A PILOT STUDY OF FIRST-LINE CHEMOTHERAPY WITH 5-FU AND PLATINUM IN ADVANCED AND RECURRENT CANCER OF THE CERVIX

F. Ghaemmaghami[1], N. Behtash[1], F. Yarandi[1], A. Moosavi[1], Gh.R. Toogeh[2] and N. Khanafshar[3]

1) Department of Gynecology and Obstetrics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
2) Department of Internal Medicine, Tehran University of Medical Sciences, Tehran, Iran
3) Vali-E-Asr Reproductive Health Research Center, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Abstract- This study was designed to assess the role of first-line chemotherapy with 5-FU and platinum in the treatment of advanced or recurrent cervical cancer. Ten patients with advanced or recurrent cancer of the cervix, with no prior chemotherapy were entered in phase II trial, from Oct. 2000 to Nov. 2001. Eight patients were treated with cis-platinum (50 mg/m^2 over 60 minutes in first day) followed by 5-FU (1 g/m^2 over 24 hours for 4 days) and two patients with impaired renal function were treated with carboplatin (300 mg/m^2 over 15 minutes in first day) followed by 5-FU (1 g/m^2 over 24 hours for 4 days) every three weeks, until progression of disease or prohibitive toxicity had been observed. Median age was 52 years (range: 28-70 years). Ten patients received a total of 42 cycles of chemotherapy. The mean number of chemotherapy cycles was 4.2 (median 4, range: 3-7). Three patients had partial response (30%, CI, 1.7 %-58.5%). Mean response duration was 198 days (range: 122-273 days). Four patients required red blood cell transfusions; three of them had grade II and one of them grade III nausea and vomiting. Two had fever and neutropenia (one developed acute renal insufficiency), and there were no treatment related mortalities. First-line chemotherapy with platinum and 5-FU for advanced and recurrent cervical cancer is promising and deserves consideration for large phase III trials.

Acta Medica Iranica, 41(2): 105-109; 2003

Key Words: Cervix, carcinoma, chemotherapy, platinum, 5-FU, palliation, toxicity

INTRODUCTION

Cervical cancer is the most common malignancy among women in the developing countries (1). Unfortunately, due to lack of widespread screening and patients' delay in seeking medical attention, most of the cervical cancers in Iran are diagnosed in advanced stages. The prognosis for this subset of patients remains poor with very few long-term survivors, especially if they are not amenable to being treated with curative intent surgery or radiation therapy. Chemotherapy has been used to treat these patients with limited success. Most of these patients had prior radiation therapy and surgery, which limits drug delivery to the recurrent lesions. Limited bone marrow reserve, frequently impaired renal function secondary to obstructive hydronephrosis, selection of resistant clones, and the fact that over 80% of tumors are squamous cell carcinomas contribute to these disappointing results.

Gynecologic cancers of non-ovarian origin continue to be a medical problem, if local therapy with surgery and/or radiation therapy fail. Management of advanced stages of metastatic disease remains relatively ineffective with poor survival for stages III and IV ranging from a few months to 25% at 5 years (2).

Cis-platinum is the single most active agent in the treatment of cervical carcinoma with objective response rate consistently above 25% (3). Among the other active single agents used to treat cervical cancer, doxorubicin, ifosfamide, 5-fluorouracil, methotrexate, and mitolactol have generated the most interest and have been used in combination with cisplatin with varying degrees of success (4).

Cis-platinum and 5-FU were reported to have a 50% response rate in recurrent or advanced cervical cancer (5), a 94% response rate in head and neck cancers given as primary therapy (6) and 60-70% response rate when used in recurrent disease (7,8).

There have been other reports in which the use of cis-platinum and 5-FU, had lower response rates

Received: 30 June 2002, accepted: 19 February 2003

Corresponding Author:
Department of Gynecology and Obstetrics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 6937766
Fax: +98 21 6937321
E-mail: valrec2@yahoo.com

(9,10). Data that supported synergism and lack of cross- tolerance between cis-platinum and 5-FU were reported in some studies (11, 12).

The basis for this synergy may be 5-FU inhibition of DNA repair for Cis-platinum induced DNA cross-link (11). Lack of cross-resistance between these two drugs was demonstrated in the highly cis-platinum resistant human squamous cell carcinoma cell-line (SCC-25/CP). This cell-line was equally sensitive to 5-FU, as like as the parent SCC-25 cell-line (13).

MATERIALS AND METHODS

Ten avaluable patients with advanced or recurrent cervical cancer whom had been visited between Oct. 2000 and Nov. 2001 were enrolled in this study. Inclusion criteria was based on histology, proven recurrent squamous cell carcinoma or adenocarcinoma of cervix, which had relapsed after initial conventional local therapies, and for which no previous chemotherapy had been given except in the context of adjuvant setting as a radio-sensitizer in conjunction with radiotherapy, a GOG performance status < 2, white cell count > 3000/mm3, platelet count > 100000/mm3, serum bilirubin < 1.5 mg/dl and serum transaminases < 3 times normal laboratory value. Patients with serum creatinine > 1.5 mg/dl were treated with carboplatin and 5-FU.

Informed consents were obtained after satisfactory understanding of the potential risks and benefits of this treatment.

Eight patients were treated by cis-platinum and 5-FU and the other two with the combination of carboplatin and 5-FU, these patients were pretreated by 8 mg dexamethasone and 20 mg lasix and metocloperamide. We didn't use ondansetrone because of its price and difficulties of availability.

Cis-platinum (50 mg/m^2 over 60 minutes) was administered, after patient's hydration with 1000 ml of normal saline (300 ml/h) was completed (certainly hydration of the patient continued for 24 hours, 125 ml/h, for the first day) and was followed by, 5-FU (1 g/m^2) over 24 hours for 4 days.

Carboplatin, 300 mg/m^2 over 15 minutes, was administered to those two patients, followed by 5-FU 1 g/m^2 over 24 hours for 4 days.

Each of these cycles was repeated every 28 days. Granulocyte colony stimulating factors were initiated for grade III or IV neutropenia. Chemotherapy was withheld for a white cell count below 3000/mm^3 and platelet count below 100000/mm^3 and counts were repeated biweekly until they met the above criteria for the next course of chemotherapy. By using the GOG scoring system, we assessed toxicity.

Complete response was defined as the total disappearance of all clinically or radiologically measurable lesions lasting for at least a month. Partial response was defined as a 50% reduction in the sum of the two perpendicular diameters of all lesions measurable clinically or radiographically lasting at least 1 month. Progression of disease was defined as the appearance of new lesions or more than a 50% increase in the sum of the two perpendicular diameters of any prior lesion with 8 weeks of initiating treatment. The term, stable disease, was used for response that fell in between a progression and a partial clinical response.

This duration of response was measured from the time of the initial documented response to the first sign of disease progression. The time to progression was measured from the time of first study drug administration to documented progressive disease or initiation of second line therapy.

This protocol was initiated on 9/1/2000 and data were gathered up to 9/1/2001. Patients were considered as responsive if they had received at least two cycles of chemotherapy or had demonstrated significant progression after one course of this treatment.

RESULTS

The median age of the patients was 52 years (Range 28-70).

Eight patients had recurrent disease and one persistent disease. The last patient, who was 28 years old, had stage II-A cancer (bulky) and underwent preoperative radiotherapy and radical hysterectomy. Because of lymph node metastasis, chemotherapy was started. We could not calculate the response of this patient, because there was no measurable disease and for the time being and after passing 3 chemotherapy cycles, she is still alive without disease.

Recurrence in eight patients was limited to just one site, but just one of the patients had involvements at multiple sites (Pelvic and abdominal cutaneous metastasis on the drain site), and one of them had para-aortic lymph node metastasis (Table 1).

The most common site for recurrence was pelvis (recto-vaginal septum) and it occurred in eight of the patients.

The FIGO staging at primary diagnosis distribution showed, 2 of the patients in stage I-B, 3 in stage II-A,

and 5 in stage II-B. All of the patients had squamous tumors and the most common symptoms were vaginal discharge and pelvic pain.

All patients had received radiation therapy as a primary treatment or in recurrence state, but no one got para-aortic or abdominal radiation. All patients were avaluable for response.

During their treatment, 5 of these patients had a symptomatic response, 1 transient symptomatic response and 3 had no symptomatic response (Table 2).

Symptomatic response was assessed retrospectively by careful review of all medical and nursing annotation and was recorded as absent, transient response, or response throughout treatment, with reference to the symptoms requiring palliation.

Three patients (30%) (CI 95%, 1.6%-58.4%) demonstrated partial clinical response to chemotherapy with mean duration of 6.6 months (198 days) (CI 95%, 122- 273). None of the patients had complete response and despite their disease are still alive. Four patients (40%) (CI 95%, 9.4%-70%) were being stable, but one of them died because of cardiopulmonary arrest (8 weeks after completeness of chemotherapy). Two patients (20%) had progressive disease and despite discontinuation of chemotherapy died because of renal insufficiency. Median time to progression was 228 days (Range: 116-329 days). Only two patients (20%) required granulocyte colony stimulating factors (Table 3).

Patients received a total number of 42 cycles of chemotherapy. Mean was 4.2 cycles (median 4, range 3-7). In 7 (16%) cycles we had GOG grade 3/4 neutropenia, in 15 (35%) cycles, GOG grade 2/3 nausea, and in 8 (19%) cycles GOG grade 2/3 vomiting. No serious diarrhea or mucositis in our patients was noticed (Table 4).

Table 1. Treatment characteristics of patients receiving chemotherapy

Primary treatment	**Frequency**
Radiation	5
Surgery	1
Surgery + radiation	4
Site of recurrence	**Frequency**
Pelvic	8
Pelvic & distant	1
Distant	1
Histopathology	**Frequency**
SCC	10
Grade I	1
Grade II	7
Grade III	2
FIGO staging at primary diagnosis	**Frequency**
I-B	2
II-A	3
II-B	5
III-A	-
III-B	-
IV-A	-
IV-B	-

Table 2. Quality of life versus response category

Symptoms / Response	**Absent**	**Transient absence**	**Absent through treatment**	**No response**
Partial	2	1	-	-
Stable	3	-	-	1
Progressive	-	-	-	2

Table 3. Incidence of hematological toxicity

Toxicity / Grade	**Anemia**	**Granulocytopenia**	**Thrombocytopenia**
0	24(57.14%)	31(73.81%)	40(95.24%)
1	7(16.67%)	3(7.14%)	1(2.38%)
2	11(26.19%)	1(2.38%)	1(2.38%)
3	1(2.38%)	5(11.90%)	0(0.0%)
4	0(0.0%)	2(4.76%)	0(0.0%)

Table 4. Incidence of non-hematological toxicity

Toxicity / Grade	Nausea (%)	Vomiting (%)	Diarrhea (%)	Alopecia (%)	Mocusitis (%)
0	15 (35.71)	26 (61.90)	39 (92.86)	41 (97.62)	36 (85.71)
1	12 (28.57)	8 (19.05)	0 (0.0)	1 (2.38)	0 (0.0)
2	12 (28.57)	6 (14.29)	2 (4.76)	0 (0.0)	1 (2.38)
3	3 (7.14)	2 (4.76)	1 (2.38)	0 (0.0)	5 (11.90)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

DISCUSSION

Response to combined chemotherapy in advanced or recurrent cervical cancer varies from 16 to 69%, depending on the size of study, site of lesions, and prior radiotherapy (3). Southwest Oncology Group reported results of a phase II randomized trial study on 114 evaluable patients, comparing single agent chemotherapy (cisplatin) with cisplatin+ mitomycin, cisplatin+ vincristine+ bleomycine (MVBC), and cisplatin + mitomycin C (MC) (14). The cisplatin arm was terminated due to problems in patient accrual. The clinical response rate was 22% for patients receiving MVBC and 25% for those on MC, which was similar to the response obtained in the 9 patients on single agent Cisplatin.

One of the largest trials to date in which randomized 454 patients to three arms is the study conducted by GOG. cisplatin alone compared with cisplatin+ mitolactol and cisplatin+ ifosfamide (15).

All arms got the same amount of Cisplatin (50 mg/m^2). The cisplatin + ifosfamide arm had a statistically significant higher response rate (31.1% versus 17.8%) and a longer progression-free interval (4.6 months versus 3.2 months) compared to single agent Cisplatin, but at the cost of greater toxicity and no improvement in the overall survival. The cisplatin+ mitolactol arm showed no difference in these parameters compared to single agent cisplatin.

Chiara, et al., using cisplatin and 5-FU, showed that toxicity was acceptable and manageable. The most important side effect was dose-cumulative neurotoxicity. They had 61% objective response (1 complete and 10 partial). Median duration of response was 11 months (3-23) and the actual survival rate after 36 months follow-up was 43.3% (16).

The major potential toxicities from cisplatin + 5-FU are nephrotoxicity from cisplatin and mucositis and diarrhea from 5-FU. Nephrotoxicity can be prevented by vigorous pre-hydration. Continuous infusion 5-FU has been demonstrated to be more efficacious than bolus doses. Moreover toxicity was decreased by reducing the duration of infusion from 120 hours to 96 hours, without affecting efficacy (17).

Considering our study, we believe that toxicity was manageable and could have been improved by using growth-stimulating factor. As a matter of fact by observing myelosuppression, as one of the most common side effects in this combined chemotherapy, we speculate that by using growth-stimulating factor, we could be able to overcome this problem. We pre-medicated our patients with dexamethasone and metoclopramide for managing their gastrointestinal side effects, but after all we should add that by using ondansetrone we might have less gastrointestinal side effects. Unfortunately because of lack of availability and its price we did not use it in a regular basis on our patients. Furthermore, among those with recurrent disease, we are able to provide pain palliation in the majority of them who presented with pain, even in the absence of objective response. This kind of palliation has been noted by others (18).

On the whole, we are able to pretend that, this pilot study showed combination of cisplatin and 5-FU, can be acceptable for its significant anti-tumor activity, low toxicity and relatively good palliative properties, in chemotherapy of recurrent or advanced cervical cancer.

At last, we can suggest that, a prospective randomized trial, which compares this therapy and cisplatin alone, can be of some critical value for evaluating 5-FU role in this combination therapy.

REFERENCES

1. Sankaranarayanan R, Wesley R, Somanathan T, et al. Visual inspection of the utrine cervix after the application of acetic acid in the detection of cervical carcinoma and its precursors. Cancer 1998; 83 (10): 2150-2158.

2. Trudeau M, Seymour R, Stanimir G, et al. A phase II trial of mitomycine, ifosfamide and cisplatin in recurrent carcinoma of cervix. Int J Gynecol Cancer 2000; 10: 2070-2111.

3. Alberts DS, Garcia D, Mason-liddil N. Cisplatin in advanced cancer of the cervix: an update. Semin Oncol 1998; 18(53): 11-24.

4. Thigpen T, Vance RB, Khansur T. The platinum compounds and paclitaxel in the management of carcinoma of the endometrium and the uterine cervix. Semin Oncol 1995; 22(512): 67-72.

5. Wade JL, Richman GM, Senekjian E, et al. Objective response in advanced carcinoma of the cervix using cis-platinum and infusion 5-flourouracil (5-FU) chemotherapy. Proc Am Soc Clin Oncol 1984; 3:172.

6. Decker DA, Derlichman A, Jacobs J, et al. Adjuvant chemotherapy with cis-diamine dichloroplatinum II and 120-hour infusion 5-FU in stage III, IV squamous cell carcinoma of the head and neck. Cancer 1983; 51: 1353-1355.

7. Rowland KM, Taylor SG, Spiers AS, et al. Cisplatin and 5-FU infusion chemotherapy in advanced recurrent cancer of the head and neck: an eastern cooperative oncology group pilot study. Cancer Treat Rep 1986; 70: 461-464.

8. Kish J, Weaver A, Jacobs J. Cisplatin and 5-FU infusion in patient with recurrent and disseminated epidermoid cancer of the head and neck. Cancer 1984; 53: 1819-1824.

9. Weiss GR, Green S, Hannegan EV, et al. A phase II trial of cisplatin and 5-FU with allopurinol for recurrent or metastatic carcinoma of the uterine cervix: a southwest oncology group trial. Gynecol Oncol 1990; 37: 354-358.

10. Bonomi P, Blessing J, Ball H, et al. A phase II evaluation of cisplatin and 5-FU in patients with advanced squamous cell carcinoma of the cervix: a gynecologic oncology group study. Gynecol Oncol 1989; 34: 357-359.

11. Beaupain R, Dionet C. Effects of combined treatments of cis-diammine dichloroplatinum II, 5-FU, and x-rays on growth of human cancer nodules maintained in countinous organotypic culture. Cancer Res 1985; 45: 3150-3154.

12. Schabel FM, Trader MW, Laster WR. Cis-diammine dichloroplatinum II aombination chemotherapy and cross-resistance studies with tumors of mice. Cancer Treat Rep 1979; 63: 1459-1473.

13. Teichers BA, Cucchic A, Lee JB, et al. Alkylating agents: in vitro studies of cross-resistance pattern in human cell line. Cancer Res 1986; 46: 4379-4383.

14. Albert DS, Kronmal R, Baker LH, et al. Phase II randomized trial of cisplatin chemotherapy regimens in the treatment of recurrent or metastatic squamous cell cancer of the cervix: a southwest oncology group study. J Clic Oncol 1987; 5:1791-1795.

15. Omura G, Blessing J, Vaccaiello L, et al. A randomized trial of cisplatin versus cisplatin+ mitolactol versus cisplatin + Isofosphamide in advanced squamous carcinoma of the cervix by the gynecologic oncologic group. Gynecol Oncol 1996; 60: 120-126.

16. Chiara S, Consol R, falcone A, et al: Cisplatin and 5- fluorouracil in advanced and recurrent cervical cancer. Tumor, 1988; 31: 74(4): 471-474.

17. Kish JA, Ensley JF, Jacob J, et al. A randomized trial of cisplatin + 5-FU infusion and cis + 5-FU bolus for recurrent and advanced squamous cell carcinoma of the head and neck. Cancer 1985; 56: 2740-2744.

18. Kaern J, Trope C, Abeler V, et al. A phase II study of 5-FU/ cis in recurrent cervical cancer. Acta Oncol 1990; 29: 25-28.