Primary Treatment of Stage III Ovarian Carcinoma with Sequential Chemotherapy and Whole Abdominal Radiation Therapy

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A prospective phase II clinical treatment trial of 13 patients with previously untreated optimal surgically resected (≤1 cm) stage III ovarian carcinoma was conducted at the University of Michigan Hospitals. The treatment regimen after surgical resection consisted of chemotherapy followed by whole abdomen and pelvic radiation therapy. Chemotherapy consisted of four cycles of 50 mg/m² cisplatin and 1000 mg/m² cytoxan. This was followed by whole abdomen radiation therapy with a planned total dose of 30 Gy to the whole abdomen and then a 20-Gy boost to the pelvis. Six of 13 patients received a paraaortic radiation boost. There was minimal acute toxicity, but delayed toxicity was encountered with 38% of patients developing a bowel obstruction. Nine patients had reassessment laparotomy: 5 second-look laparotomies and 4 laparotomies for bowel obstruction. Two of these 9 patients died of septic complications after surgery. Nine patients died with disease, 1 patient is alive with advanced disease, and only 3 patients are alive with no evidence of disease. Actuarial 3-year survival and progression-free interval was 26 and 20%, respectively. Primary treatment consisting of sequential chemotherapy and whole abdomen radiation in the dose and scheme utilized did not improve the survival over what could be expected utilizing one of these treatments alone. It was associated with increased delayed toxicity. © 1993 Academic Press, Inc.

INTRODUCTION

Ovarian cancer is the leading cause of death from gynecologic malignancies; approximately 60–75% of patients are diagnosed initially with stage III disease. Optimal cytoreductive surgery has improved the response to chemotherapy, progression-free interval, and survival [1–4]. However, relapse rates remain high and the overall survival has not improved over the last several decades

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[5–11]. After chemotherapy, only 30–40% of patients with stage III ovarian cancer have a negative second-look laparotomy [12–16]. Up to 50% of patients with a negative second look will eventually develop recurrent disease [15,17]. Treatment after cytoreduction is frequently chemotherapy, although whole abdominal radiation therapy (WAR) has been utilized in certain institutions with success. With the acceptance that chemotherapy and WAR are both active treatments in ovarian cancer, it was postulated that sequential chemotherapy and WAR would reduce recurrence rates.

Cisplatin has been demonstrated to be one of the most effective agents for ovarian carcinoma [18]. A Gynecologic Oncology Group study demonstrated that there was no significant advantage of doxorubicin in addition to cisplatin and cyclophosphamide in patients with stage III optimal ovarian carcinoma [12]. Thus, based on information when the protocol was established, cisplatin and cytoxan were chosen for chemotherapy.

WAR has also demonstrated promising results as primary therapy after initial surgical debulking in patients with microscopic or small residual tumor volume [19–21]. WAR has been used as salvage therapy to treat patients with recurrent disease at second-look laparotomy [11, 22–28]. Prolonged progression-free intervals with salvage WAR were best achieved in patients with no residual or microscopic disease after second-look debulking [19,20,23,25,27]. However, the response rates of salvage WAR with macroscopic or small-volume disease after second-look surgery have been varied. Several authors report poor progression-free intervals and survival [23,25,28,29] while other authors report favorable responses [11,20,27]. WAR as salvage therapy after full course chemotherapy, however, can have increased com-

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plications such as myelosuppression or bowel obstruction [11,22,25,26,28]. Rosen felt that by limiting the number of chemotherapy cycles to four to six improved tolerance for subsequent salvage therapy with WAR was obtained [30]. The optimum number of chemotherapy cycles for ovarian cancer is unknown, but it would be expected that after less intensive systemic chemotherapy (four cycles) WAR would be better tolerated.

The National Cancer Institute reported 28 patients of stages III–IV ovarian carcinoma with concurrent chemotherapy and WAR with no improvement over chemotherapy alone [31]. One-third had stage IV disease, one-half had residual disease after cytoreductive surgery in excess of 2 cm, and 43% had bulky (>5 cm) disease at initiation of chemotherapy. All these factors would be risk factors for treatment failure. Thus, we limited our patients to optimal resection of less than 1 cm.

Based on this background, a prospective phase II study at University of Michigan Hospitals of optimally debulked stage III epithelial ovarian carcinoma was undertaken to evaluate the toxicity and efficacy with the sequential treatment of four cycles of chemotherapy followed by whole abdomen radiation therapy.

MATERIALS AND METHODS

Eligible patients had optimal cytoreductive surgery for stage III epithelial ovarian carcinoma with no residual tumor masses after initial surgical resection larger than 1 cm in diameter. Although the protocol did allow for pelvic/periaortic node dissection, only one patient had this performed. Patients were enrolled after informed written consent was obtained. Chemotherapy was initiated within 2 weeks of surgery. They received four cycles of chemotherapy followed by whole abdomen and pelvic radiation therapy. Operative reexploration was not performed between chemotherapy and WAR. Patient responses were evaluated clinically every 3 months or by reassessment laparotomy. Patients were offered a second-look laparotomy after sequential chemotherapy and WAR. Five patients selected a second-look laparotomy as a treatment option, and four had assessment of disease at surgical exploration for bowel obstruction. The reassessment laparotomy findings in these nine patients took priority over the clinical evaluation.

All patients received chemotherapy consisting of four cycles of 50 mg/m^2 cisplatin and 1000 mg/m^2 cyclophosphamide administered every 21 days with no delays.

WAR was started within 4 weeks of the last chemotherapy cycle. The University of Michigan technique for whole abdominal irradiation has been recently described [32]. It involves a computerized tomography of the patient in the treatment position to verify that the entire peritoneal surface is included in the treatment field. The typ-

ical whole abdominal field extends 3 cm superior to the diaphragm on maximum expiration, laterally to cover the widest portion of the peritoneal surface, and inferiorly 2 cm below the obturator foramen. Anterior and posterior (APPA) opposing fields were used. Total dose was planned to be 30 Gray (Gy) given in 30 fractions. This low dose per fraction was chosen in an attempt to minimize acute hematologic and long-term gastrointestinal complications. The time, dose, fractionation (TDF) of this scheme is closely equivalent to the TDF of 22.5 Gy in 18 fractions, the Princess Margaret Hospital standard [21]. Two of the patients received only 23 and 25 Gy due to myelosuppression necessitating more than a 2-week treatment break. Because of potential toxic renal effects of cisplatin chemotherapy, posterior kidney blocks were utilized, limiting the kidneys to 15 Gy while no liver shielding was employed. An APPA paraaortic field was originally planned in the protocol, however, only 6 of 13 patients received paraaortic radiation between 9 and 16 Gy. It was discontinued in later patients due to concern about toxicity. Following WAR, the pelvic field was treated through opposing anterior and posterior fields to a median dose of 15 Gy (range, 12.6 to 27 Gy), with a median dose per fraction of 1.8 Gy (range, 1.25 to 2 Gy). The median total dose to the pelvis was 4600 (range, 4260–5000); 15 Mev photons were used in all patients.

Patients were followed for toxicity during and after treatment. Chemotherapy and radiation therapy dose modifications were allowed for myelosuppression, genitourinary toxocity, neurotoxicity, and gastric toxicity. After completion of treatment the patients were followed for tumor recurrence, survival, and long-term morbidity. No patients were lost to follow-up. Performance status was evaluated according to Gynecologic Oncology Group criteria. Survival and progression-free interval rate were measured from the initial cytoreductive surgery and calculated using the Kaplan–Meier method. The surgical staging system was established in 1985 by the International Federation of Gynecology and Obstetrics (FIGO).

RESULTS

Thirteen patients were entered into the study from March 1987 to March 1989 and were followed from 9 to 42 months, with a mean of 28 months. The mean age of the patients was 56 years. All patients had a performance status of zero or one. The FIGO stage was distributed with 2 stage IIIa, 3 stage IIIb, and 8 stage IIIc. One patient had a pelvic/periaortic lymph node dissection as part of staging and the lymph nodes were negative. The remainder of the patients had no gross lymphadenopathy. Following surgery three patients had no gross residual disease. All 13 patients received four cycles of chemotherapy and radiation therapy. Acute toxicity from

radiation therapy was minimal. The WAR was delayed in 3 patients due to myelosuppression because of a decrease in WBC to <3000, or platelet count <100,000, but all completed therapy with the longest delay being 1 week in these patients. Gastrointestinal complaints of nausea, vomiting, and diarrhea were noted in 4 patients, but all were mild with no patients requiring hospitalization.

Delayed toxicity occurred in five patients (38%). All five required one or more hospital admissions for symptoms of small bowel obstruction. Four patients required surgical correction and all were found to have small diffuse persistent carcinoma in the abdomen and pelvis. Extensive adhesions were present in all four patients. It was felt that the obstruction was due to adhesions or radiation changes and not carcinoma. There was no large, bulk disease encasing or compressing the bowel to cause obstruction. One had extensive radiation fibrosis of the distal ileum resulting in obstruction. Among the six patients who received paraaortic radiation in addition to WAR, three developed a bowel obstruction. The single patient who had a paraaortic node dissection followed by WAR did not develop a bowel obstruction.

Upon completion of chemotherapy and radiation, all patients were clinically free of disease as determined by normal CA 125 levels, normal pelvic exam, and/or normal CT scan. In addition to the four patients surgically explored for bowel obstruction, five patients had a second-look laparotomy with three having persistent disease in the abdomen and pelvis. One of the two patients with negative second-look laparotomy recurred vaginally 1 year later, while the other remains free of disease 18 months later.

Two of the nine patients (22%) who underwent second-look laparotomy or reexploration for bowel obstruction died of postoperative complications both from adult respiratory distress syndrome and sepsis: one secondary to bowel anastomosis leakage performed to repair an enterostomy made in dissecting dense adhesions, and the other from wound infection.

Four patients who did not undergo reassessment laparotomy were followed by pelvic exams, CA 125 levels, and CT scans. Two of these four patients developed recurrent disease in the pelvis documented by fine-needle aspiration. The two remaining patients have no evidence of disease at 25 and 42 months from diagnosis.

Other variables which could influence survival were evaluated. These included stage and amount of residual disease at initial surgery (Table 1). All eight patients with macroscopic disease from 2 mm–1 cm died with disease, while three of five patients with microscopic (no gross residual) or small macroscopic (less than or equal to 2 mm) disease are alive with no evidence of disease. Two of three patients with no gross residual disease remain

TABLE 1
Patient Outcome Related to Stage and Amount of Residual Disease after Cytoreductive Surgery

	Stage			Residual disease		
	IIIa (N=2)	IIIb (N=4)	IIIc (N=7)	No gross (N=3)	<2 mm (N=2)	≤1 cm (N=8)
Alive, no evidence of disease (N=3)	1	1	1	2	1	0
Died with disease (N=10)	1	3	6	1[a]	1	8

[a] Alive with advanced disease.

free of disease, and the remaining patient is alive with disease at 40 months.

Thus, 10 of 13 patients (77%) had recurrent disease either at reassessment laparotomy or a documented recurrence. The actuarial progression-free rate is 20% at 36 months (Fig. 1). The mean progression-free interval is difficult to assess since 7 of 8 (87%) patients had recurrent disease at laparotomy that otherwise would not have been detected, but were considered as the end of progression-free interval.

The actuarial 36-month survival rate was 26% with a median survival of 30 months (Fig. 2). Presently 9 patients are dead of disease, 1 is alive with advanced disease, and 3 are currently alive without evidence of disease. Of the 10 patients with recurrent disease, 8 patients were treated with second-line chemotherapy consisting of cisplatin/etoposide, and 2 died of postoperative complications before adequate treatment could be given.

DISCUSSION

In this dosage regimen there does not appear to be a benefit of using sequential chemotherapy and WAR as
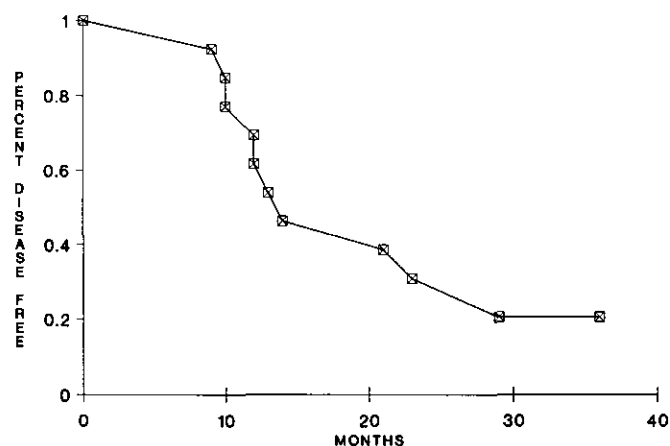

FIG. 1. Percentage disease-free interval of stage III ovarian carcinoma from initial treatment of surgical cytoreduction, chemotherapy, and whole abdomen radiation to recurrence (N = 13).
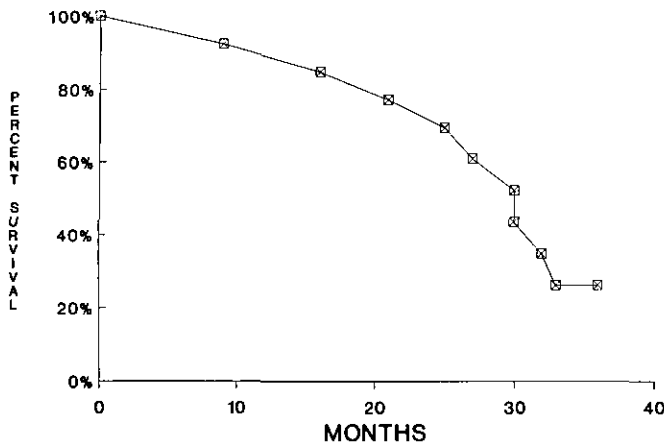
FIG. 2. Percentage survival of stage III ovarian carcinoma after initial treatment of surgical cytoreduction, chemotherapy, and whole abdomen radiation ($N = 13$).

primary treatment in optimally cytoreduced stage III ovarian carcinoma patients. The overall actuarial progression-free rate of only 20% at 3 years and a 26% 3-year survival is not markedly superior to that reported for chemotherapy alone [1,2,4,12–16,33]. The study was terminated after 13 patients had been entered because the delayed bowel toxicity began to appear and the disease-free interval did not significantly improve over that of published series utilizing chemotherapy alone.

The acute toxicity was minimal with all patients completing the therapy of combined chemotherapy followed by WAR with only three delays in radiation therapy. This low acute toxicity rate may be due to the reduction of chemotherapy to four cycles which is consistent with other reports of better tolerance of WAR with decreased cycles of chemotherapy [30,31]. Alternatively, the improved tolerance of WAR with minimal acute toxicity may be due to the open field technique with decreased daily dose of 1 Gy. However, the presentation of small bowel obstruction in 5 of 13 patients (38%) with 4 requiring surgical correction represents a high rate of delayed toxicity. Other studies confirm the bowel toxicity of chemotherapy and WAR with bowel obstruction reported by Stephenson and Buchler of 33% [34], Eifel et al. of 38% [35], and Schray et al. of 21% [36]. Eifel reported 34 patients receiving split-course abdominopelvic radiation after chemotherapy and second-look laparotomy. Fourteen patients (38%) had small bowel obstruction, but all had recurrent abdominal disease at the time [35]. Also, 20 patients (54%) had undergone more than two surgeries prior to radiation raising the issue of adhesions contributing to obstruction. Thus, radiation is only one factor that contributes to possible bowel obstruction [35].

Pickel reported only one bowel obstruction of 26 patients receiving chemotherapy and radiation [37]. How-

ever, 10 patients (38%) were only stage I or II and no second-look laparotomy was done after radiation, suggesting that these factors might explain the lower bowel obstruction rate than in other reports. Yet in our study second-look laparotomy was also not performed after chemotherapy and the bowel obstruction rate was still high. The 22% mortality of the 9 patients undergoing reassessment laparotomy after WAR is high and is probably related to poor healing of the bowel anastomosis and incision which resulted in sepsis and death in 2 patients.

Such delayed toxicity is not justified unless improved survival of progression-free interval is achieved. Since three of five patients with bowel obstruction symptoms received paraaortic boost in an APPA fashion this may play a role in the high rate of obstruction. Future studies might avoid paraaortic radiation or boost the paraaortic area with a four-field technique instead of two-field which might reduce the dose to bowel and a subsequent rate of bowel obstruction.

Although this study utilized WAR as part of primary treatment, the disappointing survival and progression-free interval are consistent with reports of salvage whole abdomen radiation as being of limited or no benefit [11,22–24,26–28,36]. A critical factor in other reports of whether WAR demonstrated a beneficial response was the presence of microscopic or no gross residual disease [20,21,23,25,28,31,34,36–38]. This report is consistent with these findings since 2 of 3 patients with no gross residual disease after cytoreductive surgery are alive free of disease and the third is a relatively long-term survivor with disease at 40 months. Even with optimal cytoreductive surgery, all patients with macroscopic residual disease, 2 mm to 1 cm, died of disease. Other authors have reported that any small gross residual disease at second-look operation does not respond favorably to salvage treatment with WAR [23,25,27–29,37]. Kuten et al. reported 43 patients with advanced ovarian cancer who after a complete clinical response to chemotherapy underwent a second-look laparotomy followed by consolidation WAR. A 100% 2-year survival was obtained in 5 patients with negative second-look, and 66% 5-year survival in 18 patients with microscopic disease at second-look [38], but only a 5% 3-year survival of 14 patients with minimal residual disease (<2 cm) at second-look. Kuten et al.'s favorable survival results in the first two groups were not achieved in our study and the amount of residual disease seems to be a key factor in their series. Kuten et al. had an increased number of patients with microscopic residual disease and this may be due to the more intensive chemotherapy of 6–11 cycles of cisplatin and adriamycin, or it may be due to Kuten's inclusion of eight stages I–II patients who are more likely to have less residual disease than stage III patients.

A metaanalysis of cisplatin plus cytoxan versus cisplatin, adriamycin, and cytoxan (CAP) indicated a survival benefit for CAP [39]. However, the dose intensity was higher in the CAP group, indicating that the beneficial effect may be due more to dose intensity than the presence of adriamycin. Possibly further combination studies need to look to different chemotherapy regimens such as taxol or adriamycin for improved response.

Our disappointing results may be secondary to the amount of residual disease prior to radiation. It was postulated that when disease was no greater than 1 cm after cytoreductive surgery the four cycles of cisplatin and cyclophosphamide could decrease the remaining implants to microscopic or at least minimal levels so that WAR would have maximum benefit. We did not design the study with an exploratory laparotomy after chemotherapy because the surgery would potentially increase risks of WAR from increased adhesion formation. All patients had normal CA 125 levels and no clinical evidence of disease before radiation therapy which might imply small residual disease. But without an exploratory laparotomy between chemotherapy and WAR, the size of any remaining tumor implants after four courses of chemotherapy cannot be certain. Kuten reported in 14 patients undergoing WAR with residual tumor nodules less than 2 cm, a 36-month survival of only 5% [38].

The poor results may be from some alteration of the carcinoma by the chemotherapy rendering it less responsive to the consolidation radiation therapy. Chemotherapy may give rise to the chance of developing treatment-resistant clones of cells as projected by the Goldie–Coldman hypothesis [40]. This hypothesis suggests that cancer cells exposed repeatedly to the same chemotherapy mutate at a constant rate to a drug-resistant clone. In an attempt to overcome this effect, a study by the National Cancer Institute used concurrent chemotherapy and radiotherapy for stages III and IV ovarian carcinoma to try and destroy resistant clones by alternating different regimens to prevent repopulation of the resistant clones [31]. The results, however, were no different than those with chemotherapy alone. Dembo et al. [19,21] and Weiser et al. [20] reported excellent response rates in patients who received WAR as primary treatment with no prior chemotherapy.

In optimally (≤1 cm) debulked stage III patients treated by primary chemotherapy with WAR in the dose and scheme utilized, the survival or progression-free interval is not improved over previous reports with chemotherapy alone. The high level of delayed morbidity of bowel toxicity may be related to the paraaortic radiation and future studies might avoid this. As indicated in this study and other reports, treatment failures involving WAR seem related to the presence of any macroscopic disease. Further studies with microscopic residual disease

that could improve outcome might try different chemotherapy, dose levels, and sequencing with WAR.

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