Low Dose Cisplatin as a Radiation Sensitizer in Management of Locally Advanced Squamous Cell Carcinoma of the Uterine Cervix: Evaluation of Acute Toxicity and Early Response

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Purpose: To evaluate possible acute toxicity and early response of concurrent radiation therapy and low dose daily cisplatin as a radiosensitizer in patients with locally advanced uterine cervical carcinomas.

Materials and Methods: From December 1996 to January 1999, 38 previously untreated patients with locally advanced squamous cell carcinoma of the uterine cervix (from stage IIB to stage IIIB) were treated at Inha University Hospital. All patients underwent standard pretreatment staging procedures after the initial evaluation by gynecologists and radiation oncologists. Sixteen patients with huge cervical mass (>4 cm) were submitted to the group treated with concurrent radiation therapy and low dose daily cisplatin while the remainder was treated with radiation therapy alone. Radiation therapy consisted of 4500 cGy external beam irradiation to whole pelvis (midline block after 3060 cGy), 900–1000 cGy boost to involved parametrium, and high dose-rate intracavitary brachytherapy (a total dose of 3000–3500 cGy/500 cGy per fraction to point A, twice per week). In the group treated with low dose cisplatin concurrently, 10 mg of daily intravenous cisplatin was given from the 1st day of radiation therapy to the 20th day of radiation therapy. Acute toxicity was measured according to expanded common toxicity criteria of the NCI (C) Clinical Trials. Early response data were analyzed at minimum 4 weeks' follow-up after completion of the treatment protocol.

Results: Hematologic toxicity was more prominent in patients treated with radiation therapy and cisplatin. Six of 16 patients (37.5%) treated with radiation therapy and cisplatin and one of 22 patients (4.5%) treated with radiation therapy alone experienced grade 3 leukopenia. In Fisher's exact test, there was statistically significant difference between two groups regarding leukopenia ($P=0.030$). There was no apparent difference in the frequency of gastrointestinal and genitourinary toxicity between two groups ($P=0.066$). Three of 16 patients (18.7%) treated with radiation therapy and cisplatin and two of 22 patients (9.1%) treated with radiation therapy alone experienced more than 5 kg weight loss during the treatment. There was no statistically significant difference on weight loss between two groups ($P=0.63$). Two patients on each group were not evaluable for the early response because of incomplete treatment. The complete response rate at four weeks' follow-up was 80% (16/20) for the radiation therapy alone group and 78% (11/14) for the radiation therapy and cisplatin group. There was no statistically significant difference in early response between two treatment groups ($P=0.126$).

Conclusion: This study led to the conclusion that the hematologic toxicity from the treatment with concurrent radiation therapy and low dose daily cisplatin seems to be more prominent than that from
the treatment of radiation therapy alone. There was no grade 4 hematologic toxicity or mortality in both groups. The hematologic toxicity in both treatment groups seems to be well manageable medically. Since the risk factors were not balanced between two treatment groups, the direct comparison of early response of both groups was not possible. However, preliminary results regarding early response for patients with bulky cervical tumor mass treated with radiation therapy and low dose daily cisplatin was encouraging. Longer follow-up is necessary to evaluate the survival data. A phase III study is needed to evaluate the efficacy of concurrent daily low dose cisplatin with radiation therapy in bulky cervical cancer.

**Key Words:** Cervical cancer, Concurrent chemoradiotherapy, Radiation sensitizer

**INTRODUCTION**

Radiation therapy (RT) alone is currently considered as the standard treatment for patients with locally advanced cervical carcinoma. Despite the introduction of megavoltage machines and the improved brachytherapy techniques, locally advanced cervical cancer patients with a huge cervical mass treated with radiation treatment alone have shown a high rate of local recurrences and distant metastases. This has led to the investigation of a number of alternative approaches designed to increase the radiation effect such as radiation treatment with hypoxic cell sensitizers, hyperbaric oxygen, and adjuvant chemotherapy. However, these treatment modalities published to date demonstrated very limited success and sustained improvement in terms of pelvic control or survival rate. Therefore, new and innovative therapeutic approaches are clearly needed.

The study conducted by the European Organization for Research and Treatment of Cancer (EORTC) for advanced lung cancer disclosed significant benefits for patients treated with concurrent radiotherapy and daily low dose cisplatin (daily 10 mg/m²) compared to those of patients treated with radiotherapy alone or concurrent radiotherapy and weekly cisplatin. Based on these data, the feasibility study of daily low dose cisplatin as a radiation sensitizer with pelvic radiation therapy for patients with locally advanced cervical carcinoma is designed to analyze the early response and acute toxicity of this regimen in comparison to those of radiation therapy alone.

**MATERIALS AND METHODS**

1. Patient Entry Criteria and Evaluation

From December 1996 to January 1999, 38 previously untreated patients with carcinoma of the cervix were entered in the study. Eligible criteria included FIGO stage IIB to IIIB, histopathologic confirmation, no previous history of malignancy, and performance status greater than 70 on the Karnofsky scale. Adequate bone marrow reserve and normal renal and liver functions were requisites for entry into the study. The international Federation of Gynecology and Obstetrics (FIGO) staging criteria were used. Initial pelvic examination was performed by a gynecologist and a radiation oncologist. Staging evaluation included a physical examination, cystoscopy, chest X-ray, computer tomography (CT) scan of the abdomen and pelvis, MRI of the pelvis, complete blood counts and blood chemistries. Patients with suspicious para-aortic lymph nodes on CT of the abdomen and pelvis were excluded from the study.
Patient's characteristics are outlined in Table 1. These groups were not balanced in terms of tumor size. There were more patients with bulky (>4 cm) cervical mass in concurrent radiation therapy (RT) and low dose cisplatin (cisplatin) group than those in radiation therapy (RT) alone group (P=0.0137).

2. Treatment Regimens

Patients were grouped as RT alone group and concurrent RT and cisplatin group after the completion of staging procedures. The external beam radiation therapy (EBRT) was administered using an isocentric set-up and a four field box technique on a 10 MV photon linear accelerator. The superior margin of the radiation field was the L5-S1 junction, the lower margin was the caudal pole of obturator foramen, and the lateral boundaries were 1.5 cm outside of pelvic sidewalls. Patients were treated on prone position with a full bladder. A dose of 3060 cGy was delivered in 5 days a week at 180 cGy per fraction. After this, midline block was added up to 4500 cGy using parallel opposed anterior and posterior ports. Parametrial boost up to 5400 cGy was administered to the involved side (s).

Intracavitary radiotherapy was given using a high dose-rate (Ir-192 source) remote afterloading unit following 3060 cGy external beam radiotherapy (EBRT), once a week while receiving EBRT and twice a week after finishing EBRT to a total dose of 3000 cGy prescribed at point A in six insertions of 500 cGy each.

Cisplatin was administered as intravenous bolus 30 minutes before the irradiation at a daily dose of 10mg from the first day of EBRT to 20th day of EBRT on an outpatient basis except for one patient who wished to be treated as an inpatient.

3. Evaluation Criteria

Early response to the treatment were evaluated by pelvic examination and appropriate imaging studies. Response data were gathered and analyzed at 4 weeks' follow-up after completion of treatment protocol. A complete remission (CR) was defined as the complete resolution of all measurable disease and a partial response was defined as a 50% reduction of the initial tumor size.

Acute toxicity was measured and recorded according to expanded common toxicity criteria of the NCI (C) Clinical Trials.

During the course of radiation therapy, patients were assessed and recorded weekly regarding the presence of treatment related symptoms. Blood counts were checked and recorded weekly as well.

4. Statistical Analysis

The Fishers exact test was used for the comparison of variables between RT alone group and concurrent RT and cisplatin group.

RESULTS

1. Early Response

Evaluation of early response was possible in 34 patients (20 patients of RT alone group and 14 patients of concurrent RT and cisplatin group) out of 40 patients treated following the protocol, since four patients had less than four weeks of follow-up after the completion of treatments and two patients gave up further treatment after one week of radiation treatment due to financial or personal problems.

2. Table 2. Comparison of Early Response by Treatment Regimen (total number=34)

<table>
<thead>
<tr>
<th></th>
<th>RT alone (n=20)</th>
<th>RT cisplatin (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>16 (80)</td>
<td>11 (78)</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>4 (20)</td>
<td>3 (22)</td>
</tr>
</tbody>
</table>

Table 2 shows the early response for the two regimens. The complete response rate at four weeks' follow-up was 80% for the RT alone group and 78% for concurrent RT and cisplatin group. There was no statistically significant difference in early response to each treatment group by Fisher's exact test (P=0.126).
2. Acute Toxicity

Treatments were generally well tolerated and no patient required a treatment break for more than one week because of acute toxicity. Two patients of concurrent RT and cisplatin group who refused further radiation treatment after one week of radiation treatment were excluded from the analysis of acute toxicity. Table 3 shows acute hematologic toxicities of both groups. No grade 4 acute toxicities were observed. Hematologic toxicity was more prominent in the concurrent RT and cisplatin group. Six of the sixteen patients (37.5%) treated with concurrent RT and cisplatin and one of the twenty-two patients (6.2%) treated with RT alone experienced grade 3 leukocytopenia. In Fisher's exact test, there was statistically significant difference between the two groups regarding leukocyte count ($P=0.030$). But these grade 3 leukocytopenia patients recovered to the level of more than 2000/L of leukocyte count after 3 or 4 days' rest and the treatments could be resumed with no more than one week's rest. Platelet count, hemoglobin, and hematocrit showed less than grade 3 acute toxicity.

Table 3. Acute Hematologic Toxicity (total number=38)

<table>
<thead>
<tr>
<th>Toxic effect</th>
<th>RT alone</th>
<th>RT cisplatin</th>
<th>RT alone</th>
<th>RT cisplatin</th>
<th>RT alone</th>
<th>RT cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Platelet</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hg</td>
<td>6</td>
<td>10</td>
<td>3</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hct</td>
<td>7</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4. Acute Gastrointestinal and Genitourinary Toxicity (total number=38)

<table>
<thead>
<tr>
<th>Toxic effect</th>
<th>RT alone</th>
<th>RT cisplatin</th>
<th>RT alone</th>
<th>RT cisplatin</th>
<th>RT alone</th>
<th>RT cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/Vomiting</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abd. Pain</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysuria</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5. Weight Loss During Treatment (total n=38)

<table>
<thead>
<tr>
<th>Weight loss</th>
<th>RT alone</th>
<th>RT cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nill</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>&lt;5 kg</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>5~10 kg</td>
<td>13</td>
<td>3</td>
</tr>
</tbody>
</table>

DISCUSSION

The majority of patients with locally advanced carcinoma of the uterine cervix which are not cured usually die with uncontrollable local disease in the pelvis.1) Even in the presence of metastatic disease, local relapse may produce symptomatic problems including pain, fistulae and leg edema. Since the addition of surgery or conventional chemotherapy has not altered this significantly, it would
appear that the investigation of radiation sensitizing agents in the management of this disease is advisable.

Cisplatin has been shown to have modest advantage in advanced, metastatic, or recurrent carcinoma of the uterine cervix.7) It forms covalent links between platinum and DNA, RNA, and other proteins; these crosslinks give rise to critical lesions in the presence of radiation.8) Cisplatin, given before irradiation, causes an increase in the slope of the radiation dose-response curve. Experimental data suggest that the antitumor activity may be greater if cisplatin is administered by continuous infusion. In addition, with continuous infusion, thiphasic decay of the drug occurs with terminal half-life of 24 hours.10) Some complications such as nephrotoxicity can be reduced with continuous infusion.

This study was based on the report from Schaake-Koning et al.,6) where significant survival benefit was displayed in patients treated with RT plus daily low-dose cisplatin (6 mg/m2 before each radiation fraction) for locally advanced non-small cell carcinoma of the lung with the European Organization for Research and Treatment of Cancer (EORTC). Before the phase III study that compares survival rate and late toxicity, we have assessed the early response and acute toxicity of daily low-dose cisplatin with concurrent radiation therapy compared to those of radiation therapy alone to evaluate the feasibility of this regimen for locally advanced carcinoma of the uterine cervix. Although the two groups were not balanced in terms of the tumor size, since all patients in the concurrent RT and cisplatin group had bulky cervical mass of more than 4 cm and only 59% of patients in RT alone group had bulky cervical mass of more than 4 cm (P=0.0137), our study revealed that the early responses in both groups were similar. This may indicate that concurrent RT and cisplatin regimen may improve local control for patients with bulky cervical tumor.

Choo and associates11) treated 45 patients in a randomized study with either radiation or radiation plus cisplatin. Cisplatin was administered weekly at a dose of 25 mg/m2. At the time of first intracavitary implant, a complete response was noted in 55% of those treated with chemoradiotherapy, but it was noted in only 20% of those treated with radiation alone. The other small series of studies reported by Piver and associates12) include nine patients, all with extensive paraaortic lymph node metastasis. A complete response was noted in 78% and a partial response was noted in 32% but there was no increase in 5-year survival rate.

Micheletti et al.13) reported a phase II trial to assess the efficacy and local toxicity of the combination of low doses of cisplatin and pelvic radiotherapy in patients with locally advanced carcinoma of the cervix. Nine patients were classified as stage IIB and 14 patients as stage IIIB. 60 Gy external beam irradiation (46 Gy to pelvis[1] 14 Gy boost to cervix uteri and parametria) plus one low dose rate intracavitary treatment to a dose of 8 Gy to point A was given. Cisplatin (3 mg/m2/day) or carboplatin (12 mg/m2/day) was also given for 6 weeks starting on the first day of radiotherapy. The treatment was well tolerated and no patient required radiotherapy discontinuation. Complete response was seen in 74% (17/23) of the patients. Actuarial overall and disease-free survival rates at 33 months were 69.1% and 65.2%, respectively. The combination of cisplatin and radiotherapy appears to be an effective regimen for the patients with locally advanced carcinoma of the cervix and caused a relatively low rate of late gastrointestinal complications. Hus WL et al.14) treated 30 patients with Stage IIIB cervical cancers using synchronous radiotherapy, 5-fluorouracil (5-FU), and daily low-dose cisplatin. Continuous infusion of 5-FU 750 mg/m2 was given for 5 days during the first and third week of pelvic irradiation. Cisplatin (6 mg/m2) was given 30 min before every irradiation in the second and fourth week. The complete response rate was 87%. The 3year local control rate was 77%. The 3-year overall and disease-free survival rate was 66% and 56%, respectively. Toxicities were acceptable. This preliminary result indicates that this synchronous combination treatment is feasible.

It is apparent that radiation therapy alone is not successful in producing prolonged survival in a significant number of patients with bulky primary lesions.15) In this study, the radiation therapy and concurrent use of cisplatin as a radiation sensitizer, although the majority of patients with bulky cervical mass were in the concurrent RT and cisplatin group, showed similar early response rate compared with the radiation therapy alone. This result may indicate that the simultaneous administration of low dose daily cisplatin as a radiation sensitizer is a moderately effective regimen.

The major toxicity was hematologic. Five of the eleven patients (54.4%) in concurrent RT and cisplatin group and one of the sixteen patients (6.2%) in RT alone group had leukocyte counts of less than 2000/mm2. Treatment was temporarily suspended at these stages. After 3-4 days’ rest, the leukocyte counts were recovered to a normal value. Historically the treatments with radiotherapy alone have reported a 0-2% incidence of leukopenia and thrombocytopenia.16) No mortality or life-threatening complications were associated with these hematologic toxic reactions.

CONCLUSION

This study led to the conclusion that the hematologic toxicities of daily low dose cisplatin with concomitant radiation therapy seemed more prominent than those of radiation therapy alone. There was no grade 4 hematologic
toxicities or mortality in either group. The hematologic toxicity in both treatment groups was medically manageable. The concomitant administration of daily low dose cisplatin does not seem to compromise the delivery of standard dose of radiation therapy. Since the risk factors such as mass size were not balanced in two treatment groups, the direct comparison of early response of both group was not possible. However early complete response was similar in both groups despite all the patients in concurrent RT and cisplatin group had bulky cervical mass while only one half of the RT alone group had bulky cervical mass. This preliminary results indicate that concurrent RT and cisplatin regimen may improve local control for high risk patients with bulky cervical mass.

The number of patients was too small and follow-up period was too short to evaluate the survival rate in this study. Since the risk factors were not balanced, we could not compare the early response of both groups directly. But preliminary results are encouraging for patients with bulky cervical mass treated with concurrent RT and cisplatin. Longer follow-up is necessary to evaluate the survival data. A phase III study is needed to evaluate the efficacy of daily low dose cisplatin with concomitant radiation therapy in management of bulky cervical cancer.

REFERENCES

cisplatin

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