหลวเกรด 3 ร้อยละ 7.1 ในการศึกษานี้ไม่พบผลข้างเคียงเกรด 4 หรือการเสียชีวิตที่เกี่ยวเนื่องกับการรักษา

สรุป : Irinitecan เป็นยาเคมีบำบัดที่สามารถให้พร้อมกับการรักษาด้วยรังสีได้ในผู้ป่วยมะเร็งปากมดลูกระยะลุกลามเฉพาะที่ โดยให้ผลการรักษาที่มีประสิทธิภาพและผลข้างเคียงที่ยอมรับได้

คำสำคัญ : มะเร็งปากมดลูก, รังสีรักษา, ยาเคมีบำบัดอิริโนทีแคน

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