Concurrent Weekly Taxol Versus Weekly Cisplatin with Radiotherapy in the Treatment of Locally Advanced Cervical Cancer

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Abstract

Objective: To compare compliance, toxicity, and outcome as regard overall survival and progression free survival of weekly taxol vs. weekly cisplatin administration concurrently with radiotherapy in locally advanced cervical cancer.

Material and Methods: This prospective study included 57 women FIGO stage IB2-IVA cervical cancer or with postsurgical pelvic recurrence. Patients randomized into two groups, group I (29 patients) received a weekly cisplatin 40mg/m² and group II (28 patients) received weekly 50mg/m² taxol concurrently with radiotherapy. The difference of compliance and toxicity profiles between the two arms were investigated, and the overall and progression free survival were analysed.

Results: Patients and tumor characteristics were similar in both arms, except the median tumor size was larger in group II (5.5cm) but not significant (P= ). The mean number of chemotherapy cycles was comparable, with 88.4% and 84% of patients receiving 4 doses in group I and II, respectively. There was no statistically significant difference of compliance between the two arms (p>0.05). Two years Progression free survival rate was 45% in arm I and 38% in arm II, with no statistically significant difference (p=0.8). The median overall survival in arm I was 27 months and, 26 months in arm II, with no statistically significant difference (p=0.16).

Conclusion: This small prospective study shows that weekly paclitaxel does not provide any clinical advantage over weekly cisplatin for concurrent chemoradiation for advanced carcinoma of the cervix.


Introduction

CERVICAL cancer is one of the most common gynecologic cancer world wide [1]. The prognosis of cervical cancer is favorable in early stage while advanced disease carries a poor prognosis. Radiation therapy remains the main treatment modality for patients with advanced cervical cancer [2,3].

Several randomized trials revealed that the treatment regimens combining radiotherapy with platinum based chemotherapy improve rates of overall survival (OAS) and progression free survival (PFS) in women with stage IIIB through IVA [4-6]. At first it was reported positive result with the use of concurrent cisplatin and 5-fluorouracil (5-FU) with radiotherapy, then gradually replaced cisplatin and 5-FU with weekly cisplatin because of less toxicity with weekly cisplatin [7].

Ryu et al., reported that triweekly cisplatin 75mg/m² chemotherapy concurrent with radiotherapy was more effective and feasible than the conventional weekly cisplatin 40mg/m² [8]. However, others reported no differentiation in PFC and OAS between two groups [9].

A study by National Cancer Institute of Canada using weekly concurrent single agent cisplatin has shown no clinical benefit from this schedule [10]. This fact have stimulated interest in exploring other concurrent combination with potentially more clinical effect. The efficacy of paclitaxel has been tested in metastatic and recurrent cervical cancer with objective response rates [11]. Paclitaxel has found to have radiosensitizing effects in human cervical cancer [12,13]. The clinical feasibility of concurrent radiotherapy and paclitaxel was tested and a maximum tolerated dose of 50mg/m² per week concurrent with radiotherapy was established [14,15].

Fady et al., was reported that overall response and PFS rates with paclitaxel not superior to those with cisplatin for patients with advanced cervical cancer [16].
In our study we tried to compare between weekly cisplatin versus paclitaxel concurrent radiotherapy in patients with advanced cervical cancer as regard PFS and overall response.

Material and Methods

Patients presenting to Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital and Clinical Oncology Department, Al-Hussien University Hospital, with advanced carcinoma of the cervix, stages IB2-IVA according to the Federation Internationale de Gynecologie Obstetrique (FIGO) staging system, or with measurable central pelvic recurrence, were eligible to enroll in this phase II randomized prospective study. Inclusion criteria also included: Age <80 years, Gynecologic Oncology Group (GOG) performance status of 0-2, and adequate hematological and biochemical profile with absolute neutrophil count >1.5x10^9/L, platelets >100x10^9/L, creatinine <1.5, liver enzymes (AST and ALT) <3 x normal, and bilirubin <1.25 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 excluded.

Between October 2010 to July 2013, 57 women were enrolled and randomized to receive on a weekly basis either 40mg/m^2 Cisplatin (group I; 29 patients) or 50mg/m^2 paclitaxel (group II; 28 patients) concurrently with radiotherapy.

Treatment:

Chemotherapy:

Patients were randomized into two groups: Group I treated with weekly cisplatin and group 2 treated with weekly paclitaxel. Group I patients received weekly cisplatin at a dose of 40mg/m^2 diluted in 250mL of 0.9% sodium chloride was administered i.v. over 1h. Premedication consisted of dexamethasone 8mg IV, and a 5HT3-receptor antagonist as antiemetic with hydration at least 500mL of 0.9% sodium chloride was injected i.v before and after cisplatin administration. Group II patients were treated with weekly paclitaxel 50mg/m^2 given intravenously in 500cc of glucose 5% in a glass container over three hours. Premedication consisted of dexamethasone 8mg IV, avil 1ml IV, Ranitidine 50mg IV, and a 5HT3-receptor antagonist as antiemetic. Planned treatment was for an average of 5-6 cycles to coincide with the duration of external beam radiation.

Radiation therapy:

All patients were treated with a combination of external-beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT). External-beam radiotherapy was delivered to the whole pelvis through a four-field box technique using 6-10-MV photons. The planned total dose to the whole pelvis was 45-50Gy in 25-28 fraction over 5-5.5 weeks. When patients had bulky parametrial tumors or gross lymph node metastases, an additional 5-10Gy was applied to boost the external dose to the lesion to a total of 55-60Gy with central shields (CS) inserted during EBRT of additional 5-10Gy to reduce organ at risk (OAR) exposure depending on tumor shrinkage. Central shields (CS) was carried about 4cm in width at the isocenter of the field. Low Dose Rate (LDR) brachytherapy was used after the completion of EBRT using two insertions with 137 Cs source. These include the placement of an intrauterine tandem with vaginal ovoids, the addition of the ovoids or ring to the tandem applicator may be used to provides a dose distribution that encompasses the at-risk paracervical tissues while providing a lower dose distribution to the bladder and rectum. In addition, dose to the bladder and rectum can be reduced further with the use of vigorous packing. The choice of applicator is governed by physician preference and comfort level, as well as patient anatomical considerations. Applicator placement typically requires intravenous conscious sedation or general anesthesia for patient comfort. Once the applicators are in place, treatments are traditionally planned using orthogonal radiographs to define prescription and normal tissue points of interest (Fig. 1). Dose to surrounding organs at risk were calculated at bladder, rectal and pelvic points. The planned dose prescribed to the point A was 30-40Gy in 1 to 2 fractions according to the tumor volume. The total dose prescribed to the point A combining EBRT with ICBT was not more than 75-85Gy. To avoid the negative impact of treatment prolongation, it was recommended that the overall treatment time ranged between 7 to 8 weeks. Dose to surrounding organs at risk were calculated at bladder, rectal and pelvic wall points (point B) (Fig. 2).

Baseline evaluation and follow-up:

Tumor size was assessed clinically by examiner prior to, and following treatment. Initial work-up included a complete blood and platelet counts (CBC), creatinine (Cr), liver function tests (SGPT, Alk.P., Gamma GT). Abdominopelvic CT or MRI, and chest X-ray (CXR). During treatment, patients had weekly CBC, Cr, and liver function tests. Patients who developed any allergic reac-
tions during cisplatin and paclitaxel, were subsequently pretreated with dexamethasone 8mg orally every 8 hours for three doses prior to the admission for chemotherapy. After completing therapy, Patients were followed-up by physical examination, and Papanicolaou smear every 3 months for 2 years, and every 6 months for thereafter. Chest X-ray, abdominopelvic CT or MRI was performed every 6 months.

Recurrence of disease was defined as the presence of tumor histologically or radiologically. Any suspicious lesion on CT scan was followed-up with CT scans every 3 months until the recurrence was confirmed clinically.

Compliance to treatment:
Hematologic, gastrointestinal, renal, and neurotoxicities were evaluated after each cycle of chemotherapy according to the NCI Common Terminology Criteria for Adverse Events, version 3.0.

Study end points:
The primary endpoints were treatment response, overall survival, and time to relapse. Time to relapse was defined from the the date of first assess with complete response to the date of recurrence. Patients with progressive disease who never achieved complete response, were censored for progression at the end of radiation therapy, which is approximately 2 and half months from the date of entry. Disease free survival was defined as alive with no evidence of disease at the time of last follow-up or dead without evidence of disease. Survival was calculated from the date of entry to the date of death or last follow-up. Treatment related toxicity was assessed as a secondary endpoint. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria grading system. The incidence, severity, and causal relation to treatment of these events were compared between treatment groups.

Statistical methods:
Cumulative survival rates was estimated by the Kaplan-Meier method and compared using the Logrank tests. Chi-square and the student’s t-test were used for comparative analyses. Statistical significance was defined as $p<0.05$. Data were analyzed using a SPSS program version 16.0.

Results
Patient’s characteristics:
From October 2010 to July 2013, 57 patients were recruited and randomly assigned into two treatment arms, either arm I with 29 patients or arm II with 28 patients. In arm I, 3 were excluded from all analyses: 2 because of incorrect initial staging, 1 who could not subsequently be contacted and in arm II, 3 patients who refused the treatment regimen after randomization. A total of 51 patients received complete treatment as defined per protocol or with an acceptable variation.

The baseline characteristics of the study patients are shown in Table (1). Age, histology, stage distribution and lymph node involvement were not different in both groups. Only median tumor size was slightly larger for group II patients (5.5cm) compared to that of group I patients (4cm), but this was not statistically significant ($p=0.16$).

Compliance to treatment:
The two based chemoradiation regimens were tolerated very well, with 88.4% and 84% of patients receiving 4 doses of scheduled chemotherapy cycles for the weekly cisplatin and paclitaxel arms, respectively. There was no statistically significant difference of compliance between the two arms ($p>0.05$). There were only 5 patients with radiation delay due to toxicity (2 cases in the cisplatin arm and 3 cases in the paclitaxel arm) (Table 2).
Progression free survival

Table (1): Clinical characteristics of patients with locally advanced cervical cancer.

<table>
<thead>
<tr>
<th>Character</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. %</td>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>51</td>
<td>55</td>
</tr>
<tr>
<td>Performance status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13</td>
<td>50</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>34.6</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>15.4</td>
</tr>
<tr>
<td>Stage:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIB</td>
<td>17</td>
<td>65.4</td>
</tr>
<tr>
<td>Stage III</td>
<td>5</td>
<td>19.2</td>
</tr>
<tr>
<td>Stage VIA</td>
<td>4</td>
<td>15.4</td>
</tr>
<tr>
<td>Histology:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>25</td>
<td>96.2</td>
</tr>
<tr>
<td>Non-SCC</td>
<td>1</td>
<td>3.8</td>
</tr>
<tr>
<td>Median tumor size (cm)</td>
<td>4 (2.6-7)</td>
<td>5.5 (4-10)</td>
</tr>
<tr>
<td>Pretreatment imaging:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive pelvic LN</td>
<td>14</td>
<td>53.8</td>
</tr>
<tr>
<td>Positive para-aortic LN</td>
<td>2</td>
<td>7.7</td>
</tr>
<tr>
<td>Enrolled as pelvic recurrence</td>
<td>3</td>
<td>11.5</td>
</tr>
</tbody>
</table>

Table (2): Compliance to treatment in patients with locally advanced cervical cancer.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. %</td>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy cycles: &gt;4 cycles</td>
<td>23</td>
<td>88.4</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>26</td>
<td>100</td>
</tr>
<tr>
<td>Completed as scheduled</td>
<td>24</td>
<td>92.3</td>
</tr>
<tr>
<td>Delayed 1-2wk</td>
<td>2</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Toxicity of treatment:

Treatment related acute toxicity is listed in Table (3). Both groups had comparable hematological toxicity, but more patients in group II had severe diarrhea (44% vs. 26.9%), and allergic reactions (20% vs. 7%). In group II, 4 patients, chemotherapy had to be discontinued because of drug-related allergic reactions. Also, delay in chemotherapy was more common with group II than with group I patients (33% vs. 20%), but this difference was not statistically significant ($p>0.05$).

Response:

Response assessment was done 4-6 weeks after the completion of treatment by doing Abdomino-pelvic CT or MRI. Overall response rate was 73% in arm I (12 patients achieved complete response (CR) and 7 patients achieved partial response (PR) while OAR was 68% in arm II (10 CR, 7 PR), with no statistically significant difference between the two groups ($p>0.05$).

Survival:

At two years, local control rates were 90% for group I and 83% for group II ($p=\text{NS}$). Most of the recurrences occurred in distant sites (4 patients, 15%) in the arm 1 and (5 patients, 20%) in the arm 2, including the para-aortic lymph node and lung parenchyma. Progression free survival at 2-years was 45% at arm I and 38% with arm II, with no statistically significant difference ($p=0.8$). Results of Kaplan-Meier estimates of relapse free survival in both treatment arms are shown in Fig. (3).
Cervical cancer is one of the leading causes of cancer incidence and mortality in women all over the world. Concurrent chemoradiotherapy was the standard treatment approach for locally advanced cases using platinum-based chemotherapy [17]. Although it is widely accepted that cisplatin-based chemoradiation is the standard treatment for locally advanced cervical carcinoma, many drugs were tried in this setting to improve on what can be achieved by concurrent cisplatin [18,19]. The aim of this study is to elicit other chemotherapeutic agent (paclitaxel) concurrent with radiotherapy in comparison with the standard regimen (cisplatin). The result of this small phase II study showed comparable outcome as regard two-year overall survival 80% in cisplatin group vs 75% in paclitaxel group and progression-free survival 45% in cisplatin and 38% in paclitaxel in addition to similar response rate 73% in group I and 68% in group II with no superiority of paclitaxel over cisplatin as weekly regime. In spite of a little survival benefit in cisplatin group but this statistically insignificant that may be became more evident at prolonged follow-up or due to median tumor size was slightly larger for group II patients (5.5cm) compared to that of group I patients (4cm).

Our result is comparable to data came from Fady et al., [16] at two-year survival analysis that showed more or less the same survival 78% for cisplatin and 73% for paclitaxel group.

The same result was found in Lanciano et al., larger study by the GOG which also compared concurrent either weekly cisplatin or protracted 5-fluorouracil (5-Fu) infusion. The results of that study showed no superiority of the experimental 5-Fu arm and the study was prematurely closed [20].

The idea of including chemotherapy concurrent with radiotherapy was started after 1999 where randomized studies including nearly 2,000 patients were published, demonstrating that survival rate with concomitant chemotherapy (RT/CT) based on cisplatin was superior than that obtained with radiation alone [4,21,22].

Afterwards, a meta-analysis based on 19 trials (17 published and two unpublished) including 4,580 patients corroborated these findings, confirming that chemoradiation offers an absolute survival benefit of 12% at 5 years [23].

An update of the aforementioned meta-analysis strongly suggests that chemoradiation improves overall survival and progression-free survival, whether or not platinum was used, with absolute benefits of 10 and 13%, respectively [24].

In all previous studies of cervical cancer paclitaxel were used in conjunction with either cisplatin) or carboplatin but was never used alone for CTRT. Most of these studies were phase I [25]. The number of patients enrolled in these studies varied between 8 and 35 patients and the rates of progression-free survival ranged between 39 and 88%. The dose-limiting toxicity was primarily hematological and small intestinal toxicities [14,26,27].

In this study the toxicity profile was comparable in both groups as regard hematological toxicity with more GIT toxicity in group II, diarrhea (44% vs. 26.9%), and more allergic reaction also, in group II (20% vs. 7%). Also, a delay in chemotherapy was more common with group II than with group I patients (33% vs. 20%), but this difference was not statistically significant ($p>0.05$). The toxicity profile seen in this study tends to be more in paclitaxel group which was the reverse reported by Vijayakumar et al., [28], that may be attributed to different radiotherapy technique used in Vijayakumar trial which used anterior and posterior portals in cisplatin group while used four fields in paclitaxel group, but in our trial we used four fields technique in both groups.

On other hands, our toxicity profile was comparable to data reported by Fady et al., The rate of gastrointestinal (GI) toxicity as severe diarrhea, was high in both arms although slightly higher in the paclitaxel arm, and in general, more chemotherapy delays were encountered in this group. This result was also reported in the preliminary
pilot phase I study by Hennequin et al., 26% had grade 3 small bowel toxicity and in addition to grade 3 bladder toxicity and grade 4 mucositis [29].

DiSilvestro et al., [30], reported similar result in his phase I/II trial evaluating toxicity profile of paclitaxel and cisplatin weekly regimen, two had grade 3 or 4 gastrointestinal (GI) toxicities and seven experienced grade 3 or 4 neutrophil toxicity.

**Conclusion:**

All the previous data were supporting the use of concurrent cisplatin with radiotherapy in treatment of locally advanced cervical cancer. On other hand the data supporting the use of paclitaxel in this setting was weak. The conclusion of our study demonstrates non superiority of paclitaxel over cisplatin in concurrent setting an addition to more GIT toxicity and more allergic reaction. These data show that concurrent chemoradiation for advanced cervical cancer using weekly paclitaxel was not superior to concurrent cisplatin and was possibly associated with more severe gastrointestinal toxicity and more allergic reactions. In contrast, progression free survival and two year survival were similar failure at distant sites remains high in both groups, which may indicate the need for additional effective therapy.

**References**


20- LANCIANO R., CALKINS A., BUNDY B., et al.: Randomized comparison of weekly cisplatin or protracted...


