ORIGINAL ARTICLES

A ten-year remission maintained by 6272 mg (3920 mg/m^2) cumulative dose of cisplatin-based chemotherapy for recurrent epithelial ovarian cancer

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Summary

Since cisplatin is a heavy metal, renal and neurotoxicity is considered to be dose limiting in solid tumors. The current case is unusual in that remission has been maintained in a patient with recurrent epithelial ovarian cancer by cisplatin-based chemotherapy without evidence of renal or neurotoxicity, while receiving a total dose of 6270 mg (3920 mg/m^2) of cisplatin over 11½ years.

Key words: Chemotherapy; Cisplatin; Ovarian cancer.

Introduction

Because in 1979 recurrent cervix cancer after previous pelvic radiation was considered incurable by cytotoxic chemotherapy, we initiated a protocol of maintenance cisplatin-based chemotherapy every two months in a small subset of patients who achieved complete response to first line cis-Diamminedichloroplatinum II (cisplatin) based chemotherapy [1]. At the time of that report, five patients had received uninterrupted cisplatin-based chemotherapy for 5, 4.5, 2.3, 2.3, and 1.5 years. All five patients remained in complete remission after receiving a total cumulative dose of cisplatin of 2523 mg (1530 mg/m^2), 2408 mg (1655 mg/m^2), 1496 mg (880 mg/m^2), 1325 (970 mg/m^2), and 1640 mg (950 mg/m^2) respectively. No renal toxicity occurred as measured by serum creatinine levels. The only documented toxicity was asymptomatic hypomagnesemia. Three additional patients in the study in complete remission on cisplatin-based chemotherapy voluntarily discontinued chemotherapy and all subsequently developed uncontrolled recurrent cervix cancer and died of their disease.

Although a small percent of women with advanced stage epithelial ovarian cancer are cured by first-line cisplatin-based chemotherapy, the ten-year progression-free survival is less than 10% and, thus, recurrent epithelial ovarian cancer is incurable in most instances [2]. Based on our experience in prolonged cisplatin-based chemotherapy in recurrent cervix cancer, we initiated a similar protocol of maintenance cisplatin-based chemotherapy in 1982 in women who achieved a complete response to platinum-based salvage chemotherapy [3]. Patients were continued on maintenance chemotherapy every eight weeks. Compared to patients who refused maintenance chemotherapy, patients who receive prolonged maintenance chemotherapy had a significantly longer disease-free interval from the date of recurrence (median 35.0 months versus 6.0 months, p=0.001).

The purpose of this paper is to report the clinical course and toxicity details of one patient from this study who to date has received a cumulative dose of 6272 mg (3920 mg/m^2) of cisplatin for recurrent epithelial cancer over a 12-year period.

Materials and Methods

Cisplatin was administered in 0.45% sodium chloride in 5% dextrose over six hours. Furosemide diuresis and 20% mannitol diuresis preceded cisplatinum in administration. Post-cisplatinum hydration consisted of 0.5% sodium choloride in 5% dextrose.

Complete clinical remission consisted of no clinical evidence of disease on physical examination and normalization of CA125. Complete surgical remission consisted of no evidence of persistent ovarian cancer at second-look laparotomy. Progressive disease consisted of new findings on physical examination or CT of the pelvis and abdomen or chest and rising CA125.

Partial clinical remission consisted of normalization of CA125, no new evidence of disease on physical examination and stable CT findings.

Case Report

This 40-year-old was in her usual state of good health until January, 1989 when she had a feeling of vague abdominal symptoms consisting of nausea, constipation and increasing abdominal girth. A pelvic sonogram demonstrated a pelvic mass and ascites. Examination demonstrated bilateral 8 cm adnexal masses. CA125 was 232 (N= <35u). At the time of exploratory laparotomy there was metastasis to the diaphragm, omentum (38 x 15 x 8 cm), right paracecal and appendix area (4 x 5 cm) and small disease along the small bowel mesentery, cul-de-sac and rectum. There was also 3500 cc's of ascites.

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On January 31, 1989 she underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, resection of bilateral ovarian tumors, resection of cul-de-sac tumor, tumor involving her uterus, resection of tumor in the paracecal area/right pericolic area, omentectomy, resection of gastrocolic ligament tumor and appendectomy. At the end of the procedure the largest residual disease measured 5 mm. Pathology documented moderately differentiated papillary serous adenocarcinoma of the ovary with metastasis to the above areas.

Starting in February 1989 the patient was started on our protocol induction of cisplatin weekly x 4 followed by monthly cisplatin, adriamycin (doxorubicin) and cyclophosphamide (PAC) [4] (Table 1). By May 1989 she had normalized her CA125 to 11. She completed ten courses of PAC chemotherapy and tolerated it well (Table 2).

In January 1990 she underwent second-look laparotomy, multiple biopsies, bilateral pelvic lymphadenectomy, paraaortic lymphadenectomy, and peritoneal washings. All of the above were negative for persistent ovarian cancer and she was considered in complete surgical remission. She remained in clinical remission for 18 months with normal examination and normal CA125 until July 1991 when her CA125 increased to 50. Pelvic examination demonstrated a large pelvic mass. She underwent secondary debulking surgery with resection of tumor from the pelvis, anterior abdominal wall, small bowel, gastrocolic ligament and serosa of the small intestine. The pelvic tumor measured 11 x 8 x 7 cm and was attached to the vaginal apex, bladder, rectosigmoid colon and para-rectal area. At the end of the procedure the largest residual disease was less than 5 mm.

Starting in July 1991 she was then treated on our protocol of monthly DIME chemotherapy [5] (Table 1). She normalized her CA125 prior to her third course. She received 12 monthly courses of DIME chemotherapy through May 1992 and was considered to be in complete clinical remission with a normal examination and normal CA125 (less than 7).

She remained without evidence of disease until November 1993 when she developed upper respiratory symptoms. Chest χ-ray demonstrated a pleural effusion and CT demonstrated liver metastasis. She underwent thoracentesis and liver biopsy both of which were consistent with her ovarian primary. Her CA125 had increased to 206. In December 1993 she was started on our protocol of monthly cisplatin and paclitaxel as salvage chemotherapy [6] (Table 1). She normalized her CA125 by her third course of cisplatin and paclitaxel.

CT scan of the pelvis and abdomen in July 1994 demonstrated a complete regression of the liver metastasis. Her CA125 remained at 8. In July 1995 she was started on our protocol of every other month maintenance paclitaxel and cisplatin [3] (Table 3). She received 32 courses of maintenance taxol/cisplatin. In December 1999 there was a question of a new 2 cm liver metastasis on CT scan which was felt radiologically to either be persistent disease or scarring from her previous liver metastasis. Because of a normal CA125 and no clear evidence of progressive disease, she was maintained on every other month paclitaxel and cisplatin. In November 2000 her CA125 had risen from a low of 8 to 25 and by February 2001 it had increased to 35.8. A CT scan in February 2000 was diagnosed as "stable liver metastasis as compared to the previous CT scan".

Because of the rise in CA125 and now firmer radiologic confirmation of liver metastasis, the patient was restarted in February 2001 on monthly paciltaxel and cisplatin. After two monthly courses she normalized her CA125 to 17.9. As of June 2001 her CA125 had decreased to 11.1.

Serum creatinine has ranged from 1.0 to high of 1.4 mg/dl. Magnesium has ranged from 0.8 to 1.5 mg/dl. A 24-hour urine creatinine clearance done on March 21, 2001 was 1.1 (normal 0.6-1.7 g/24 hrs), creatinine was 1.1 and blood urea nitrogen was 25 mg/dl.. An audiogram done on March 21, 2001 demonstrated normal hearing bilaterally with exception of mild high frequency loss in the left ear consistent with speech reception thresholds. She had excellent discrimination bilaterally.

Table 1. — *Chemotherapy regimens.*

I. *Induction cisplatin and monthly PAC*
   1. Induction cisplatinum 40 mg/m^2 weekly x4
   2. Monthly PAC
      Cisplatin (P) 50 mg/m^2
      Adriamycin (A) 50 mg/m^2
      Cyclophosphamide (C) 750 mg/m^2
II. *Monthly DIME*
   Cisplatin (D) 20 mg/m^2 daily x3
   Ifosphamide (I) 675 mg/m^2 daily x3
   Mesna (M) 67.5 mg/m^2 day 1
   Etoposide (E) 50 mg/m^2 daily x3
III. *Monthly Taxol/cisplatin* TP
   Taxol (T) 135 mg/m^2/24 hours day 1
   Cisplatin (P) 75 mg/m^2 day 2
IV. *Maintenance every other month Taxol/cisplatin* TP
   Taxol 135 mg/m^2/24 hours day 1
   Cisplatin 50 mg/m^2 day 2

Table 2. — *Surgery, chemotherapy and response.*

Date	Surgery	Chemotherapy courses	Total cisplatin dose	Response
1/1989	Primary debulking			
2/1989-12/1989		P weekly x4 PAC monthly x10	160 mg/m^2 500 mg/m^2	CCR
1/1990	Second-look laparotomy			CSR
7/1991	Secondary debulking			
7/1991-5/1992		DIME monthly x12	720 mg/m^2	CCR
11/1993	Thoracentesis Liver biopsy			
12/1993-11/1994		TP monthly x10	750 mg/m^2	CCR
1/1995-2/2001		TP every other month x32	1600 mg/m^2	
3/2001-6/2001		TP monthly x4	200 mg/m^2	PCR
		72	3920 mg/m^2	

CCR = complete clinical response; CSR = complete surgical response; PCR = partial clinical response.

Discussion

Because cisplatin is a heavy metal, renal toxicity is considered by many to be a dose-limiting step in its use as a cytotoxic agent against solid tumors. This concern has led to the discovery of less nephrotoxic platinum compounds, such as carboplatin. Notwithstanding the discovery of other platinum compounds, cisplatin remains an important neoplastic agent.

It is now known that cisplatin nephrotoxicity can be reduced or even avoided by mannitol diuresis; furososemide diuresis; hydration before, during and after cisplatin; administration of cisplatin in chloride-rich solutions; avoidance of rapid cisplatin infusion and avoidance of concommitant nephrotoxic drugs. The current case report is unusual in that to the best of our literature search, the 6272 mg (3920 mg/m²) is by far the largest total cumulative dose of cisplatin that that any patient has ever received and over the longest period of time. It also highlights that the major toxicity to cisplatin, nephrotoxicity, can be avoided by careful attention to hydration and diuresis. Moreover, she has not developed any neurotoxicity. This case also supports the fact that a remission can be maintained by prolonged cisplatin-based chemotherapy.

Patients with recurrent ovarian cancer who are fortunate enough to achieve a second remission should be considered to have a chronic disease The current report demonstrates that recurrent ovarian cancer can be managed safely in selected patients as a chronic illness with continued cisplatin-based chemotherapy.

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