

RESEARCH ARTICLE

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

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Abstract

Cervical cancer is one of the most common gynecological cancers in Iranian women. This study was initiated to assess whether the combination of paclitaxel and cisplatin with radiation might be feasible for these patients. The aim was to assess tumor response and toxicity of weekly cisplatin and paclitaxel along with radiotherapy in the treatment of cervical cancer. Women with primary untreated squamous cell carcinoma of the cervix with FIGO stages IB2 to IIIB were treated with weekly injections of cisplatin 30 mg/m² and paclitaxel 35 mg/m² for 5-6 weeks along with radiotherapy. A total of 25 patients were enrolled in this study who completed the intended treatment. Disease was assessed prior to treatment by pelvic examination and contrast enhanced MRI of the abdomen and pelvis. Response was assessed 1 month after completion of treatment by physical examination and 3 months after also by MRI. Toxicity was assessed and was graded using RTOG grading. There was a complete response rate of 84% after 3 months. The major toxicity was grade 1 and 2 anemia (92%). The mean duration of treatment was 58 days. In conclusion, combination chemotherapy with cisplatin and paclitaxel along with radiotherapy in patients with locally advanced squamous cell carcinoma of cervix was well tolerated, in contrast to other studies, but it seems that there was no increase in tumor response and progression free survival with this treatment regimen.

Keywords: Cervical cancer - locally advanced - concurrent chemoradiation - paclitaxel - cisplatin

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Introduction

Cervical cancer is the second most common cancer among women worldwide, and patients with locally advanced cervical cancer (LACC) have a poor prognosis (Parkin et al 2005). The main curative treatment for patients with LACC has been radical.

Radiotherapy in the past century. During the period of 1999 to 2002, four large randomized trials (Whitney et al, 1999; Rose et al, 1999; Keys et al, 1999; Morris et al, 1999) and two large Meta-analysis (Green et al, 2001; Lucca et al, 2002) reported improved survival with cisplatin-based concurrent chemo radiotherapy (CCRT), making it the standard treatment for International Federation of Gynecology and Obstetrics (FIGO) Stage IB2-IVA cervical Cancer. This approach involves the use of cisplatin 40 mg/m² weekly for 6 weeks along with standard radiation (Vale, 2008). Even though concurrent chemo radiation is superior to radiation alone, five year overall survival rates continue to be low for patients with locally advanced cervical cancer (Jemal et al, 2011).

Still many patients continue to fail in the pelvis (20-25%) and at distant sites (10-20%) and Persistent pelvic disease or loco-regional recurrence is the major cause of treatment failure. The presence of large and bulky primary tumor with hypoxic areas and the presence of malignant clones resistant to chemotherapy and/or radiation are possible reasons for treatment failure (Hockett et al, 1996).

These facts have stimulated interests in exploring other concurrent combinations with potentially more clinical effect. The availability of new active drugs suggests the study of new combination regimens in this group of patients. Paclitaxel is active in cervical cancer either alone (Pignata et al, 1998) or combined with cisplatin (Kudelka et al 1996; Rose et al, 1999). In vitro, paclitaxel potentiates the antitumor activity of ionizing radiation and recruits cells in the most radiosensitive phase of the cell cycle, the G₂/M (Papadimitriou et al 1999; Tishler et al, 1994). The combination of weekly paclitaxel with carboplatin (Liebmann et al, 1994; Conley et al, 1997) or cisplatin (Belani et al, 1996) along with radiotherapy has been previously studied in head and neck cancer (Conley

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et al, 1997) and in lung cancer (Belani et al 1996; Frasci et al, 1997), where it proved to be active.

Preclinical studies have shown a radio sensitizing effect of paclitaxel in human cervical cancer cell lines (Pradier et al 1999; Britten et al, 1998).

The clinical feasibility of concurrent RT and paclitaxel was tested in phase I trials and a maximum tolerated dose (MTD) of 50 mg/m² per week concurrently with radiation therapy was established used in conjunction with radiotherapy (Chen et al, 1997; vogt et al, 1997).

Recently, several studies which used cisplatin plus paclitaxel With concurrent radiation have been reported (Pignata et al, 1998; Disilvestro et al, 2006; Liebmann et al, 1994) . These Were phase I and/or II studies which focused on evaluating Toxicities and response rates in a limited number of enrolled Patients .

These studies have demonstrated that cisplatin plus paclitaxel concurrently used with radiation show encouraging. Response rate and good tolerability in cervical cancer. In the studies, dose limiting side effects were hematologic toxicities and diarrhea. Also Chen et al.(Chen et al, 1997) did a phase I study where weekly paclitaxel was combined with 3 weekly cisplatin. The maximum tolerated dose (MTD) of this trial was reported as paclitaxel 50 mg/m²/week with cisplatin 50 mg/m² once in 3 weeks. In this study, we examine the tumor response, treatment toxicity, and outcome of Iranian patients with locally advanced cervical cancer treated by concurrent radiation therapy and chemotherapy using weekly Cisplatin and paclitaxel.

Materials and Methods

Eligibility Criteria

Women with untreated invasive squamous-cell carcinoma of the cervix of international federation of gynecology and obstetrics (FIGO) stage IIB (localized disease with parametrical involvement), stage III (extension of the tumor to the pelvic wall) or stage IV A (involvement of the bladder or rectal mucosa) referring to the Radiation Oncology department of cancer Institute Tehran University Of Medical Sciences were eligible to enroll in this phase II randomized prospective Study from July 2012 to December 2014. Patients were included in the trial after getting a written informed consent. We decided to accrue 25 patients who fulfill the inclusion criteria. All cancers were histologically confirmed. Inclusion criteria included: age <80 years; Gynecologic Oncology Group (GOG) performance status of 0-3; adequate hematological and biochemical profile with absolute neutrophil count >1.5 × 10⁹/L, platelets >100 × 10⁹/L; creatinine <1.5, liver enzymes (AST and ALT) <3 ×

normal, and bilirubin < 1.2 normal. Patients with evidence of enlarged paraaortic lymphnodes, history of peripheral neuropathy, prior radiotherapy, prior chemotherapy (neoadjuvant), hypersensitivity to cisplatin or paclitaxel, or other synchronous malignancies were considered not eligible.

Baseline and Treatment assessment

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, MRI of abdomen and pelvic, 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 < 2,000/mm³, the platelet count < 100/000 mm³ or in the event of severe (grade4) radiation induced gastrointestinal and genitourinary toxicity. Blood transfusion had done if hemoglobin < 10gr <dl. After finishing the treatment, one month and three month after that, the patients under went response evaluation, consist of physical evaluation by the same physicians who staged the patients. For response evaluation, WHO criteria for response were used, complete response was defined as the disappearance of all gross lesions for 1 months after completion of radiotherapy and absence of new lesions. Partial response was defined as a > 50% reduction of tumor size for 1 months after completion of radiotherapy. Progressive disease was defined as the appearance of any new lesion during treatment of a > 25% increase in size of local tumor. For acute and late radiotherapy toxicity RTOG classification of adverse effects was used which was evaluated during and one month of treatment. Also after 3 months of treatment MRI of patient was compared with the MRI of pretreatment for response evaluation.

Treatment Plan

35mg/m² Paclitaxel was administered intravenously slowly, immediately followed by 30mg/m² cisplatin (given intravenously over 60min) on day one of each treatment week. Both drugs were administered between 1 and 2 hour before radiotherapy. Radiotherapy was administered to the whole pelvic region in 25-28 fractions for a total of 50-50.4 Gy followed 1 or 2 weeks later for intracavitary brachytherapy. External radiotherapy was delivered using linear Accelerator machine with 18 MV photons, a four field box technique (antero posterior, postero anterior and two parallel) at a dose of 1.8-2Gy daily. Point A (reference location, 2cm lateral and 2cm superior to external cervical orifice received 85-90Gy

Table 1. Toxicities During Treatment

Toxicity	Grade I	Grade II
Anemia	84.0%	12.0%
Cystitis	68.0%	0.0%
Leucopenia	56.0%	24.0%
Diarrhea	56.0%	8.0%
Neuropathy	44.0%	0.0%

Table 2. Non Hematologic Toxicities

Toxicities	during treatment	1 month after treatment	3 month after treatment
Cystitis	68.0%	20.0%	16.0%
Diarrhea Grade I	56.0%	4.0%	8.0%
Diarrhea Grade II	8.0%	8.0%	0.0%

with external radiation and brachytherapy.

External radiation portals extended from L4-L5 junction to 3 cm below the palpable cervical growth or up to the introitus if the vagina was involved. Lateral borders were 1.5-2 cm lateral to the rim of the lesser pelvis. For lateral fields, limits were anterior edge of pubic symphysis (anterior) and S2-3 interspaces.

Results

The mean age of 25 patients that participated in our trial was 50.7 (minimum 36 and maximum 66) years. The pathology of patients were SCC in 88% and adenocarcinoma in 12%. According to the staging process: 36% of patients (9 patients) were in stage IIB, 32% stage IIIA (8 patients), 32% stage IIIB (8 patients). All of the patients were received external beam radiation therapy and they were treated by linear accelerator photon 18 MV. The average of external radiotherapy dose was 50.2GY (50-55) and average dose of internal radiotherapy was 31.4GY (7-36). The average treatment time was 10.5 weeks and the average time of follow up was 6.9 months (3-12). After one month of treatment, in clinical response evaluation 19 patients had complete response (76%) and 6 patients had partial response (24%). After three months of treatment, 21 patients had complete response (84%) and 4 patients had partial response (16%). After 3 months of treatment, all of patients were evaluated by MRI. In this evaluation 76% (19 patients) of patients didn't show any residue or metastasis intra or extra of pelvis. 2 patients had suspicious residue in cervix, which were referred to salvage surgery and in pathology report they were tumor free. During follow up systemic control of disease was 84% (21 patients). 2 patients (8%) had bone metastasis 5 and 6 months after treatment but they were disease free in cervical region. One of the patients had brain metastasis after 3 months of treatment, she also had retro peritoneal adenopathy and partial response to her tumor. The other patient had retroperitoneal adenopathy 1 year after treatment. During treatment patients were evaluated for hematologic toxicities, neuropathy, cystitis and diarrhea.

Non hematologic toxicities were evaluated one month and 3 month after treatment. Before treatment 8 patients (32%) had grade I anemia and 2 patients (8%) had anemia grade III. After treatment 21 patients (84%) had grade I anemia and 3 patients (12%) had anemia grade II and III. Treatment interrupted in 10 patients (40%) in order to hematologic toxicities (anemia or leucopenia). Average of interruption because of anemia was 2.5 days and because of leucopenia was 4.5 days. 6 patients (24%) received packed cell (average of 2 unit) because of chemotherapy induced anemia and 1 patient (4%) had 1 injection of GCSF. 15 patients (60%) continued their routine treatment.

Discussion

Radiotherapy with concurrent cisplatin has become the standard treatment for cervical cancer. Recent studies have attempted to increase the efficacy of treatment in

advanced cervical cancer by using other chemotherapeutic agents with or without cisplatin concurrent with radiation. New combinations of chemotherapy given concurrently with radiotherapy can further improve the prognosis of these patients. A recent phase III trial demonstrated that concurrent chemo radiation with cisplatin and gemcitabine followed by adjuvant cisplatin and gemcitabine is significantly superior to chemoradiation with weekly cisplatin alone with regard to progression-free survival and overall survival. However, the toxicity of cisplatin/gemcitabine chemoradiation was found to be unacceptably high in other studies, indicating the need for less toxic regimens to be developed. (Alvarez et al, 2002). In another study in thirty women with untreated invasive squamous cell carcinoma of the cervix stage IIB-IVA 60mg/m² gemcitabine followed by 35 mg/m² cisplatin were concurrently administered with radiotherapy. After 3 months of treatment, 73.3% had complete response and 26.7% demonstrated partial response to treatment. Grade 3 anemia was seen in 10%, grade 3 thrombocytopenia in 3.3% and grade 3 leucopenia in 10% of the patients (Hashemi et al, 2013). Paclitaxel was chosen for the present study because of its activity against cervical cancer and its favorable interactions with radiation (Pignata et al 1998, Rose et al, 1999). The doses reached in our trial are similar to those found in the studies of paclitaxel in lung and head and neck cancer with similar toxicity profiles. (Conley et al, 1997, Belani et al, 1996, Frasci et al, 1997). The aim of our study was to evaluate tumor response rate and the acute toxicity of this combination regimen. It is a small phase 2 study with prospective design. In this study, we achieved an 84% clinical response rate at median follow-up of 6.9 month. In similar phase II studies, Disilvestro et al noted a complete response rate of 89.4% whereas Miglietta et al. had 100% complete response rates (Disilvestro et al, 2006; Miglietta et al, 2006). The high incidence of complete response rate in Miglietta et al. is probably because they used one cycle of neoadjuvant chemotherapy followed by concurrent chemo radiotherapy.

Moreover, they used a high dose of paclitaxel (175 mg/m² once in 3 weeks for four cycles) compared to our study (40 mg/m²/week for four cycles) (Miglietta et al 2006) Our result is much similar to Varghess et al with 88% complete response (Varghess et al, 2014). MRI is better in identifying post radiation fibrosis from residual or recurrent disease. We used MRI for evaluating response rate in our patients. Pre treatment MRI of each patient was compared with MRI of three months after treatment completion. We had concordance between gynecology physical exam and MRI in 23 patients. In two patients we suspected residual disease in vaginal exam which were not confirmed in MRI. Simple hysterectomy were done in these two patients which showed complete response.

This is the superiority of our study in comparison to Varghess et al. in which CT scan were used for response evaluation. Varghess has mentioned as it was difficult to differentiate between post irradiation changes and residual disease in CT scans. Hence, there are no radiological complete responses. There were partial responses or stable disease. CT scan is probably overestimated due to inability

of CT scan to accurately detect residual disease in the post irradiated cervix (Varghess et al, 2014). In our study the most common acute serious toxicities were neutropenia (14%) and anemia (9.2%), which were manageable and lasted a short time. The mean treatment interruption was 2.5 days for anemia and 4.5 days for leucopenia. In Vargus study 20% grade 3 leucopenia was reported. There were prolonged breaks during treatment for 50% of the study population. This may be because of the high incidence of Grade 3 toxicities in this treatment group. The most common Grade 3 toxicity encountered in their study was diarrhea, (Varghess et al, 2014) While we did not have any Grade 3 toxicity. We had Grade 1 diarrhea in 14 patients (56%) and Grade 2 diarrhea in 2 patients (8%).

In Disilvestro et al the incidence of Grade 3 GI toxicity was 16% (Disilvestro et al, 2006). Miglietta et al reported no major GI toxicity (Miglietta et al, 2006). The incidence of Grade 3 GI toxicity in Keys et al was 12% (Keys et al, 1999). Other similar studies have not reported any significant diarrhea.

We observed an overall complete response rate of 84% with median follow-up of 6.9 months (range: 3-12 months). During this time we had four distant metastasis, one brain metastasis, one retro-peritoneal adenopathy and two case of bone metastasis. Interestingly two latter were disease free in cervical and par cervical region. Despite the limitation of our study such as short follow-up and no comparative arm with standard treatment regimen, our data showed that concurrent chemoradiation for advanced cervical cancer using weekly paclitaxel was not superior to concurrent cisplatin. In contrast to similar studies the regimen were well tolerated in Iranian patients with acceptable toxicity.

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