Cis-platin and 5-Fluorouracil for Recurrent, Persistent, and Metastatic Cervical Cancer

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Abstract : *From January 1986 to December 1989, 20 patients were treated with cis-platin and 5-fluorouracil for persistent, recurrent and distant metastatic cervical cancer. Eight patients (40%) responded, 2 complete and 6 partial. Median duration of response was 7 months. Median survival for the responders and for the non-responders were 17 and 9 months respectively. Toxicities were all transient in nature. (Thai J Obstet Gynaecol 1993; 5:45-49.)*

Key words : cervical cancer, chemotherapy

One of the choices for recurrent, persistent and distant metastasis of cervical cancer is salvage chemotherapy. Among the active single agents, cis-platin is the most active agent with response rate of 20-50%[1-5]. Another agent is 5-fluorouracil, and combination with cis-platin has been found effective in squamous cell carcinoma of the head and neck[6,7]. We evaluated this combination in patients with recurrent, persistent and distant metastatic cervical cancer.

Materials and Methods

Between January 1, 1986, and December 31, 1989, we treated 20 patients whose characteristics are shown in Table 1 with cis-platin and 5-fluorouracil. Fifteen had recurrent disease, ten of whom had undergone pelvic radiotherapy. Three patients had had prior surgery and 2 patients had received prior mitomycin-c as an induction chemotherapy followed by, in one case, radiotherapy and, in the other, radical hysterectomy with pelvic irradiation. Three patients had undergone simple hysterectomy because of benign disease without a diagnosis of cervical cancer preoperatively.

Ten of the fifteen patients with recurrent disease had distant recurrence. The sites of distant recurrence were supraclavicular lymph nodes, chest, jejunum and spleen, liver, and spines. Recurrence occurred in the pelvis alone in 4 patients. One had

Table 1 Characteristics of patients

Total number	20
Median age(years)	51(30-63)
Initial stage:	
Ib/IIa	3
IIb	7
III/IV	8
Unstaging	2
Histology:	
Squamous	17
Adenocarcinoma	2
Adeno-squamous	1
Status of disease:	
Persistent	3
Recurrence	
Local	4
Local+distant	1
Distant	10
Distant metastasis	2
Previous therapy:	
Radiotherapy	14
Surgery	3
Radiotherapy+surgery	1
Chemotherapy+radiotherapy	1
Chemotherapy+surgery+radiotherapy	1
Median time since primary therapy (months)*	8.5(0-38)

* Median values are followed by ranges in parentheses.

both pelvic and distant recurrence. The site of distant recurrence in this patient was the supraclavicular lymph nodes. All recurrences and distant metastases except that in the lung were histologically confirmed and tumour assessment was based on clinical and/or radiographic or ultrasonographic evaluations.

The eligibility requirements included a performance status of greater than 30% Karnofsky scale, white blood cell count >3000/mm^3, granulocytes >1500/mm^3, platelets count >100,000/mm^3, and normal renal and hepatic functions.

Treatment consisted of cis-platin 50 mg/m^2 by intravenous infusion on day 1 and 750 mg/m^2 of 5-fluorouracil by continuous intravenous infusion on day 1 through day 4 for a total of 3 g/m^2. Prehydration was given before cis-platin infusion with one-half normal saline intravenously at a rate of 300-500 ml per hour for 2-4 hours, and 100 ml of 20% mannitol infused in 20 minutes. Another 1000 ml of one-half normal saline was also infused intravenously in 6 hours immediately after cis-platin infusion. The antiemetic protocol consisted of a combination of metoclopromide, dexamethasone and diazepam.

Complete response was defined as no clinical or radiological evidence of disease lasting greater than 1 month. Partial response was defined as 50% reduction of measurable disease in a single largest diameter for at least 1 month. Non-responders had stable or progressive disease. Stable disease was defined as less than 50% reduction of measurable disease or no change. Time to progression was defined as the length of time from start of the chemotherapy to the date of reappearance or progression of disease. Survival was defined as the time from the start of chemotherapy. Patients without progression or who were still alive after completion of this study were considered as censored. Survival curve was calculated by the method of

Kaplan and Meier, and survival compared with log-rank test.

Results

The median number of chemotherapy courses was 5 (range 3-9). Table 2 shows the results of treatment. Of the 20 patients, 2 (10%) achieved complete response and 6 (30%), partial response, yielding a total response rate of 40%. The sites of complete response in 2 patients were supraclavicular lymph nodes. One of these 2 patients is still alive without disease 36 months after treatment. Although none of the patients with local recurrence had a response, one patient with persistent disease had partial response for 10 months. The sites of partial response in the other 5 patients were chest, supraclavicular lymph nodes, and spines. The median duration of response was 7 months (range 2-40). The median time to progression for the whole group was 4.5 months (range 0-40). Survival curves are shown in Fig. 1. Median survival was 11 months (95% confidence interval: 9-15 months) for all patients, 17 months (95% confidence interval: 12-21) for responders, and 9 months (95% confidence interval: 9-10) for non-responders (stable and progressive disease).

Table 2 Results of treatment

Median number of courses	5(3-9)
No. of responding	8
Complete response	2
Partial response	6
No. of non-responding	12
Stable disease	9
Progression	3
Median duration of response (months)*	7(2-40)
Median survival (months)*	11(3-36)
Median time to progress (months)*	4.5(0-40)

*Median values are followed by ranges in parentheses.

The most common toxicity was nausea and vomiting. Ten patients required continuation of antiemetic drugs. Eight patients developed anemia which required blood transfusion before starting the next course of chemotherapy. Nephrotoxicity, which was defined as an increase in serum creatinine above 2 mg% developed in 3 patients. Alopecia and peripheral neuropathy developed in 3 and 2 patients respectively. None of the patients had neutropenia or thrombocytopenia.

Discussion

In this study, the combination

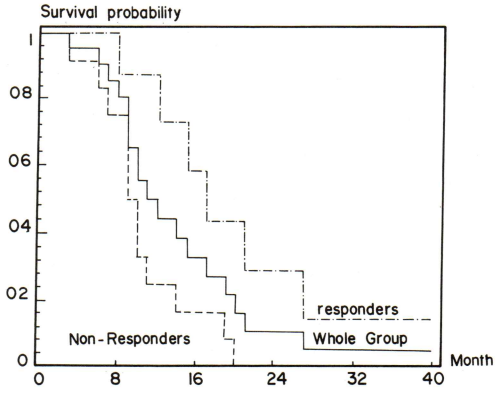

Fig. 1 Survival curve of patients with recurrent, persistent and metastatic cervical cancer treated with cis-platin and 5-fluorouracil.

Table 3 Toxic effects in cis-platin plus 5-FU-treated patients

Hematological toxicity:	
Anemia (hemoglobin<10 g/dl)	8
Leukopenia	0
Thrombocytopenia	0
Stomatitis	1
Nausea/vomiting	10
Nephrotoxicity	3
Peripheral neuropathy	2
Alopecia	3

of cis-platin and 5-fluorouracil in the treatment of recurrent, persistent and metastatic cervical cancer did not yield a high response rates as in the treatment of squamous cell carcinoma of the head and neck. Indeed, the overall response rate, 40%, is slightly lower than that of Kaern et al[8] or Rotmensch et al[9] which achieved 44% and 50% response rates respectively, using a similar regimen or of Kumar and Bhagava[10], who achieved a 66% response rate using a combination of bleomycin, ifosfamide and cis-platin. However, 10% of the patients in the current study had cervical adenocarcinoma and the dose of 5-fluorouracil was slightly low. From the study by the Gynaecology Oncology Group, there were no differences in median response or survival durations of patients treated with either low- or any intermediate-dose cis-platin regimens[11].

Neither median duration of response nor median duration of survival differed greatly from other combination chemotherapies[9,12,13] indicating that combination chemotherapy is unlikely to offer a significant survival advantage over single agent cis-platin[14]. However, responders in this study had a statistically singificant survival advantage over non-responders ($p = 0.013$, log-rank).

The toxicities of this regimen were not severe. The most common was nausea and vomiting and could be controlled by antiemetic drugs. Stomatitis, which is frequent in continuous infusion of 5-fluorouracil occurred in only one case and none of the patients developed neutropenia or thrombocytopenia. This low toxicity may be a result of the low dose of 5-fluorouracil continuous infusion. The major toxic effect of cis-platin, nephrotoxicity, was reversible.

Because this study is unable to compare the survival of the entire treated group with that of untreated patients, which is the best way to demonstrate chemotherapy effectiveness[15], it cannot conclude that the combination of these two familiar drugs, cis-platin and 5-fluorouracil, improve the therapeutic outcome. They can be used to produce 40% response rate but the survival duration is still disappointing.

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