RESEARCH ARTICLE

Concurrent Chemoradiation with Weekly Gemcitabine and Cisplatin for Locally Advanced Cervical Cancer

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Abstract

Background: For more than 80 years, the standard treatment of locally advanced cervical cancer was radiotherapy. However, based on several phase III randomized clinical trials in the past decade, concurrent cisplatin-based chemoradiotherapy is the current standard for this disease. Gemcitabine has potent radiosensitizing properties in preclinical and clinical trials, so it can be utilized simultanously with radiation. Materials and Methods: Thirty women with untreated invasive squamous cell carcinoma of the cervix of stage IIB to stage IVA were enrolled in the study in the Radiation Oncology Department of Imam Khomeini Hospital in Tehran from September 2009 to September 2010. Sixty mg/m^2 gemcitabine followed by 35mg/m^2 cisplatin were concurrently administered with radiotherapy to the whole pelvic region on day one of each treatment week for five weeks. One and three months after treatment, patients underwent a complete physical examination and MRI to determine the response to treatment. Results: The mean age of patients was 58.1±11.8 (29-78) years. After 3 months of treatment, 73.3% had complete and 26.7% demonstrated partial response to treatment. Grade 3 anemia was seen in 10%, grade 3 thrombocytopenia in 3.3% and grade 3 leukopenia in 10% of the patients. Conclusions: According to the positive results of this study in stage IIB, further phase II and III clinical trials are suggested to evaluate the role of chemoradiation using Gemcitabine for advanced cervical cancers.

Keywords: Cervical cancer - gemcitabine - radiotherapy

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Introduction

Cervical cancer is the most frequent gynecological cancer worldwide and the most frequent cancer in women in many undeveloped and developing countries, where almost half of the patients are diagnosed with locally advanced disease (Petersson, 1988).

Annually, approximately 12,710, American women are diagnosed with cervical cancer, and 4,290 die from disease (Siegel et al., 2011).

In developed countries, cervical cancer accounts for only 4.2% of new cancers, with a lifetime risk of 1%, while in developing countries such as Honduras, it remains the most frequently diagnosed cancer in women with an incidence of 29/100,000 (Jemal et al., 2003).

The highest incidence rates of cervical cancer are observed in Latin America and the Caribbean, sub-Saharan Africa and in South and Southeast Asia. According to Mousavi et al study in Iran cervical cancer was the second common cancer after breast cancer , and also it was the second mortality cause due to cancer after ovarian cancer (Mousavi et al., 2008).

The prognosis for cervical cancer patients has improved in the past decade as a result of improvements in early detection, advances in surgery and radiotherapy, development of new drugs effective in cervical carcinoma and most importantly, due to incorporation of the multidisciplinary approach in the treatment. Interestingly, the standard treatment of locally advanced disease, for almost 80 years, was radiotherapy. However, based on several phase III randomized clinical trials in the past decade, concurrent treatment with cisplatin -based chemotherapy and radiotherapy is the current standard of treatment for this disease (Eifel, 2001). This combined modality approach produces an absolute increase in 5-year survival of 12% as compared with radiation alone. These data obtained from a recent meta-analysis of randomized trials and based on analysis of individual patient data have a clear and powerful impact for countries such as Honduras, where at least half of the cervical cancer patients are diagnosed with locally advanced disease (Eifel et al., 2001).

Radiotherapy and concurrent chemotherapy were shown to improve the control of pelvic disease and significantly increased overall survival (OS) rates in five randomized trial (Duenas-Gonzales et al., 2003) and are the currently recommended treatment in locally advanced cervical cancer, following a National Cancer Institute

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(NCI) clinical announcement (NCI, 1999). Cisplatin-based chemotherapy is the most widely used, but as yet no single drug or schedule is accepted as standard.

Among the schedules used in randomized trials, weekly cisplatin 40mg/m^2 with concurrent radiotherapy seems to have the better therapeutic ratio.

Gemcitabine is a drug with a modest single-agent activity in metastatic or recurrent cervical carcinoma (Goedhals et al., 1996) but has shown definite radiosensitizing properties in preclinical trials (Lawrence et al., 1997) including in human cervical carcinoma cell lines (Mohideen et al., 1997). Gemcitabine has been tested with concurrent radiotherapy as a single agent in cervical cancer in two studies (McCormack et al., 2000).

Several preclinical and clinical studies have proven the synergy between cisplatin and gemcitabine (Kanzawa et al., 1997) and there are phase I studies testing the combination of cisplatin and gemcitabine with concurrent radiotherapy in pancreatic cancer and in non-small-cell lung cancer (NSCLC) that show different MTDs (Brunner et al., 2000).

The current study was designed to determine whether the addition of weekly gemcitabine with dose of 60mg/m^2 to a standard combination of weekly cisplatin 40mg/m^2 and concurrent radiotherapy is safe and feasible and to evaluate the efficacy of the two-drug combination in locally advanced cervical carcinoma.

Materials and Methods

Eligibility criteria

Patients with histologically confirmed squamous cell carcinoma (International Federation of Gynecology and Obstetrics IIB-IVA), previously untreated were enrolled in this study from September 2009 to September 2010.

All cancers were histologically confirmed. patients with extra pelvic disease were not eligible. No prior radiotherapy or chemotherapy was allowed. patients were required to be at least 18 years old and karnofsky performance status ≥70 with estimated life expectancy of at least 1 year. Adequate bone marrow reserve (wbc>3*109, ANC>3*109/L, Platelets>100*109/L and Hb>9gr/100ml) and normal renal function and liver function was mandatory for starting the treatment. Written informed consent was obtained from patients prior to their participation in the study.

Treatment planning

The 35 mg/m^2 cisplatin was administered intravenously over 30 minutes, immediately followed by 60mg/m^2 gemcitabine (given intravenously over 30 minutes) on day 1 of each treatment week. Both drugs were administered between 1 and 2 hour before radiotherapy. Radiotherapy was administered to the whole pelvic region in 25-27 fractions for a total dose of 50-54Gy, then followed by 1 or 2 weeks later by intracavitary brachy therapy.

External Radiotherapy was administered by a four field box technique (antero posterior, postero anterior and two parallel) using a co-60 machine at a dose of 2Gy daily. Point A (reference location 2cm lateral and 2cm superior to external cervical orifice); received 85-90Gy with External radiation and brachy therapy. Field borders for anterior and posterior fields were L5-S1 interspace (superior) and bottom of the obturator foramen or the lower extention of the tumor with 2-3 margin and laterally 1cm beyond lateral margins of bony pelvic wall. For lateral fields, limits were anterior edge of pubic symphysis (anterior) and S2-S3 interspace (posterior).

Baseline and treatment assessments

All patients underwent a complete physical examination including pelvic examination by a multidisciplinary team (Gynecologic oncologist and radiation oncologist) to determine the clinical stage according to FIGO classification .Patients had chest X-ray, abdominal and pelvic CT-scan, complete hematology and chemistry tests and sigmoidoscopy or cystoscopy if necessary.

Hematology and chemistry test was obtained before each chemotherapy injection. Radiation and chemotherapy was stopped if the WBC count was <2000/mm^3, the platelet count <100,000/mm^3 or in the event of severe (grade 4) radiation induced gastrointestinal and genitourinary toxicity. Blood transfusion had done if Hb<10gr/dl.

Patients underwent response evaluation, consist of vaginal and rectal examination one and three month after finishing chemoradiation treatment. Pelvic MRI was done three months after treatment. For response evaluation, WHO criteria were used, complete response was defined as the disappearance of all gross lesions for 1 month after completion of radiotherapy and absence of new lesions. Partial response was defined as a >50% reduction of tumor size for 1 month after completion of radiotherapy. Progressive disease was defined as the appearance of any new lesion during treatment or a >25% increase in size of local tumor. For acute and late radiotherapy toxicity RTOG classification of adverse effects was used.

Results

Patients characteristics

The mean age of thirty patients that participated in our trial was 58.13±11.83 (minimum 29 and maximum 78) years. According to the staging process, 56.6% of patients were in stage IIB,13.3% stage IIIA,16.7% stage IIIB ,6.7% stage IVA and 6.7% had LN+. All of the patients were received external beam radiation therapy and they were treated by Cobalt 60 machine. Sixty six point seven percent of patients received total dose of 54Gy, 13.3% 52Gy and 20% 50Gy.

Results of treatment

Clinical response to our treatment in first evaluation and after 3 months and clinical response according to

Table 1. Response to Therapy in Follow Up 1 and 3 Months After End of Treatment

Response to treatment	Physical exam after 1 months	Physical exam after 3 months
Complete response	66.7% (20)	73.3% (22)
Partial response	33.3% (10)	26.7% (8)
No response	-	-

Table 2. Treatment Results According to Stage in Physical Exam 3 Months After Therapy

Stage of disease	Complete response	Partial response
2B	16 (94.1%)	1 (5.9%)
3A	2 (50%)	2 (50%)
3B	3 (60%)	2 (40%)
4A	1 (50%)	1 (50%)
4A LN+	0	2 (100%)

Table 3. Shows Hematologic Side Effects during Treatment in 3 Weekly Evaluation

Grade		1st evaluation	2nd evaluation	3rd evaluation
Anemia	1	40%	36.6%	36.6%
	2	23.3%	33.3%	33.3%
	3	0	10%	0
Leucopenia	1	3.3%	33.3%	13.3%
	2	6.6%	10%	40%
	3	0	10%	10%
Thrombocytopenia	1	3.3%	3.3%	33.3%
	2	0	0	6.6%
	3	0	0	3.3%

Table 4. Shows Rate of Gastrointestinal, Genitourinary and Skin Side Effects during Treatment and 3 Months after Therapy

Side effects: Grade		During treatment	3 months after therapy
Nausea and vomiting:	2	36.7%	0
	3	13.3%	0
Cystitis:	2	33.3%	30%
	3	10%	0
Diarrhea:	2	46.7%	10%
	3	10%	0
Dermatitis:	2	36.7%	6.7%
	3	10%	0

stages of patients were recorded in Table 1 and 2, in order.

As shown in Table 2, by increasing stage from 2B to 3B and 4 LN+, the rate of response is decreasing significantly ($p<0.05$).

After 3 months of treatment, all of patients were evaluated by MRI. In this evaluation 53.2% (16 cases) of patients didn't show any residue or metastasis intra or extra of pelvis. Sixteen point seven percent (5 cases) of patients had residue up to 2.5cm in cervix, who were referred to salvage surgery.

Seven patients (23.3%) had evidences of metastasis in liver (2 cases), para aortic LAP (3 cases)and pelvic wall (2 cases). It is important to notice that 5 of these 7 cases were free of any residue or disease in cervix.

As shown in Table 3, this treatment induced increasing of grade 1 of leucopenia in 2nd evaluation and grade 1 of thrombocytopenia in 3rd evaluation significantly ($p<0.05$). Fourteen patients (46.7%) received packed cell [minimum 2 units and maximum 3 units (1 patient)] and 12 patients got injections of G-CSF during treatment (minimum 1 unit and maximum 2 units).

Hospitalization of patients because of hematologic toxicities or oral intolerance occurred in 5 patients (16.7%) and treatment interrupted in 8 patients (26.7%)in range of 2-7 days in order to hematologic and skin side effects or oral intolerance.

Discussion

The radiosensitizing properties of gemcitabine are well recognized even if the intimate mechanism of action is only partially understood. Based on the preclinical studies, various mechanisms have been proposed, which include inhibition of DNA repair, increasing apoptosis rate, or inducing cell cycle redistribution, causing cells to accumulate in a more radiosensitive phase of the cell cycle. Finally, exposure to gemcitabine produces a dNTP (deoxynucleotriphosphate) pool perturbation in the cell that, in combination with cell cycle redistribution into the S phase, impairs the repair of DNA damage induced by radiation.

The combination of radiotherapy and gemcitabine has been studied in pancreatic carcinoma (Okusaka et al., 2004) cervical carcinoma (Porras et al., 2003a; 2003b), NSCLC (van Putten et al., 2003) and head and neck cancer, whereas the combination of gemcitabine and cisplatin has been extensively evaluated *in vitro* and *in vivo* in different clinical scenarios.

The combination of gemcitabine and cisplatin has been studied extensively and has shown a synergic interaction in several in vitro studies, although the mechanism remains unclear (Brunner et al., 2003).

Five randomized phase III clinical trials and Zarba et al. (2003) and Peters et al. (2000) have shown a survival advantage for cisplatin-based concurrent chemo-radiotherapy over radiotherapy alone. Of these trials, 3 were performed in locally advanced disease, and in all these studies, local control, DFS and OS were better in the concurrent cisplatin/radiotherapy arm than with radiotherapy alone. However, even with the best results, the local recurrence is still high (around 19-24%).

Zarba et al. (2003), in a phase I–II study of weekly cisplatin and gemcitabine with concurrent radiotherapy in locally advanced cervical carcinoma, determined the MTD (Mean Toxic Dose) for gemcitabine to be 150mg/m^2 concurrent with cisplatin 40mg/m^2 every week and daily external radiotherapy. Furthermore, they recommended a phase II dose of gemcitabine at 125mg/m^2 plus cisplatin 40mg/m^2 weekly and external radiotherapy for locally advanced disease resulting in 36 patients showing an overall response of 97.3% with 88.8% of complete responses, 8.3% of partial responses and 2.7% of stable disease. Toxicity was moderate with grade 3/4 toxicity in <20%, with a median follow-up of 26 months, 19.4% of patients relapsed, and the 3-year disease-free survival and overall survival were 67% and 72% respectively.

Another study using the same combination of gemcitabine/cisplatin/radiotherapy Alvarez et al. (2001; 2002) investigated the feasibility of a low-dose gemcitabine/cisplatin regimen with concurrent radiotherapy in 50 patients with locally advanced cervical cancer. External beam radiation was delivered to the whole pelvic region in 23 fractions over 5 weeks, for a total dose of 46Gy. In addition, two brachy therapy insertions were made at the end of the third and fifth week. Concurrent chemotherapy consisted initially of gemcitabine 20 mg/m^2 and cisplatin 30mg/m^2 twice weekly. The dosage of cisplatin was subsequently reduced to once weekly after

the first 3 patients develop grade 3/4 hematologic toxicity. There were 86% complete responses, 3% partial responses and 3% achieve disease stabilization.

As, in our trial the rate of hematologic toxicities were: thrombocytopenia 3.3% grade 3, 9.9% leucopenia grade 3, and 10% anemia grade 3. The rates of complete responses were 73.3% and partial responses 26.7%, 3 months after treatment.

Only one study has compared directly multiagent systemic chemotherapy versus single agent cisplatin during concurrent RT. In an international multicenter randomized trial, 515 women with IIB to IV cervical cancer randomly assigned to concurrent cisplatin (40mg/m^2 weekly for six weeks) with external beam RT (50.4GY) followed by brachytherapy versus the same dose of weekly cisplatin plus gemcitabine (125 mg/m^2 weekly for six weeks) with external beam RT (50.4GY) and followed by brachy therapy.The experimental group also received two additional 21-day cycles of adjuvant gemcitabine (1000 mg on days 1 and 8) and cisplatin (50mg/m^2 on day 1 only) after brachytherapy. At three years, Gemcitabine – containing therapy was associated with better PFS (3 –year PFS was 74 versus 65%) and overall survival. However these improvements came at the cost of greater treatment related toxicity. Grade 3 and 4 toxicity during therapy were more frequent overall in the experimental arm (87 versus 46), and there was two deaths possibly related to treatment in this group as well. There were also more significantly hospitalization in the experimental group (30 versus 11 percent). Most of the excess toxicity occurred during chemoradiotherapy, the incidence of late toxicities in both groups were similar (Duenaz-Gonzalez et al., 2011).

In another similar trial by Aghili et al. (2010) complete and partial response in treatment of locally advanced cervical cancer were 80% and 13.3% in order. Side effects were 19% cystitis, 15% proctitis and 18% vaginitis. The difference between our trial and aghilis, was that in their trial 72.5% of cases were in stageIIB and in our trial 56.6% were in stage IIB and the others were in more advanced stages. It may answer our low complete response.

In another study by Amouzegar Hashemi. (2009) with chemoradiation of locally advanced cervical cancers with cisplatin, 81% had complete response in 18 months and 19% had locoregional recurrence or metastasis.

The difference between our trial and Amouzegar Hashemi. (2009) trial was that 61% of patints were in stage IB or lower, but in our trial 56.6% were in stage IIB or more advanced stages which can describes the lower rate of our complete responses.

In other words, the two important factors that may be responsible for our lower responses are the higher stages of our patients and the long interval between time of radiotherapy end and brachytherapy's start.

According to our investigation, this trial is one of the few trials that has used MRI of pelvis for evaluating the responses after end of chemoradiation treatment. In our study from 28 patients who were evaluated by MRI, 53.3% had normal abdomen and pelvis MRI, 16.7% had residues in cervix and 23.3% had evidences of mass of pelvic wall, lymphadenopathy of paraaortic or liver metastasis.

Despite new treatments strategies, cervical cancer has still lots of local recurrence in advance stages. There are many phase II studies for adding gemcitabine to standard chemoradiation.

To validate these findings, a randomized phase III trial should be stablished to evaluate the chemoradiation treatment with cisplatin and radiotherapy by linac, with or without gemcitabine in cancer institute. The results of this study will help to establish the role of gemcitabine in the treatment of locally advanced cervical carcinoma.

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