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Concurrent pelvic radiation with weekly low-dose cisplatin and gemcitabine as primary treatment of locally advanced cervical cancer: A phase II study

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Original Article

Abstract

Purpose: This study was done to evaluate response, compliance and survival of weekly low dose cisplatin (20 mg/m^2) and gemcitabine (125 mg/m^2) concurrently with pelvic radiation as primary treatment of stage IIB-IIIB cervical cancer. **Methods:** External radiation consisted of 50 Gy/25 fractions using 6-10 MV photon followed by 600 cGy boost to parametrium if it was still felt thickened. Then, intracavitary radiotherapy to deliver 60 Gy at point A. Chemotherapy consisted of gemcitabine at a dose of 125 mg /m^2 was given by i.v infusion over 30 minutes immediately after cisplatin 20 mg /m^2 weekly for 5 weeks during EBRT. Forty–five eligible patients received the treatment protocol. **Results:** Toxicity was tolerable and manageable. No grade 4 toxicity while grade 3 was recorded in hematologic one only. In order of frequency; diarrhea, nausea and vomiting, and anemia (50%, 40%, 35.5%) were most common adverse events. Overall clinical response rate was 93.4% with pathological complete response of 62.2%. After median follow-up of 20 months, 2-year survival and progression-free survival rates were 90.5% and 81% respectively. **Conclusion:** Weekly combination of low- dose cisplatin and gemcitabine given concurrently with pelvic radiotherapy in primary treatment of locally advanced cervical cancer resulted in a high response rate with a good compliance. Further exploration is needed for the use of this approach prior to incorporating it into routine clinical care through phase III clinical trial.

Keywords: Cervical Carcinoma; Gemcitabine; Chemo-Radiotherapy; Cisplatin

Introduction

Uterine cervical cancer is the second most common female malignancy in the world.[1] However, the incidence of it has decreased markedly in recent decades following the introduction of screening programs.[2] Usually cervical carcinoma presents as a locally advanced disease with parametrial infiltration in about half of the women especially in developing countries due to lack of early detection programs. Co-chrane meta-analysis in nearly 5000 patients strongly suggested that chemo-radiotherapy leads to greater disease-free and overall survival rates and better local control than with radical radiotherapy alone in locally advanced cervical cancer.[3] Induction chemo-radiotherapy can be followed by surgical consolidation. This approach has a sound theoretical bases as surgery may eliminate residual disease which otherwise could be resistant to chemo-radiation.

Gemcitabine has shown promising results in some phase I and II trials as a radiosensitizing agent.[4-6] Gemcitabine is activated intracellulary by deoxycytidine kinase and is converted into two active metabolites gemcitabine diphosphate and triphosphate which target DNA and RNA. It is considered to be an attractive compound to combine with ionizing radiation for several reasons: 1) It may inhibit repair of the DNA damage caused by radiation leading to increased cell death; 2) It may induce cell redistribution causing cells to accumulate in more radiosensitive phase of cell cycle; 3) Increased the radiosensitvity of hypoxic cells due to tumor shrinkage. Mc Cormach *et al.*[7] used gemcitabine with radiation in patients with locally advanced cervical cancer and concluded that gemcitabine is more potent radiosensitier than cisplatin while Srivastava *et al.*[8] found that cisplatin appeared to be better than gemcitabine when used as radiosensitizer.

This study was undertaken to evaluate the efficacy and safety of a concurrent regimen of gemcitabine / cisplatin and radiotherapy in women with stage IIB-IIIB cervical carcinoma.

Methods and Materials

Women with untreated invasive squamous cell carcinoma of the cervix of FIGO stage IIB-IIIB were enrolled in this study

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from April 2010 to December 2013. All cases were confirmed histologically. Each patient was required to undergo a complete physical examination, pelvic examination, chest radiography, intravenous pylography (IVP) and abdomino-pelvic magnetic resonance imaging (MRI). Sigmoidoscopy and cystoscopy were performed if needed. All patients were to have ECOG performance status score of 0 – 2, adequate bone marrow reserve (ANC >1500 /mm^3, platelet count >100.000 / mm^3 and Hb ≥10 g /dL), renal function (serum creatinine ≤1.5 mg /dl), liver function (bilirubin <2 times upper limit of normal (ULN) and SGOT<3 times ULN). Patients with diseases outside the pelvis or with para-aortic lymph node were excluded from the study.

Radiotherapy

External beam radiotherapy (EBRT), 50 Gy/25 fractions was delivered using 6-10 MV photon beam through 4 field box technique. Typical field borders were; upper border was at L4-5 inter space; lower border at lower most part of obturator foramen and was modified according to vaginal extent of the disease; anterior border was at the anterior symphysis pubis and the posterior border at S2-S3 junction. Additional 600 cGy may be boosted to the invaded parametrium if was still felt thickened on evaluation by pelvic examination.

For intracavitary radiotherapy (ICRT), patients were referred to other centers after completion of EBRT. All patients received single application of ICRT to deliver 20 Gy at point A.

Chemotherapy

Gemcitabine at a dose of 125 mg /m^2 was given by i.v infusion over 30 minutes in 300 ml normal saline immediately after cisplatin 20 mg /m^2 weekly for 5 weeks during EBRT, beginning on first day of radiation. Cisplatin infusion was administered with adequate pre and post hydration; started 12h before infusion. Prophylactic antiemetic (dexamethasone, ranitidine and ondansetron) were given before cisplatin.

Chemotherapy and radiotherapy toxicity were assessed according to Common Terminology Criteria for Adverse Events V3 [9] and RTOG classification [10] respectively.

When hematological toxicity was≥ grade 3, chemotherapy and radiotherapy were withheld. For grade 2 hematological toxicity only chemotherapy was withheld. When non hematological acute radiation morbidity was≥ grade 3, radiation was interrupted.

Response to treatment was assessed according to response evaluation criteria in solid tumors (RECIST) [11] after 3 weeks of end of treatment.

Surgery was scheduled within 4-6 weeks after completion of chemoradiotherapy for patients who became operable. Histopathological response to treatment was defined as complete regression (pCR) with no residual tumor cells and subtotal regression (PSR) with < 10% viable tumor cells.

The end points of this study were response rate, tolerability, overall survival (OAS) and progression free survival (PFS) rates. The OAS was calculated from date of start treatment to date of death or lost follow-up while PFS was calculated from date of end of treatment to date of documented progression. Patients were assessed every 3 months for first year then every 6 months thereafter by clinical examination and abdomino pelvic MRI.

Statistical analysis: SPSS version15.0 (Chicago, IL, USA) was used. Data expressed as Number and percentile. OAS and PFS assessed by using Kaplan-Meier.

Results

A total of 45 patients were treated on protocol. Pre-treatment clinical characteristics are summarized in **Table 1**. Median age was 44 years. About 49% of patients had ECOGPS of 0. Most patients had stage IIB (60%). Moderately differentiated squamous cell carcinoma was found in 49% while ulcerative pathology was reported in 64.5%.

TABLE 1: Patients characterestics (n = 45).

Character	N (%)
Age	
Median (range)	44(27-68)
ECOGPS	
0	22(48.9)
1	18(40)
2	5(11.1)
FIGO Stage	
IIB	27(60)
IIIA	12(26.7)
IIIB	6 (13.3)
Grade	
Well differentiated	16(35.5)
Moderately differentiated	22(48.9)
Poorly differentiated	7(15.6)
Gross pathology	
Ulcerative	29(64.5)
Exophytic	10(22.2)
Infiltrative	6 (13.3)

TABLE 2: Acute toxicities.

Toxicity	Grade							
	1		2		3		4	
	N	%	N	%	N	%	N	%
Neutropenia	4	8.9	6	13.3	2	4.4	0	0
Thrombocytopenia	6	13.3	7	15.6	1	2.2	0	0
Anemia	8	17.8	5	11.1	3	6.6	0	0
Nausea/vomiting	10	22.2	8	17.8	0	0	0	0
Dermatitis	5	11.1	3	6.6	0	0	0	0
Proctitis	7	15.6	5	11.1	0	0	0	0
Cystitis	6	13.3	8	17.8	0	0	0	0
Diarrhea	11	24.4	12	26.7	0	0	0	0

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TABLE 3: Response rate.

Response	N	%
Complete response (CR)	34	75.6
Partial response (PR)	8	17.8
Stable disease (SD)	2	4.4
Progressive disease (PD)	1	2.2
Pathological complete response (pCR)	28	62.2

All patients completed the treatment protocol with interruption in 3 patients only (6.6%) of about 3-6 days. Toxicity was moderate. The incidence and severity of acute toxicities are shown in **Table 2**. No grade 4 toxicity was recorded while grade 3 was found in hematologic one only. Fortunately, neither reported ototoxicity nor nephrotoxicity. Among hematologic adverse events; anemia was the most common (35.5%) followed by thrombocytopenia (31%). Diarrhea, nausea and vomiting, and cystitis were found in respect to order of frequency as following: 51%, 40%, 31%.

Overall clinical response rate was 93.4%; stable and progressive diseases were 4.4% and 2.2% respectively. Operable patients underwent type III radical hysterectomy with bilateral pelvic lymphadenectomy and pathological complete response was 62.2% (**Table 3**).

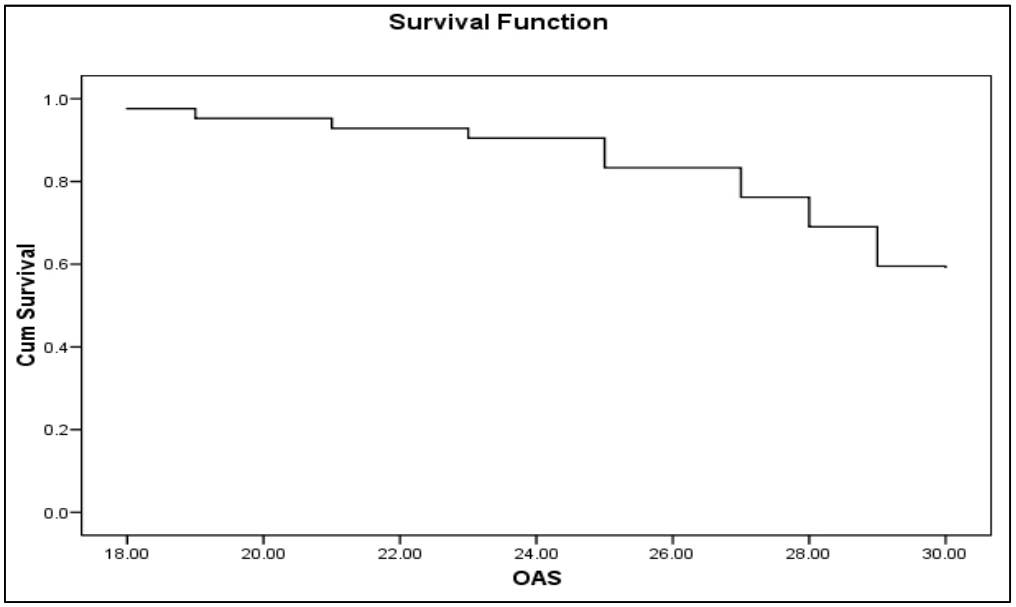

FIG. 1: Overall survival of all cases.

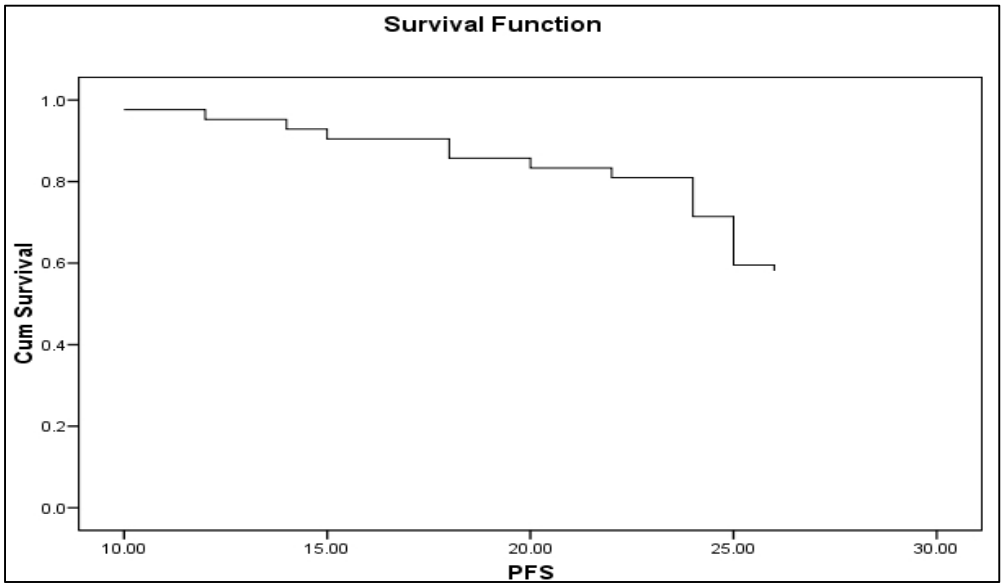

FIG. 2: Progression free survival.

During follow-up period, two patients died of unrelated causes of diseases; so survival rates were assessed in 43 patients. **Figure 1** and **Figure 2** showed 2-year overall survival (OAS) and progression –free survival (PFS) rates (90.5% and 81%) respectively. After median follow-up of 20 months; median survival time was 30 months while that of PFS was 26 months.

Discussion

Treatment of carcinoma of the cervix has evolved immensely over the last decade. For locally advanced carcinoma of the cervix, overall prognosis has always been somber until the shift in the treatment paradigm came with concurrent chemoradiotherapy protocol. The most standard approach is the use of concurrent cisplatin 40 mg/m^2 weekly along with radiation but locoregional failure range from 30% to 40%.[12, 13] Gemcitabine is a cell cycle specific cytotoxic agent that has shown antitumor activity against a variety of solid tumors e.g. lung, pancreas, breast and bladder.

Hernandez *et al.* [14] have demonstrated the radiosensitizing effect of gemcitabine against cervical cancer cell line. Overall toxicity was acceptable and tolerable. No patients demonstrated ototoxicity or nephrotoxicity in this study. However; previous study using weekly cisplatin 40mg/m^2 had reported ototoxicity in 10% [15] while nephrotoxicity occurred in 42.9% in a study using weekly combination of gemcitabine with this standard dose of cisplatin.[16]

Among hematologic toxicity; anemia was the most common (35.5%) followed by thrombocytopenia (31%) then neutropenia (26.6%) with grade 3 in 4.4% and no grade 4 that comparable to finding by Umanzor *et al.*[6] However; Zarba *et al.*[5] recorded grade 4 neutropenia in 4%. Anemia was found in 50% of patients treated with gemcitabine 125mg/m^2 and cisplatin 40mg/m^2.[4] In our study; diarrhea, nausea and vomiting were the most common non hematologic adverse events (51% and 40% respectively) with no grade 3 nor 4 toxicity while Khalil *et al.*[17] reported grade 3 and 4 diarrhea in 36.6% when used cisplatin 40mg/m^2 concurrent with radiotherapy. Grade 1 and 2 diarrhea was observed in 50% of patients treated with gemcitabine 300mg/m^2 [4] and 2-year survival rate of 63% while that in our study was 94% but their patients were of stage IB2-IVA. Overall clinical response rate in our study was 93.4%, 2-year OAS and PFS rates were 90.5% and 81% respectively. In a study conducted by Pattaranutaporn *et al.*[4] response rate was comparable to ours. Also, Zarba *et al.* [5] had comparable response rate but with higher toxicity may be due to higher dose of cisplatin. Overall response rate was higher than that using cisplatin only 40mg/m^2 (79.6%).

Conclusion

Weekly combination of low- dose cisplatin and gemcitabine given concurrently with pelvic radiotherapy in primary treatment of locally advanced cervical cancer resulted in a high response rate with a good compliance. Further exploration is needed for the use of this approach prior to incorporating it into routine clinical care through phase III clinical trial.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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