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## STATE-OF-THE-ART IN THE MANAGEMENT OF CANCER

### OVARIAN CANCER — PART III

#### CURRENT TREATMENT APPROACHES

Treatment of ovarian cancer involves a multimodality approach, including cytoreductive surgery, radiation therapy and single agent or combination chemotherapy. In early-stage disease, surgical removal of the tumor/ovary(s) is the mainstay of therapy, but in advanced-stage disease tumor excision is often impossible because of intra-abdominal cavity metastases. In advanced disease, surgery is employed for tumor debulking followed by chemotherapy. However, although high response rates (65%-80%) are observed on platinum-based chemotherapy in primary ovarian cancer, median survival is only 21-30 months and disease-free survival is only about 20% at 10 years. Second-line chemotherapy treatments elicit low response rates, resulting in poor survival outcomes.

#### CYTOREDUCTIVE SURGERY

Oophorectomy and salpingo-oophorectomy are performed for a variety of reasons, among them ovarian and breast cancer (see Exhibit 1). In 1995 Medicare reported 7,914 ovarian cancer related surgeries, representing \$20.4 million in total charges, of which Medicare reimbursed 43.4% (see Exhibit 2).

The overall goal of cytoreductive surgery, a critical component in the management of ovarian cancer, is to leave the patient with minimal residual disease. In metastatic disease, all peritoneal surfaces may be involved and extensive tumor spread must be debulked.

Successful primary cytoreductive surgery is associated with improved survival. In the 1970s it was reported that duration of survival among patients treated by chemotherapy after surgery was directly related to the amount of residual

disease after primary cytoreduction. Mean survival was 39 months among patients with no residual disease, compared to 29 months for residual disease <0.5 cm and 11 months for residual disease >1.5 cm (Devita, Principles and Practices of Oncology, 4th edition, 1993). In a Gynecologic Oncology Group (GOG) study that evaluated cisplatin in combination with cyclophosphamide with and without doxorubicin, it was found that there was a difference in the progression-free interval and survival of patients with no gross residual disease compared with those with gross residual disease <1 cm (Omura GA, et al, JCO, 1989 Apr, 7(4):457-65).

### Second Look Surgery

Second look surgical reassessment is used to surgically re-explore patients who completed a planned course of treatment after initial surgical staging and cytoreduction. The chances of a patient having a negative second look surgical reassessment is directly related to disease stage, grade of tumor and the amount of residual disease after initial cytoreduction. A review of 16 reports involving 1,255 patients, noted that 53.9% had residual disease after primary cytoreduction (Rubin SC and Lewis JL Jr, Critical Reviews in Oncology/ Hematology, 1988, 8(1):75-91). Approximately 50% of patients who are clinically without evidence of disease still have residual disease (Devita, *ibid*).

Unlike the well-established role of primary cytoreductive surgery, secondary surgical cytoreduction in the management of ovarian cancer is controversial. The utility of a second look has been questioned because prognosis is poor for those with positive second look, and there is a high recurrence rate of patients with negative second look. Some published studies report a benefit while others do not. Second look surgery involving 32 patients that reduced 38% of tumors to optimal residual disease (1.5 cm), increased median survival to 20 months, compared with 5 months for 20 patients who could not be cytoreduced (Berek JS, et al, Obstet Gynecol, 1983 Feb, 61(2):189-93). Others, however, saw no survival benefit in secondary cytoreduction (Luesley DM, et al, Obstet Gynecol, 1984 Sep, 64(3):421-6).

In a more recent study, use of secondary cytoreduction was evaluated in 61 patients with surgery leaving a tumor of 2 cm in diameter. Median survival was 27.1 months in the optimally-treated group and 9 months for

**Exhibit I**  
**Number of In-patient Ovarian Procedures in the USA**

ICD-M-9 Code	Procedure	Procedure Volume in 1994 (#)
65.1	Diagnostic biopsy	7,000
65.2	Local excision/destruction of ovarian lesion/tissue	53,000
65.22	Wedge resection	<5,000
65.29	Bisection/cauterization/partial excision	49,000
65.3	Unilateral oophorectomy	22,000
65.4	Unilateral salpingo-oophorectomy	79,000
65.5	Bilateral oophorectomy	9,000
65.6	Bilateral salpingo-oophorectomy	335,000
65.61	with removal of both ovaries and tubes	321,000
65.62	with removal of one ovary and tubes	13,000

39 patients whose surgery was suboptimal. Other variables associated with statistically significant longer survival, and a significantly higher probability of achieving a successful secondary cytoreduction, included age ≤55 years at the time of secondary cytoreduction, interval from initial diagnosis to secondary cytoreduction of >12 months, residual disease at initial staging laparotomy of <2 cm, and a complete clinical response to a cisplatin-based first-line regimen. Multivariate analysis, when adjusted for the above variables, confirms the survival benefit of successful secondary cytoreduction. There was one postoperative mortality and 10% of those successfully cytoreduced and 18% of unsuccessfully cytoreduced patients experienced some degree of postoperative morbidity (Segna RA, et al, JCO, 1993 Mar, 11(3):434-9).

In an attempt to ascertain the benefit of secondary surgical cytoreduction for advanced (persistent or recurrent) epithelial ovarian cancer (EOC), researchers at the Department of Obstetrics and Gynecology at UCLA School of Medicine, searched the English language literature to identify reports from clinical trials pertaining to secondary cytoreductive surgery for EOC. Particular emphasis was placed on those studies allowing secondary procedures to be grouped into four clinical scenarios, namely recurrent disease, second look laparotomy (SLL), interval cytoreduction, and progressive disease. The meta-analysis indicated that:

- patients with recurrent disease, particularly after a prolonged disease free interval, may derive a significant survival benefit from optimal debulking
- cytoreduction that leaves a small amount of macroscopic disease in patients whose disease is in complete clinical remission with macroscopic disease detected at the time of SLL, may provide

some survival benefit, but the degree of that benefit is unclear

- patients who undergo suboptimal primary debulking and later demonstrate a favorable response to induction chemotherapy, may derive a modest survival advantage from an optimal interval cytoreductive procedure (Bristow RE, et al, Cancer, 1996 Nov 15, 78(10):2049-62)

**Prophylactic Oophorectomy**

Prophylactic oophorectomy should be reserved for women with documented inherited ovarian cancer syndromes (ovarian cancer in two or more first-degree relatives in two successive generations). In the absence of genetic markers of ovarian cancer risk, accurate pedigrees are the only means of identifying women at risk. However, the majority of women with two or three relatives with ovarian cancer will not have hereditary ovarian cancer syndrome and their lifetime probability of ovarian cancer is only about 7% (Trimble EL, et al, Obstet Gynecol, 1991 Dec, 78(6):1023-6). The three ovarian cancer syndromes with incomplete penetrance and variable expression that have been described are site-specific ovarian cancer, hereditary breast-ovarian cancer (HBOC) syndrome, and the Lynch II syndrome which is a combination of breast, ovarian, endometrial, gastrointestinal, and genitourinary cancer. It is estimated that the lifetime probability of ovarian cancer rises from about 1.6% in a 35-year-old woman without a family history of ovarian cancer to about 5% if she has one relative and 7% if she has two relatives with ovarian cancer. The lifetime

probability may decrease to about 3-4% if she has taken oral contraceptives for 5-9 years. However, women from families with hereditary ovarian cancer syndromes may have as high as a 50% lifetime risk of ovarian cancer. Risk of ovarian cancer in women from families with hereditary ovarian cancer syndromes is sufficiently high to warrant prophylactic oophorectomy but for women with one relative with ovarian cancer, the lifetime probability is not high enough to warrant oophorectomy (Kerlikowske K, et al, Obstet Gynecol, 1992 Oct, 80(4):700-7).

In a study presented at Symposium 12 at the 1997 Annual Meeting of the American Association of Cancer Research (AACR), Henry T. Lynch, MD, of Creighton University School of Medicine (Omaha, NE), who first identified the Lynch syndrome, and colleagues, found that approximately 76% of women from families with HBOC syndrome who were provided with genetic counseling considered prophylactic oophorectomy as a viable option. Among 141 women from HBOC families who underwent prophylactic oophorectomies, 103 (73%) had been tested for BRCA1 or BRCA2. Of these, 47 (46%) were found to be carriers of one of these genes, 50 (46%) were found to be negative, and results from 6 individuals (5%) were still pending at the time of presentation of this data. Sixty-nine percent of women from families with Lynch II syndrome said they would consider surgery if they were found to carry a hereditary non-polyposis colorectal cancer (HNPCC) gene. However, primary peritoneal carcinomas have been reported to occur following bilateral salpingo-oophorectomy (Tobacman JK, et al, Lancet, 1982 Oct 9, 2(8302):795-7). These tumors have the same histology as primary EOC and, presumably, arise

**Exhibit 2  
Surgeries and Outlays for Ovarian Cancer in Medicare Patients in 1995**

Procedure	Total Surgeries (#)	Total Charge (\$)	Charge per Procedure (\$)	Medicare Outlay (\$)	% Covered	Coverage per Procedure (\$)
Oophorectomy; partial or total, unilateral or bilateral*	767	1,425,462	1,858	688,107	48.3	897
Resection; with bilateral salpingo-ooporectomy and omentectomy	1,422	2,570,343	1,807	1,107,964	43.1	779
Resection; with total abdominal hysterectomy & lymphadenectomy	1,710	4,997,049	2,922	2,309,779	46.2	1,351
Resection; with radical dissection for debulking	2,661	8,593,319	3,229	3,616,533	42.1	1,359
Laparotomy; for staging or restaging (second look)**	1,354	2,860,561	2,112	1,145,969	40.1	846
<b>Total</b>	<b>7,914</b>	<b>20,446,734</b>		<b>8,868,352</b>	<b>43.34</b>	

\*With para-aortic and pelvic lymph node biopsies, peritoneal washings, peritoneal biopsies, diaphragmatic assessments, with or without salpingectomy(s), with or without omentectomy

\*\*With or without omentectomy, peritoneal washing, biopsy of abdominal and pelvic peritoneum, diaphragmatic assessment with pelvic and limited para-aortic lymphadenectomy

in the same primordial tissues that develop into ovaries during fetal development. The risk of this unlikely event is unknown.

If surgical prophylaxis is chosen, the optimal age to perform such a procedure has not been established. Because there is little evidence that women with a family history of ovarian cancer develop tumors at a substantially younger age than women without such a family history, and because ovarian cancer rarely occurs in women <45 years-of-age and is uncommon even among 45 year olds with a family history of ovarian cancer, prophylactic oophorectomy can probably be delayed until women are in their 40s.

### RADIATION THERAPY

Radiation therapy assumes several roles in the management of various stages of ovarian cancer (see FO, p 233). It has traditionally been used as an adjuvant treatment after maximal surgical cytoreduction in patients with inoperable tumors not responding to chemotherapy, as salvage treatment with persistent disease and as palliation in incurable disease with metastatic deposits. Also, whole abdominal radiation therapy (which includes the entire peritoneal surface and diaphragm) may improve survival in patients with minimal residual disease.

Several studies that compared abdominopelvic or pelvic radiation with single agent chemotherapy in patients with minimal residual disease, demonstrated a superior outcome with abdominopelvic irradiation. When pelvic radiation therapy with or without chlorambucil was compared to abdominopelvic irradiation in patients with Stage I-III disease, within a minimum follow up of 7 years, survival difference for 76 patients treated with abdominopelvic radiation was significantly superior to that of 71 patients treated with pelvic radiation and chlorambucil (46% versus 31%). This survival benefit was seen only in patients with small macroscopic residual disease or no residual disease (Dembo, et al, Am J Obstet Gyn, 1979;134:793-80).

Two radiation therapy extended-field techniques have been used in the treatment of ovarian cancer, open field and moving strip technique. The open field technique uses large anterior and posterior portals to encompass the entire peritoneal cavity. Radiation is usually delivered at a rate of 800 to 1000 cGy/week. Total dose to the lower abdomen is usually 5500 cGy delivered in 27 fractions. When the upper abdomen is treated the dose is 3000-4000 cGy delivered in 15-20 fractions over 21 to 33 days (Devita, Practices and Principles of Oncology, 4th edition, 1993). The kidneys and liver are shielded to protect them from radiation damage.

The moving strip technique divides the peritoneal cavity and the strip is advanced daily down the abdomen. The dose to each point in the abdominal cavity is usually 3000 cGy delivered in 10 fractions over 12 days. An additional dose of 2000 cGy in 10 fractions over 12 days is delivered to the pelvis by an open field tech-

nique (Devita, *ibid*). Randomized studies that compared these techniques have shown <1% difference in 5-year survival rates. The open field technique is used most frequently because of late toxicity seen more often with the moving strip technique.

Radiation therapy is also used in advanced disease. Several hyperfractionated schedules have been tried. The delivery of two doses of radiation (120-150 cGy/fraction) within 5- to 6-hour intervals between fractions, theoretically results in greater killing of tumor cells (Devita, *ibid*). Forty percent of Stage III patients with residual tumor after induction therapy treated with 80 cGy fractions twice daily for a total dose of 2600-3060 cGy to the whole abdomen and an additional 1500-1920 cGy to the pelvis, were alive after a follow-up period of 8-48 months (Morgan L, et al, Gynecologic Oncology, 1988 Sep, 31(1):122-36). Other investigators, however, report high morbidity associated with this procedure from small bowel obstruction and enteritis.

Acute morbidity of radiation therapy includes enteritis whose severity is directly related to the volume irradiated and the dose. Diarrhea, nausea, vomiting and weight loss are common with high-dose radiation therapy to the lower abdomen. Severe bowel stenosis and bleeding, requiring surgery, has also been reported. Another common side effect is hematopoietic toxicity, but blood counts usually return to normal a short time after treatment. Other complications include nephritis when dose exceeds 2300 cGy, liver abnormalities, bloating and, in some cases, basal pneumonitis (Devita, *ibid*).

### CHEMOTHERAPY

Ovarian cancer is primarily treated by chemotherapy; approximately 75% of all patients diagnosed with ovarian cancer will undergo one or, more likely, several rounds of chemotherapy (see Exhibit 3). Chemotherapy of EOC has undergone a major transformation in the past twenty years which is expected to continue as new agents emerge with activity in all stages of this chemosensitive disease. Drugs approved for the treatment of ovarian cancer are listed in Exhibit 4. One of the most active drugs in the management of EOC has been cisplatin which was introduced in the late 1970s and became the standard treatment in the 1990s. Although effective alone, in most cases cisplatin has been combined with cyclophosphamide. Meta-analyses of clinical trials performed in the last twenty years confirmed that platinum-based combination therapy was more effective than monotherapy and became the regimen of choice in the treatment of advanced ovarian cancer. Carboplatin, another platinum-based agent developed in the 1980s, was also deemed equivalent to cisplatin in terms of efficacy and was less toxic. For more information on platinum-based anti-cancer agents, see FO pp 16-21. Use of various platinum-based combination therapies in ovarian cancer has helped maintain a growing worldwide market for cisplatin (Platinol; Bristol-Myers Squibb) and carbo-

platin (Paraplatin; Bristol-Myers Squibb), estimated to have reached \$535 million in 1996.

Two novel chemotherapeutics, paclitaxel (Taxol; Bristol-Myers Squibb) and topotecan (Hycamtin; SmithKline Beecham), with distinctly unique anti-tumor activities, belonging in the taxane and camptothecin drug families, respectively, were recently introduced new options for the treatment of advanced ovarian cancer. Other agents within these families are also expected to be approved for the ovarian cancer indication. Also, many other approved and marketed chemotherapeutics for other anti-tumor indications are being evaluated in the management of various stages of ovarian cancer.

In the late 1980s, taxanes were found to be active in EOC and, importantly, in platinum-resistant cases. Numerous clinical trials were undertaken to investigate the role of taxanes in the treatment of all stages of ovarian cancer as monotherapy (see FO, pp 176-179), in combination with platinum-based drugs (see FO, pp 180-181) or in combination with other drugs and/or modalities. Combining paclitaxel with a platinum-based drug was shown to improve all outcome measures in patient with sub-optimal disease when compared to the standard cyclophosphamide and cisplatin combination regimen. Taxanes are currently being investigated in all stages of ovarian cancer and are expected to be approved for first-line treatment of advanced ovarian cancer in combination with a platinum agent and may also play a role in earlier, less advanced disease. Before the role of taxanes in the treatment of EOC can be categorically defined, however, issues relating to optimal dose, schedule of administration and combination therapy need to be resolved. The worldwide market for taxanes, namely paclitaxel (Taxol; Bristol-Myers Squibb) and docetaxel (Taxotere; Rhône-Poulenc Rorer) that have been approved for several indications (see FO, pp 436-437), has grown rapidly to reach \$902 million in 1996. Numerous generic versions of paclitaxel are in development (see FO, pp 182-183). Anzatax was launched by Faulding (Parkside, SA, Australia) in Australia in 1995 under a license obtained from NaPro BioTherapeutics (Boulder, Colorado). Yewtaxan, a paclitaxel developed by Yew Tree Pharmaceuticals BV (Haarlem, The Netherlands), jointly owned by Nycomed (Oslo, Norway) and OPG/Pharmachemie (Haarlem, The Netherlands), was launched in South Africa and approved in the Netherlands in 1997. An NDA was also filed in 1997 in the USA for yet another paclitaxel, Paxene, in development by Baker Norton Pharmaceuticals (Miami, FL), a unit of Ivax (Miami, FL), also in collaboration with NaPro BioTherapeutics.

Another agent, the topoisomerase I (topo I) inhibitor topotecan, commercialized by SmithKline Beecham as Hycamtin, was approved in the USA in May 1996 and launched in June 1996 as second- or third-line treatment of metastatic ovarian cancer (see FO, pp 528-539). If, as expected, paclitaxel moves to first-line therapy in ovarian

cancer, the worldwide market opportunity for topotecan in ovarian cancer could reach \$400 million.

### Primary Disease

Primary chemotherapy is indicated for all stages of ovarian cancer with the exception of well- or moderately-differentiated Stage IA or IB disease that is treated by surgery alone and is associated with disease-free survival exceeding 90%. Systemic or intraperitoneal (IP) chemotherapy is indicated after surgery in patients with Stage I disease that is poorly differentiated, Stage IC disease and Stage IIA or IIB. Investigators at the NCI consider Stage IIC ovarian cancer which is associated with a poor prognosis, an advanced-stage disease that should be treated with aggressive chemotherapy, similar to that recommended for Stages III and IV.

**Single-agent chemotherapy** for ovarian cancer has been attempted using a variety of drugs such as cisplatin, carboplatin, doxorubicin, melphalan, chlorambucil, cyclophosphamide and thiotepe that have resulted in comparable response rates ranging from 33% to 65%. One of the most active single agents in ovarian cancer is cisplatin; cisplatin monotherapy elicits response rates ranging from 25% to 40%. In randomized trials cisplatin demonstrated a longer duration of response and survival than cyclophosphamide [Lambert HE and Berry RJ, *BMJ* (Clinical Research Ed.), 1985 Mar 23, 290(6472):889-93]. Carboplatin monotherapy also exhibits similar response and overall survival rates as cisplatin but is less toxic (Taylor AE, et al, *JCO*, 1994 Oct, 12(10):2066-70). Modern chemotherapy trials in advanced stage ovarian cancer reveal that platinum-based therapy results in a median survival in the range of two years and a median disease-free survival in the range of 12-14 months. Side effects include nausea and vomiting, bone marrow suppression, ototoxicity, peripheral neuropathy and nephrotoxicity.

Use of doxorubicin, another first-line agent in the treatment of ovarian cancer that elicits response rates of approximately 30% (Ozols RF and Young RC, *Sem Onc*, 1984 Sep, 11(3):251-63), was popular in the 1980s in the management of EOC. Its main toxicity is myelosuppression but is not associated with nephrotoxicity, ototoxicity or peripheral neuropathy. Hexamethylmelamine (HMM), another alkylating agent, exhibits an overall response rate of 32% (Wharton JT, et al, *Amer J Obstet Gynecol*, 1979 Apr 1, 133(7):833-44). Reduced gastrointestinal, hematologic and neurologic toxicity was noted with this agent on a 14-day monthly schedule.

**Combination chemotherapy** has improved disease response rates and enhanced survival outcomes compared to monotherapy. Generally, a multi-agent regimen includes an organo-platinum compound such as cisplatin or carboplatin, and one or two of such drugs as cyclophosphamide, paclitaxel or doxorubicin. Cycles of therapy are repeated every 3-4 weeks, depending on tox-

**Exhibit 3**  
**Women Administered Chemotherapy for Ovarian Cancer in Selected World Regions in 1995**

Patient Status	USA (#) <sup>1</sup>	North America (#) <sup>1</sup>	Europe (#)	Former USSR (#)	Japan (#)	Triad <sup>4</sup> (#)
New cases of ovarian cancer	26,700	28,800	47,985	25,127	6,942	83,727
Cases requiring primary chemotherapy	19,758	21,312	34,939	19,473	5,207	62,627
First relapse cases	15,411	16,623	27,252	15,189	4,061	48,849
Total estimated first relapse cases <sup>2</sup>	22,327	24,083	39,481	22,005	5,883	70,769
Total estimated second relapse cases <sup>3</sup>	14,512	15,654	25,663	14,303	3,824	46,000
Total estimated third relapse cases (minimal possibility of cure) <sup>3</sup>	12,335	13,306	21,813	12,158	3,251	39,100
Total chemotherapy cases	68,932	74,355	121,896	67,939	22,048	218,299
5-year survival of chemotherapy patients	5,740	6,089	9,445	4,613	1,474	17,008
Total deaths	14,800	16,150	28,612	15,830	3,949	48,711

<sup>1</sup> 1996 figures

<sup>2</sup> Includes women diagnosed with ovarian cancer in previous years who were treated by chemotherapy and were remissant that entire year and those first-diagnosed in the current year who have suffered a relapse

<sup>3</sup> Includes women who were treated by chemotherapy in prior years but relapsed

<sup>4</sup> North America, Europe (excluding the former USSR) and Japan

icity. Numerous other combinations have been evaluated or are currently in clinical trials (see Exhibits 5 and 6).

Combination of cisplatin and cyclophosphamide has been the standard treatment regimen for primary advanced ovarian cancer for many years. Unfortunately, long term disease control with this regimen was less than 10% in women with incompletely resected Stage III disease and less than 5% in those with Stage IV disease. When cyclophosphamide and cisplatin were compared with cisplatin and paclitaxel in a randomized clinical trial involving 410 patients with Stage III and Stage IV ovarian cancer and residual masses <1 cm after surgery, 73% in the cisplatin/paclitaxel group responded to therapy as compared to 60% in the cisplatin/cyclophosphamide arm. Treatment consisted of cisplatin (75 mg/m<sup>2</sup>) and cyclophosphamide (750 mg/m<sup>2</sup>) or cisplatin (75 mg/m<sup>2</sup>) preceded by a 24-hour infusion of paclitaxel (135 mg/m<sup>2</sup>). Known prognostic factors were similar in both groups. Progression-free survival was 18 months and 13 months in the cisplatin/paclitaxel and cisplatin/cyclophosphamide arms, respectively, and survival was 38 months versus 24 months. Adding paclitaxel as a first-line therapy improves duration of progression-free survival and of overall survival in women with incompletely resected Stage III and Stage IV ovarian cancer (McGuire WP, et al, NEJM, 1996 Jan 4; 334:1-6). Currently, combination of cisplatin and paclitaxel represent the new standard of care in primary advanced disease. A very effective combination uses paclitaxel (135 mg/m<sup>2</sup>) administered as a

24-hour infusion, followed by cisplatin (75 mg/m<sup>2</sup>); paclitaxel dose may be escalated to 170 mg/m<sup>2</sup> (Rowinsky EK, et al, JCO, 1991 Sep, 9(9):1692-703).

A dose-intensive regimen of carboplatin which exhibits similar effectiveness as cisplatin when combined with cyclophosphamide (Swenerton K, et al, JCO, 1992 May, 10(5):718-26) or paclitaxel for primary EOC, produced similar results as the cisplatin/paclitaxel regimen. Thirty-nine patients with Stage III and Stage IV disease who initially underwent tumor debulking, were treated with 6 cycles of chemotherapy on a 21-day cycle, also incorporating G-CSF. Paclitaxel was escalated as a 3-, 24- or 96-hour infusion. Dose limiting toxicity (DLT) was neutropenia. MTD of carboplatin was 471 mg/m<sup>2</sup> and for paclitaxel 135 mg/m<sup>2</sup> over 24 hours and 175 mg/m<sup>2</sup> over 3 hours. Overall response rate was 75% with a median progression-free survival of 15 months (Bookman MA, et al, JCO, 1996 Jun, 14(6):1895-902).

The value of adding doxorubicin to a platinum-based regimen remains unresolved. Numerous randomized trials comparing cisplatin and cyclophosphamide (CP), and cyclophosphamide, cisplatin and doxorubicin (CAP) failed to show a significant doxorubicin benefit. A randomized clinical trial involving 349 women [176 treated with cyclophosphamide (1 g/m<sup>2</sup>) plus cisplatin (50 mg/m<sup>2</sup>) and 173 with cyclophosphamide (500 mg/m<sup>2</sup>), cisplatin (50 mg/m<sup>2</sup>) and doxorubicin at (50 mg/m<sup>2</sup>)] with Stage III EOC with <1 cm residual lesions, did not demonstrate a significant difference in progression-free interval

(median 22.7 months versus 24.6 months) or survival (mean 31.2 months versus 38.9 months) (Omura GA, et al, JCO, 1989 Apr, 7(4):457-65).

However, a meta-analysis of four of the largest trials involving 1,200 patients, revealed a statistically significant survival benefit with CAP ranging from 5% to 7% and also reported an improved pathologic complete remission (The Ovarian Cancer Meta-Analysis Project, JCO, 1991 Sep, 9(9):1668-74). A more recent review (A'Hern, et al, JCO, 1995; 13: 726-732) of data from two large analyses [the Advanced Ovarian Cancer Trialists Group (AOCTG), BMJ, 1991, 303:884-893 and Williams CJ, et al, Sem Onc, 1992 Feb; 19:120-128] and the Ovarian Cancer Meta-Analysis Project, suggest that the addition of doxorubicin significantly improved survival suggesting future trials of paclitaxel versus doxorubicin in combination with cisplatin.

Recently published data (Covens A, et al, Cancer, 1996 May 15, 77(10):2086-91) examined the cost effectiveness of combined paclitaxel and cisplatin therapy to the current regimen of cisplatin and cyclophosphamide. The average lifetime cost per patient in Canada was Cdn \$50,054 compared with a cost of Cdn \$36,837 for usual care. The main cost drivers were hospitalization and drugs. The incremental cost per live saved with the cisplatin/paclitaxel combination was Cdn \$20,355/lives gained. The authors concluded that a cisplatin/paclitaxel regimen appears to be a cost-effective first-line agent. The incremental cost compared favorably with other life saving strategies, for example the use of beta blockers for low risk MI survivors which averages Cdn \$16,000 per life saved.

### Drug Resistance

Intrinsic and acquired drug resistance in advanced-stage EOC are the main reasons for ineffective therapy. Among mechanisms of resistance to alkylating agents and platinum compounds are decreased drug accumulation, increased drug inactivation in the cytosol and increased DNA repair (Ozols RF, et al, Gynecol Onc, 1993 Oct, 51(1):90-6).

Modulation of chemotherapy resistance may provide a new means of improving response rates in ovarian cancer. High-dose chemotherapy involving dose-intensification to levels which may overcome drug resistance or abolish large enough fractions of cancer cells to prevent formation of resistant clones, is one way of solving this problem. One approach to enhance cisplatin cytotoxicity in platinum-resistant cell lines is use of cyclosporin, whose activity may be attributable to blocking platinum-induced increases in c-fos and H-ras (Runowicz CD, et al, Cancer, 1995 Nov 15, 76(10 Suppl):2028-33). In a phase I clinical trial completed by GOG involving heavily pretreated patients, combining cyclosporin (4 mg/kg/day) with cisplatin (75 mg/m<sup>2</sup>) resulted in a response rate of 25% (Manetta A, Cancer, 1994 Jan 1, 73(1):196-9).

### Recurrent/Refractory Disease

Although 60%-80% of patients respond to initial chemotherapy, the vast majority relapse within a short period of time. Platinum-sensitive patients, i.e., those who initially responded to a platinum-based regimen but subsequently relapsed, can often be palliated by re-treatment with a platinum compound. Recurrent disease is associated with a dire long-term prognosis but, although hardly ever cured, some patients may be rendered disease-free for an extended period of time when re-treated by chemotherapy. Single agent cisplatin or carboplatin is warranted in platinum-sensitive individuals. Generally, if recurrent disease is documented six months after platinum therapy, the patient has an enhanced chance of responding to cisplatin. The longer the time since platinum treatment the greater the likelihood of responding to cisplatin or carboplatin.

In platinum-refractory cases, the first option is paclitaxel. In 1989 it was reported that paclitaxel produced a response rate of 24% in platinum-resistant ovarian cancer (McGuire WP, et al, Annals Int Med, 1989 Aug 15;111(4):273-9). Among 27 paclitaxel-treated patients who had progressed during or within 6 months of prior platinum therapy, the overall response rate was 33% (18 CR and 4 PR) and rose to 44% (3 CR and 4 PR) in 16 patients whose disease appeared 6 months after cisplatin therapy (Thigpen JT, et al, JCO, 1994 Sep, 12(9):1748-53).

Various combinations of paclitaxel and other agents are also being evaluated (see Exhibits 5 and 6). A phase II study of paclitaxel and ifosfamide enrolled 14 patients with advanced disease (9 patients had Stage III and five had Stage IV disease) who were previously treated with cisplatin (12 were also previously treated with ifosfamide). Treatment consisted of paclitaxel (135 mg/m<sup>2</sup>) as a 24-hour infusion on day one of the first 21-day cycle which was escalated to 175 mg/m<sup>2</sup> on subsequent cycles if no Grade 4 toxicity occurred. Ifosfamide (1.8 g/m<sup>2</sup>) was administered on days two and three in addition to mesna. There were 8 PRs (57%) and disease stabilized in 4; median survival was 10 months. Toxicity included myelosuppression in 10 patients, Grade 3 leukopenia in 7 and Grade 4 in 3. No episodes of fever and neutropenia occurred (Pucci F, et al, ASCO96, Abs. 838:301). Also see p 567 of this issue.

It has also been proposed that a 2- or 3-drug regimen may be a more effective combination. Because paclitaxel has synergistic activity with cisplatin and cyclophosphamide and because different mechanisms appear to repair DNA damage induced by these three agents, the possibility of a multi-synergistic combination appears to be worth exploring. In a phase II clinical trial, initial therapy combining cyclophosphamide (750 mg/m<sup>2</sup>), paclitaxel (250 mg/m<sup>2</sup>), and cisplatin (75 mg/m<sup>2</sup>) followed by G-CSF (10 µg/kg/day) was administered every 3 weeks in a group of patients with poor prognosis (>3 cm of residual disease after surgery). Thirty-six percent of patients

**Exhibit 4  
Chemotherapeutics Approved Worldwide for the Treatment of Ovarian Cancer**

<b>Brand Name □ Generic Name (Number) □ Supplier □ Affiliates</b>	<b>Description □ Mechanism of Action □ Indication</b>	<b>Delivery □ Dosage □ Average Wholesale Price (AWP) □ Treatment Costs</b>	<b>Market Status □ Comments</b>
Adriamycin PFS □ doxorubicin □ Pharmacia & Upjohn  (also Rubex; Bristol-Myers Squibb)	Cytotoxic anthracycline antibiotic isolated from <i>Streptomyces peucetius</i> var. <i>Caesius</i> ; DNA topoisomerase I and II inhibitor □ binds nucleic acid by intercalating DNA base pairs	Injection □ 60-75 mg/m <sup>2</sup> (monotherapy), single injection, q 21 days; 40-60 mg/m <sup>2</sup> (in combination) single injection, q 21-28 days □ \$241.56 for 50 mg	Multi-source widely used anti-cancer agent
Adriamycin RDF □ doxorubicin HCL □ Pharmacia & Upjohn	As above	Injection □ same as above □ \$230.00 for 50 mg	Same as above
Alkeran □ melphalan; L-PAM, L-phenylalanine mustard, L-sarcosylsin □ Glaxo Wellcome	Phenylalanine derivative of nitrogen mustard; alkylating agent □ forms interstrand DNA cross links □ palliative treatment of non-resectable EOC	PO □ 0.2 mg/kg daily for 5 days, q 4 to 5 weeks □ \$1.70 for 2 mg	
Anzatax □ paclitaxel □ Faulding □ NaPro Bio Therapeutics (licensor)	Taxane □ advanced breast and ovarian cancer	Injectable	A (1/95) and L (95) > Australia and New Zealand; L(96) > China (by Foshan Faulding), Hong Kong and to markets in the Middle East
CeeNu, Belustine, CiNu, Citostal, Lucostin, Lucostine □ Iomustine (NSC-79037) □ NCI (NIH); Roger Bellon (Rhône-Poulenc Rorer), Bristol-Myers Squibb, Lundbeck, Abic (Teva), Medac, Almirall	Cytostatic alkylating agent	PO	L > WW (outside the USA); L > USA □ brain cancer and Hodgkin's disease
Campto □ irinotecan; CPT-11 □ Yakult Honsha and Daiichi Pharmaceuticals (Japan)	Water soluble semi-synthetic derivative of camptothecin; topoisomerase I inhibitor	IV	A and L (94) > Japan □ NSCLC, cervical and ovarian cancer
Cytosan □ cyclophosphamide □ Mead Johnson Oncology	Alkylating agent; synthetic compound chemically related to nitrogen mustards □ cross links DNA □ adenocarcinoma of the ovary	Injection, PO □ 40-50 mg/kg IV in divided doses over 2-5 days; 10-15 mg/kg q 7-10 days; 3-5 mg/kg twice weekly □ \$2.91 for 50 mg	Multisource anti-cancer with broad indications
Ethiol, Ethiofos, Gammaphos □ amifostine (NSC-29696, WR-2721) □ U. S. Bioscience □ Southern Research Institute (licensor), ALZA Pharmaceuticals (marketer USA), Schering-Plough (marketer Europe), Eli Lilly	Organic thiophosphate; prodrug that is dephosphorylated by alkaline phosphatase to an active free thiol metabolite □ cytoprotective □ reduces cumulative renal toxicity associated with repeated administration of cisplatin in advanced ovarian cancer	Injection □ starting dose of 910 mg/m <sup>2</sup> daily as a 15-minute IV infusion 30 minutes prior to chemotherapy □ \$312.00 for 500 mg	USA sales (\$ mil.) 1996 (4-12/96): 9.4
Farmorubicin □ epirubicin □ Pharmacia & Upjohn	Second generation anthracycline antibiotic		L > outside the USA □ leukemia and solid tumors including breast, ovarian and bladder cancer
Frone □ Ares Serono	Fibroblast-derived interferon-β □ adjuvant therapy for ovarian cancer		L > outside the USA

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Hexalen, Exastat, Hexastat, Hexinauras □ hexamethylmelamine (HMM), altretamine (KB-913, NSC-13875) □ U. S. Bioscience □ ALZA Pharmaceuticals	Synthetic s-triazine derivative □ palliative treatment of persistent or recurrent ovarian cancer following first-line therapy with cisplatin and/or alkylating agent-based combination	PO □ 260 mg/m <sup>2</sup> /day divided in 4 oral doses for 14 or 21 consecutive days, q 28 days □ \$4.50 for 50 mg	L > WW
Hycamtin □ topotecan (NSC-609699, SK&F-104864) □ SmithKline Beecham	Semi-synthetic derivative of camptothecin; topoisomerase I inhibitor □ relieves torsional strain in DNA by inducing reversible single strand breaks □ third-line therapy for metastatic ovarian cancer	IV □ 1.5 mg/m <sup>2</sup> as a 30-minute IV infusion daily for five days, q 21 days (a minimum of four courses is recommended) □ \$509.44 for 4 mg (UK, USA) □ \$1,627 per cycle for 4 cycles (\$6,508)	A (5/96) and L (6/96) > USA; A (10/6) > EU and L (1/97) > UK USA sales (\$ mil.) 1996: 23.5 WW sales (\$ mil.) 1Q97: 18
Hydrea □ hydroxyurea □ Bristol-Myers Squibb Oncology	DNA synthesis inhibitor □ inoperable ovarian cancer	PO □ 80 mg/kg, q third day (intermittent therapy); 20-30 mg/kg daily (continuous therapy) □ \$1.42 for 500 mg	L > WW
Navelbine □ vinorelbine tertrate, NVB (KW-2307) □ Pierre Fabre; Kyowa Hakko, Glaxo Wellcome	Semi-synthetic vinca alkaloid; norvinblastine derivative □ interferes with microtubule assembly; inhibits mitosis at metaphase	Injection □ \$49.18 for 1 ml	A > EU (France, Spain, Portugal, Italy, Luxembourg); also indicated for lung and prostate cancer and pediatric malignancies
Neosar □ cyclophosphamide □ Pharmacia & Upjohn	Alkylating agent; synthetic compound chemically related to nitrogen mustards □ adenocarcinoma of the ovary	Injection □ 40-50 mg/kg IV in divided doses over 2-5 days or 10-15 mg/kg IV dose, q 7-10 days or 3-5 mg/kg IV dose twice weekly □ \$5.39 for 100 mg	
Paraplatin □ carboplatin □ Bristol-Myers Squibb Oncology	Heavy metal (platinum) compound; alkylating-like agent □ covalently binds DNA; forms interstrand DNA cross links □ combination therapy for advanced ovarian cancer and secondary palliative treatment of recurrent ovarian cancer	IV □ 360 mg/m <sup>2</sup> IV once q 4 weeks as monotherapy or 300 mg/m <sup>2</sup> once, q 4 weeks in combination therapy □ 50 mg at \$84.78, 150 mg at \$254.28, 450 mg at \$797.15 □ \$5,831	Patent expires 8/98; 9/04 WW sales (\$ mil.) 1993: 265.0; 1994: 275.0; 1995: 320.0; 1996: 375.0 USA sales (\$ mil.) 1994: 140; 1995: 180
Platinol □ cisplatin □ Bristol-Myers Squibb Oncology	Heavy metal (platinum) compound □ first-line chemotherapy for metastatic ovarian cancer; monotherapy or combination therapy for metastatic ovarian cancer	IV □ 75-100 mg/m <sup>2</sup> , q 4 weeks (in combination with cyclophosphamide); 100 mg/m <sup>2</sup> (monotherapy), q 4 weeks	Patent expired 12/96 WW sales (\$ mil.) 1993: 145; 1994: 155; 1995: 165; 1996: 160 USA sales (\$ mil.) 1994: 120; 1995: 125
Platinol-AQ □ cisplatin □ Bristol-Myers Squibb Oncology	Same as above	Injection □ \$184.84 for 50 mg; \$369.65 for 100 mg □ \$2,400	
Taxol □ paclitaxel (BMS-181339) □ Bristol-Myers Squibb; NCI	Taxane; semi-synthetic natural product obtained from <i>Taxus baccata</i> ; antimicrotubule agent □ enhances microtubule assembly and stabilizes microtubules □ second-line treatment of metastatic ovarian cancer	IV □ administered to pre-medicated ovarian cancer patients at 175 mg/m <sup>2</sup> IV over 3 hours, q 3 weeks □ \$182.63 for 6 mg/ml (5 ml) □ \$8,590-\$11,025	A (4/94) and L (94) > USA and globally WW sales (\$ mil.) 1994: 340; 1995: 580; 1996: 813
Taxol (as above)	As above □ first-line treatment of metastatic ovarian cancer	As above	A (96) > UK
Taxotere □ docetaxel (NSC-628503, RP-56976) □ Rhône-Poulenc Rorer □ Chugai (co-development and marketing, Japan), NCI	Taxane □ acts on cellular microtubules, promoting their assembly and blocking their breakdown		As of early 1997, it had regulatory clearance in 49 countries for various cancer indications WW sales (\$ mil.) 1996: 89

Thioplex □ lyophilized thiotepa □ Immunex; American Home Products	Alkylating agent; nitrogen mustard-derived agent; ethylenimine-type compound □ releases ethylenimine radicals which disrupt DNA bonds; selectively reacts with DNA phosphate groups to produce chromosomal cross-linking; blocks nucleoprotein synthesis □ palliative treatment of ovarian adenocarcinoma	Injection □ rapid IV administration of 0.3-0.4 mg/kg at 1-4 week intervals □ \$83.94 for 15 mg	L > USA and Canada □ Immunex owns manufacturing process patents for thiotepa in the USA and Canada that expire in 2007
Yewtaxan □ paclitaxel □ Yew Tree Pharmaceuticals BV (jointly owned by Nycomed and OPG/Pharmachemie			L (97) > South Africa and A (97) > The Netherlands

had a pathologic response and 9 patients had no visible disease at second look surgery. The progression-free survival at 18 months was 71% (Devita, Principles and Practices of Oncology, Supplement, 1996).

In addition to topotecan, irinotecan (CPT-11), another commercially available topo I inhibitor, is also being evaluated in advanced ovarian cancer. CPT-11 (50-60 mg/m<sup>2</sup>), administered on days 1, 8, and 15, combined with cisplatin (50-60 mg/m<sup>2</sup>) administered on day 1, was evaluated in 18 patients with relapsed or metastatic ovarian cancer. The objective response rate was 55% (2 CR, 4 PR, 4 SD). Dose-dependent neutropenia >Grade 3 which occurred in 50% of patients, was the DLT with CPT-11 (Sugiyama T, et al, ASCO96, Abs 796:291).

Other treatment options in this setting using commercially available drugs reported to have response rates in the 10-25% range include HMM, 5-fluorouracil in combination with leucovorin, ifosfamide, oral vepesid, gemcitabine (see this issue, p 567), liposomal doxorubicin, treosulfan, vinorelbine, pyrazoloacridine and tamoxifen (see Exhibits 5 and 6).

In one trial, HMM administered at 260 mg/m<sup>2</sup> orally *qd* for 14 days, followed by 14 days rest, resulted in median survival of approximately 11 months. Side effects included GI toxicity, moderate neurologic (sensory) toxicity, mild neutropenia and thrombocytopenia (Manetta A, et al, Gynecol Onc, 1990 Jan, 36(1):93-96). This is a simple regimen making HMM a viable choice in the management of recurrent disease. HMM appears to require metabolic activation with its metabolic intermediates acting as alkylating agents, but it is not directly cross-resistant with classical alkylating agents. In salvage ovarian cancer therapy, objective response rates to orally administered HMM range from 0 to 33%, while disease stabilization occurs another 8% to 78% of cases. Response rates appear to be higher in those responding to previous alkylating agent- or cisplatin-based therapy. Adding HMM to platinum-based combination regimens used for induction therapy of advanced ovarian cancer, may also improve long term survival, particularly in those

with limited residual disease. HMM is relatively well tolerated, with GI, neurological and hematological toxicities being the main dose-limiting adverse effects. On the basis of the emerging body of clinical evidence, HMM appears to have a limited role in treating persistent or recurrent advanced ovarian cancer, primarily in patients who are platinum-sensitive yet intolerant of platinum analogs (Lee CR and Faulds D, Drugs, 1995 Jun, 49(6):932-53).

Although, generally, vinca alkaloids that exert their anti-tumor effects by inhibiting microtubule assembly, have not been particularly effective in ovarian cancer, vinorelbine (Navelbine; Glaxo Wellcome), a novel semi-synthetic vinca alkaloid has elicited consistent levels of response in various clinical trials. Older studies with weekly vinorelbine (30 mg/m<sup>2</sup>), reported overall response rates of 21%. Toxicities include neutropenia, constipation, and asthenia.

Several clinical trials are under way to explore the effectiveness of liposomal doxorubicin (Doxil, Caelyx; Sequus Pharmaceuticals) in recurrent/refractory ovarian cancer. Its therapeutic index and ability to maintain long-lasting responses render Doxil an effective drug in the salvage setting. Liposomal doxorubicin may also have a role as first-line therapy in combination with taxanes and/or platinum but its efficacy must be demonstrated in clinical trials. Potential advantages of liposomal over free doxorubicin are lesser myelosuppression, better subjective tolerance, and, possibly, reduced cardiotoxicity. Further improvements in therapeutic index are likely with refinements in patient selection and in targeting such as with hyperthermia (Muggia FM, et al, Chemotherapy Foundation Symposium XIV, November 6-8, 1996, Abs. 31:39-41). For results of completed/ongoing phase II clinical trials see Exhibit 5. A phase II clinical trial is underway in gynecologic malignancies to explore activity and tolerance in a heterogeneous population exposed to radiation and high-dose chemotherapy. A phase I clinical trial of Doxil in combination with paclitaxel (pacliDOX protocol) is ongoing, as well as a clinical trial to explore the

**Exhibit 5**  
**Recently Reported Results from Various Clinical Trials in Ovarian Cancer**

<b>Drug</b>	<b>Patient Type □ Number</b>	<b>Status □ Dose and/or Regimen</b>	<b>Response Rate</b>	<b>Reference</b>
Carboplatin versus no chemotherapy	High risk Stage I EOC □ n=134		Median TTP was 14 months versus TTP 13 months with surgery	Trope C, etal, ASCO97, Abs. 1260:352a
Carboplatin + paclitaxel	Stage III and IV ovarian cancer post-surgical diagnosis and debulking □ n=39	Phase I □ carboplatin (471 mg/m <sup>2</sup> ) + paclitaxel (135 mg/m <sup>2</sup> as a 24-hour or 175 mg/m <sup>2</sup> as a 3-hour IV infusion) without initial G-CSF + G-CSF at selected doses/toxicities	75% ORR; PFS was 15 months; DLT was hematologic, primarily neutropenia	Bookman MA, etal, JCO, 1996; 14:1895-1902
Cisplatin (IP) + etoposide	Stage II-IV EOC; consolidation therapy	Phase II □ cisplatin (100 mg/m <sup>2</sup> ) + etoposide (200 mg/m <sup>2</sup> )	61% of cases did not recur at median follow-up of 36 months	Barakat R, etal, ASCO97, Abs. 1264:354a
Cisplatin + dose-escalated paclitaxel	Stage IIB-IV ovarian cancer after diagnostic or debulking surgery (n=68, 57 with available data)	Phase II □ paclitaxel (175 to 200 to 225 mg/m <sup>2</sup> elevated q 1 hour) + cisplatin (80 mg/m <sup>2</sup> ) q 3 weeks for 6 cycles	70.7% ORR; DLT was peripheral neurotoxicity	Mendiola C, etal, ASCO97, Abs. 1276:259a
Cisplatin + taxotere	Previously untreated Stage IC-IV EOC	Taxotere (75-85 mg/m <sup>2</sup> ) + cisplatin (75 mg/m <sup>2</sup> )	58% CR	Vasey PA, etal, ASCO97, Abs. 1270:256a
Cisplatin and/or paclitaxel	Suboptimal Stage III and IV EOC	Phase III □ paclitaxel 100 mg/m <sup>2</sup> versus cisplatin (200 mg/m <sup>2</sup> ) versus combination	74% ORR with cisplatin, 46% ORR with paclitaxel and 72% ORR for the combination	Brady MF, etal, ASCO97, Abs. 1257:352a
Cisplatin + doxorubicin, or cyclophosphamide versus paclitaxel + cisplatin	Stage III and IV ovarian cancer □ n=100	Cisplatin (1 mg/kg) 3-4 times per week, followed by monthly cisplatin (50 mg/m <sup>2</sup> ) or doxorubicin (50 mg/m <sup>2</sup> ) or cyclophosphamide (750 mg/m <sup>2</sup> ) for 10 cycles (n=56) versus cisplatin (75 mg/m <sup>2</sup> ) + paclitaxel (135 mg/m <sup>2</sup> ) for 6 cycles (n=44)	75% versus 89% ORR; TTR was 36 months versus 33 months; 2-year progression rate was 32% versus 44%	Piver MS, etal, ASCO97, Abs. 1277:259a
Cisplatin + paclitaxel versus carboplatin + paclitaxel	Previously untreated EOC, first-line therapy following debulking □ n=233	Phase III □ cisplatin (75 mg/m <sup>2</sup> ) + 3-hour IV infusion of paclitaxel (185 mg/m <sup>2</sup> ) q 21 x 6 (n=111) versus AUC 6 carboplatin + paclitaxel (as above) q 21 x 6 (n=122)	57% ORR (n=128) (CR 25%, PR 33%, SD 20%); to be completed 10/97	du Bois' A, etal, ASCO97, Abs. 1272:257a
Cisplatin + treosulfan	Advanced EOC	Cisplatin (100 mg/m <sup>2</sup> ) + treosulfan (5 mg/m <sup>2</sup> ) versus cisplatin (50 mg/m <sup>2</sup> ) + treosulfan (5 mg/m <sup>2</sup> )	72.1% ORR (24% CR, 8% PR, 17% SD) versus 67.2% (18% CR, 8% PR, 19% SD); significantly fewer side effects in the low dose cisplatin group	Ackermann S, etal, ASCO97, Abs. 1274:258a
Doxil (liposomal doxorubicin)	EOC □ n=52	Phase I (n=8), phase II (n=23); no limits on prior regimen, ongoing (n=21+) □ 40 mg/m <sup>2</sup> q 21 days	31% ORR; median TTP was 18 months for responders; median TTP and survival for all patients was 5.5 and 13 months, respectively	Safra T, etal, ASCO97, Abs. 1248:349a

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Epidoxorubicin + paclitaxel + carboplatin	Advanced EOC with >2 cm residual disease after debulking, Stage IIIC (n=5), Stage IV (n=3)	Phase I □ epidoxorubicin (60-75-90 mg/m <sup>2</sup> ) + paclitaxel (175 mg/m <sup>2</sup> ) as 3-hour infusion + carboplatin, q 28 days	5 PR, 3 SD; DLT is Grade 4 thrombocytopenia; no other Grade 3 non-hematologic toxicity; phase II is ongoing with epidoxorubicin (75 mg/m <sup>2</sup> ) + paclitaxel + carboplatin	Romanini A, etal, AACR97, Abs. 1504:223
Gemcitabine	Stage IIIB, IIIC, IV EOC □ n=33	Gemcitabine (125 mg/m <sup>2</sup> ) q 3 weeks for 4 weeks (n=33); followed by platinum-based regimen (n=26)	24% ORR (1 CR and 7 PR); 52.2% ORR (3 CR and 8 PR); leukopenia occurred in 37/109 treatments resulting in dose reduction	Underhill C, etal, ESMO96, Abs. 3240:69
Mitoxantrone + paclitaxel	Platinum-refractory ovarian cancer	Mitoxantrone (8 mg/m <sup>2</sup> ) + paclitaxel (180 mg/m <sup>2</sup> ) q 3 weeks (n=11), or mitoxantrone (6 mg/m <sup>2</sup> ) bi-weekly + paclitaxel (100 mg/m <sup>2</sup> ) weekly (n=7)	78% ORR (5/18 CR, 9/18 PR), mean PFS is 40 weeks	Kurbacher CM, etal, ASCO97, Abs. 1252:350a
Paclitaxel + cisplatin	Previously untreated EOC	Phase II □ 3-hour paclitaxel (200 mg/m <sup>2</sup> ) infusion followed by cisplatin (100 mg/m <sup>2</sup> ) for 3 weeks, then order is reversed	74% ORR (7 CR, 15 PR, 3 SD) for paclitaxel then cisplatin; 59% ORR (8 CR, 5 PR, 2 SD) with the reverse order	Poole C, etal, ASCO97, Abs. 1271:256a
Paclitaxel + ifosfamide	Platinum-pretreated ovarian cancer (primary resistant, n=6; secondary resistant, n=4, potentially sensitive, n=19) □ n=29	Ifosfamide (1.5 g/m <sup>2</sup> ) on days 1, 2, 3 with mensa + paclitaxel (135 mg/m <sup>2</sup> ) as a 3-hour infusion on day 3 + G-CSF (5 mg/kg) qd on days 7-11; course repeated q 3 weeks for 6 cycles	48% ORR (4 CR, 9 PR); TTP was 7 months; 63% ORR in potentially sensitive cases; 20% ORR in secondary resistant cases	Dimopoulos MA, etal, ESMO96, Abs. 333P:70
Paclitaxel or docetaxel or high-dose epirubicin	Advanced EOC, second- and third-line therapy			Van Glabbeke M, etal, ASCO97, Abs. 1265:354a
Paclitaxel + cisplatin and paclitaxel + carboplatin	Previously untreated EOC, FIGO Stage IIIB, IIB, III, IV	Phase III □ paclitaxel (175 mg/m <sup>2</sup> ) + cisplatin (75 mg/m <sup>2</sup> ) or paclitaxel + carboplatin	No significant differences in efficacy or toxicity; paclitaxel + carboplatin regimen is more feasible	Sorensen PG, etal, ASCO97, Abs. 1259:352a
Paxene (paclitaxel)	Platinum-refractory ovarian cancer □ n=143	3-hour infusion of 175 mg/m <sup>2</sup> (n=120) versus 96-hour infusion of 105-140 mg/m <sup>2</sup> (n=23)	32% ORR (7 CR, 31 PR), TTP was 3+ months in 3-hour group; 1/23 PR, 3/23 SD in 96-hour group	Gore ME, etal, ASCO97, Abs. 1251:350a
Cisplatin + cyclophosphamide ± amifostine	Stage III and IV untreated EOC □ n=26	Carboplatin (600 mg/m <sup>2</sup> ) on day 1 + cyclophosphamide (250 mg/m <sup>2</sup> ) on day 1 + platinum (100 mg/m <sup>2</sup> ) on day 8, q 4 weeks with or without amifostine	85% clinical ORR (19 CR, 3 PR); 53% pathologic ORR; median PFS was 12.9 months, median survival was 37.2 months; dose-intensive platinum regimen is effective but toxic	Shapiro JD, etal, ASCO97, Abs. 1269:355a
Topotecan	Previously-treated EOC	Phase II □ 1.5 mg/m <sup>2</sup> IV over 30 minutes, daily, for 5 days q 3 weeks versus 1.75 mg/m <sup>2</sup> over 24 hours, weekly, for 4 weeks of 6 weeks	12% (4/33 PR) for combined arms of therapy	Eisenhauer E, etal, ASCO97, Abs. 1249:349a
Topotecan	FIGO Stage III and IV EOC, platinum- or paclitaxel-refractory	1.5 mg/m <sup>2</sup> daily for 5 days as a 30-minute infusion q 21 days	16% ORR	Gwyther SJ, etal, ASCO97, Abs. 1255:351a

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Treosulfan	Recurrent ovarian cancer; second- and third-line therapy □ n=90	5 g/m <sup>2</sup> (n=73) or 7 g/m <sup>2</sup> (n=17) q 4 weeks	19% ORR (34% SD), mean survival was 32 months, median PFS in responders was 14 months	Gropp M, et al, ASCO97, Abs. 1253:350a
Vinorelbine with and without G-CSF	Refractory platinum-resistant disease □ n=23	Phase I/II □ escalated vinorelbine dose; DLT both with and without G-CSF was febrile neutropenia; recommended phase II dose is 25 mg/m <sup>2</sup> of vinorelbine daily for 3 consecutive days q 21 days with G-CSF	15% ORR; among 20 evaluable patients, there were 2 CRs and 1 PR	Gershenson DM, et al, ASCO96, Abs. 811:294
Vinorelbine + ifosfamide + GCSF	Includes patients with platinum-refractory disease; median number of prior treatment regimens is 3 (range 1-5); ongoing	Phase II □ ifosfamide (960 mg/m <sup>2</sup> ) + vinorelbine (20 mg/m <sup>2</sup> , daily for 3 consecutive days, and GCSF	31% ORR (4/13); most significant toxicity was leukopenia, with 8 patients experiencing neutropenic fever; there were 2 septic deaths	Fleming GF, et al, Chemo-therapy Foundation Symposium XIV, November 6-8, 1996, Abs. 26:33-34
<b>Legend:</b>				
TTP: time to progression		PFS: progression-free survival	ORR: overall response rate	
TTR: time to recurrence		IP: intra-peritoneal	SD: stable disease	

role of local tumor hyperthermia in combination with Doxil. All these trials are being conducted by investigators at Southern California (USC)-Norris Cancer Center (Los Angeles, CA).

A simple non-toxic regimen using tamoxifen may also be feasible in elderly patients who often cannot tolerate aggressive chemotherapy. In a phase II clinical trial involving 50 patients (median age 76, range 68-83) with advanced EOC (Stage III and Stage IV) whose estrogen receptor status was unknown, tamoxifen was administered at a dose of 20 mg *bid*. Two (4%) CR and 26 (52%) PR were observed and survival ranged between 8 and 65 months. Toxicity was limited (Gennatas C, et al, ASCO96, Abs. 782:287). Although response rates with tamoxifen reported in the literature range between 8% and 25%, use of this agent in ovarian cancer remains controversial.

A study that followed the medical care over a 3-year period in 40 women with recurrent ovarian cancer, beginning with second- or third-line chemotherapy found that the average cost of palliative care was \$53,000 (median, \$36,600; range, \$4,800 to \$162,900). Patients were treated with 2 to 4 regimens of chemotherapy since entry to the study. After a minimum follow-up of 24 months, 36 of the 40 women had died. Median survival from first relapse was 1.7 years. The average length of hospital stay was 46 days (median, 33 days; range, 0 to 185); 58% of inpatient days were for symptom management and 32% for chemotherapy. Inpatient admissions, chemotherapy medications, and outpatient visits accounted for 62%, 21%, and 8% of the total cost, respectively. Forty-five percent of the total costs, or \$24,000, was chemotherapy-related, and 43%, or \$23,000, were

attributable to supportive care (Doyle C, et al, JCO, 1997 Mar, 15(3):1000-7). A shift from inpatient to outpatient chemotherapy should improve cost efficiency in the palliative management of ovarian cancer.

### High-Dose (Density) Chemotherapy with Autologous Bone Marrow and/or Stem Cell Transplantation

Since the late 1980s, when an association was reported between outcome and dose intensity in the treatment of ovarian cancer (Levin L and Hryniuk WM, JCO, 1987 May, 5(5):756-67), the value of this approach has remained unresolved. Although various studies demonstrated that high-dose (density) chemotherapy (HDC) may result in a 100% overall response in patients with Stage II or III disease and residual tumor size >0.5 cm following laparotomy, a 5-year disease-free survival and overall survival of 23% and 33%, respectively did not differ significantly from the 5-year survival of 15% to 30% in patients with Stage III ovarian cancer achieved with conventional therapy.

Although controversial in ovarian cancer, HDC with autologous bone marrow transplants (autoBMT) and/or peripheral blood stem cell transplants (PBSCT) is being explored in numerous trials (see Exhibit 6), based on the hypothesis that rapid sequencing of different agents at or near MDT with growth factor and stem cell support may increase responses. Ongoing clinical trials using a variety of regimens in sensitive, persistent, and previously untreated EOC, usually with autoBMT and/or PBSCT, should establish the value of this approach. All types of patients in virtually any disease stage are being considered for HDC. However, studies have shown that plat-

**Exhibit 6**  
**Active Ongoing Clinical Trials for the Treatment of Ovarian Cancer**

<b>Drug (Monotherapy or Combination Therapy)</b>	<b>Status (Active as of) □ Patient Type</b>	<b>Regimen □ Comments</b>	<b>Protocol IDs □ Investigator, Organization</b>
CBDCA + CYP	Phase II (4/97) □ platinum-refractory ovarian cancer	Initial 2 hour loading dose of CYP followed by 24-hour continuous infusion; 1-hour infusion of CBDCA at hour 18, q 28 days	CHNMC-IRB-95008, NCI-H96-1106 □ Doroshov JH, Beckman Research Institute of the City of Hope
CBDCA + CYP + IFN-α	Phase II (11/96) □ advanced, recurrent, or persistent primary ovarian, fallopian tube, or peritoneal cancer	7 days of IFN-α with 26-hour infusion CYP beginning on day 3 and of CBDCA 18 hours after CYP, q 28 days	CHNMC-IRB-94061, NCI-V96-1030 □ Morgan RJ, Beckman Research Institute of the City of Hope
TAX + CBDCA or CDDP versus conventional platinum-based chemotherapy	Phase III (1/97) □ relapsed EOC	3-hour infusion of TAX followed by either CBDCA or CDDP, q 3 weeks for up to 6 courses	MRC-ICON4, EU-96051 □ Ledermann JA, Medical Research Council (UK)
TOPO	Phase II (2/97) □ recurrent, platinum-resistant or refractory ovarian cancer	24-hour continuous infusion, q 3 weeks	GOG-126H □ Park RC, Gynecologic Oncology Group
TAX	Phase II (4/97) □ recurrent or progressive advanced EOC in patients who failed 3- or 24-hour TAX infusion schedule	1-hour infusion, q week; prophylactic anti-allergy pre-medication	MSKCC-96070, NCI-G97-1139 □ Aghajanian C, Memorial Sloan-Kettering Cancer Center
TOPO	Phase II (8/96) □ platinum-refractory advanced ovarian cancer	72-hour continuous infusion	CWRCC-ICC-2893, NCI-T93-0141D □ Rose PG, Case Western Reserve University/Ireland Cancer Center
CBDCA	Phase I (3/96) □ advanced ovarian, fallopian tube or primary peritoneal cancer	IP CBDCA with continuous hyperthermic peritoneal perfusion (CHPP) for 90 minutes	NCI-95-C-0074C, NCI-T94-0140N □ Steller MA, NCI
TAX + CBDCA versus CBDCA or CAP (CTX + DOX + CDDP)	Phase III (4/96) □ advanced ovarian cancer		MRC-ICON3, EU-95035 □ Harper PG, Medical Research Council (UK)
Adjuvant chemotherapy with platinum-containing regimen (CBDCA or CAP)	Phase III (1/97) □ resected early-stage ovarian cancer		MRC-ICON1, EU-91002 □ Williams CJ, Medical Research Council (UK)
CBDCA + TAX followed by PBPC rescue	Phase I/II (3/97) □ advanced ovarian cancer	PBPC mobilized with CTX and G-CSF; 24-hour infusion of TAX on day 1 and CBDCA on day 2; 1/4 harvested PBSC re-infused on day 4; 4 courses	MDA-DM-93092, NCI-V96-1005 □ Mehra R, University of Texas, M. D. Anderson Cancer Center
CBDCA+ TAX with PBSC support following PBSC mobilization with CTX + TAX + G-CSF	Phase I/II (5/96) □ Stage III/IV EOC	3-hour infusion of TAX and CBDCA with PBSC support	IHC-IP-9501, NCI-V95-0793 □ Ford CD, Intermountain Health Care
TAX followed by PBSC mobilization with G-CSF	Phase I/II (4/96) □ metastatic breast, EOC, germ cell ovarian and testicular cancer		YALE-HIC-7676, NCI-V95-0724, YALE-01153 □ Burtness BA, Yale Comprehensive Cancer Center
CTX + CBDCA + TAX induction followed by L-PAM and PBSC rescue	Phase II (12/96) □ Stage III/IV EOC		YALE-HIC-8752, NCI-V96-1093 □ Rutherford TJ, Yale Comprehensive Cancer Center

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PBPC mobilization with CTX + TAX followed by sequential courses of CBDCA + TAX + L-PAM with PBPC rescue	Phase II (10/96) □ resected advanced ovarian cancer		GOG-9501 □ Fennelly D, Gynecologic Oncology Group
TAX+ CBDCA versus stem cell-supported CBDCA + DHAD + CTX, followed by bone marrow reconstitution	Phase III (6/97) □ persistent low-volume EOC		GOG-164 □ McGuire WP, Gynecologic Oncology Group
TXT	Phase I (2/97) □ untreated advanced malignancy with hepatic dysfunction, including ovarian cancer	1-hour infusion of TXT	CHNMC-PHI-08, NCI-T96-0028H, LAC-USC-PHI-08 □ Doroshow JH, Beckman Research Institute of the City of Hope
Vinorelbine (VNB)	Phase II (9/96) □ relapsed or refractory EOC		SWOG-9324 □ Rothenberg ML, Southwest Oncology Group
I-MAP (IFF/mesna + MITO + DOX + CDDP) with G-CSF	Phase II (2/97) □ advanced primary ovarian and peritoneal cancer and inoperable genital carcinosarcoma	I-MAP with G-CSF, q 4 weeks; IFF and MITO doses are increased by 10% on subsequent courses, toxicity permitting	MAYO-936101, NCI-V96-1074 □ Edmonson, JH, Mayo Clinical Cancer Center
TSPA + BU + L-PAM, followed by autologous or syngeneic marrow or PBSC transplant	Phase II (4/96) □ advanced solid tumors including ovarian cancer and refractory hematologic malignancies	BU (12 mg/kg) + L-PAM (100 mg/m <sup>2</sup> ) + TSPA (500 mg/m <sup>2</sup> ), followed (36 to 48 hours after) by PBSC and/or purged or autologous or syngeneic bone marrow transplantation	FHCRC-779.01, NCI-H93-0264 □ Bensinger WI, Fred Hutchinson Cancer Research Center
VP-16	Phase II (12/96) □ advanced EOC and cervical cancer	Prolonged oral VP-16	GOG-26LL □ Rose PG, Gynecologic Oncology Group
IFF + TAX	Phase I (12/96) □ EOC, extra-ovarian papillary serous tumor, or other pelvic malignancy refractory to CDDP-based regimen		GOG-9201 □ Markman M, Gynecologic Oncology Group
CBDCA followed by high-dose and maintenance TAX	Phase II (12/96) □ Stage IV ovarian, fallopian tube and peritoneal cancer		SWOG-S9618, SWOG-9618 □ Markman M, Southwest Oncology Group
IFN- $\alpha$ versus no further treatment	Phase III (7/95) □ Stage III ovarian cancer with no evidence of disease following platinum-based chemotherapy	Adjuvant IP IFN- $\alpha$	SWOG-8790, INT-0083 □ Alberts DS, Southwest Oncology Group
CDDP + TAX	Phase II (11/96) □ Stage III EOC	IP CDDP and intravenous and IP TAX	SWOG-S9619, SWOG-9619, E-S9619 □ Rothenberg ML, Southwest Oncology Group; Wadler, Eastern Cooperative Oncology Group; Stuart GC, NCIC-Clinical Trials Group
TAX followed by CDDP	Phase III (5/96) □ Stage III/IV EOC	24- versus 96-hour infusion of TAX + CDDP	GOG-162 □ Spriggs DR, Gynecologic Oncology Group
CBDCA + TAX	Phase III (2/97) □ resected Stages IIA-C EOC	3 versus 6 courses	GOG-157 □ Young RC, Gynecologic Oncology Group
Adjuvant platinum-based chemotherapy (CDDP or CBDCA with or without other agents) versus no adjuvant therapy	Phase III (4/96) □ Stage I/II EOC		EORTC-55904 □ Trimbos, JB, EORTC Gynecological Cancer Cooperative Group
TAX + CDDP alone versus TAX + CDDP with interval secondary cytoreductive surgery	Phase III (6/97) □ resected Stage III EOC		GOG-152 □ Rose PG, Gynecologic Oncology Group

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CTEC regimen (CBDCA + paclitaxel + VP-16 + CTX) with G-CSF support	Phase I (4/97) □ newly-diagnosed advanced EOC and fallopian tube or peritoneal papillary serous cancer	TAX, CBDCA, and CTX IV on day 1 and VP-16 PO on days 1-3; G-CSF SQ on day 4 until neutrophil recovery, q 21-28 days for up to 6 courses	DFCI-96061, NCI-V96-1107 □ Cannistra SA, Dana-Farber Cancer Institute
TAX + CBDCA + prolonged oral VP-16	Phase I (1/97) □ untreated ovarian, peritoneal and tubal cancers		GOG-9603 □ Rose PG, Gynecologic Oncology Group
TAX + CDDP + CTX with G-CSF support	Phase II (5/96) □ newly diagnosed Stage III/IV EOC		NCI-95-C-0055C, NCI-T94-0162N, NCI-CPB-349iKohn EC, NCI
CBDCA + TAX with PBSC mobilization by filgrastim	Phase II (6/97) □ newly diagnosed advanced EOC	3 courses of standard dose chemotherapy (CDDP + 24-hour infusion of TAX) followed by stem cell harvest; CTX + 3-hour infusion of TAX on day 1 with filgrastim support on day 3; patients with adequate stem cell harvest are administered a 24-hour infusion of TAX on day 1 + single dose of 1-hour infusion of CBDCA on day 2	MDA-DM-96104, NCI-G96-0997 □ Champlin RE, University of Texas, M.D. Anderson Cancer Center
CBDCA + CTX followed by AutoBMT and PBSC rescue	Phase I (12/95) □ platinum-sensitive EOC		JHOC-9434, NCI-V94-0544 □ Armstrong DK, Johns Hopkins Oncology Center
Multi-cycle, escalated-dose chemotherapy followed by TAX + CDDP	Phase II (11/96) □ Stage IIIC/IV ovarian, fallopian tube or primary peritoneal cancer	CTX followed by 24-hour infusion of TAX with G-CSF support (24 hours after TAX completion); CBDCA + CTX followed by PBSC and G-CSF, q 2 weeks for 3 courses	MSKCC-96048, NCI-H96-1046 □ Shapiro F, Memorial Sloan-Kettering Cancer Center
VP-16 + CTX + DOX with PBSC and G-CSF support	Phase II (11/96) □ Stage IIB-IV advanced EOC	G-CSF for 5 days prior to and during PBSC harvest; continuous infusion DOX over days -11 through -8, VP-16 on days -6 through -4, and CTX on day -3; PBSC on day 0 and additional G-CSF from day 1 until hematologic recovery	CHNMC-IRB-90186, NCI-V96-1028 □ Morgan RJ, Beckman Research Institute of the City of Hope
Gemcitabine (NSC-613327) + 5-FU	Phase I (5/97) □ refractory pancreatic, colorectal, breast, cervical, non-small cell lung (nsclc), ovarian, and prostate cancer	Weekly gemcitabine (at one dose level below the MTD) for 3 weeks + continuous infusion 5-FU over 21 days, q 28 days	UCCRC-8261, NCI-G97-1157 □ Mani S, University of Chicago Cancer Research Center
TAX + CDDP + TOPO with or without G-CSF support	Phase I (4/97) □ newly diagnosed Stage III/IV advanced ovarian cancer	TAX + CDDP on day 1, followed by TOPO on days 1-5 and G-CSF support on day 6 until neutropenic recovery, q 21 days for a total of 8 courses	GOG-9602 □ O'Reilly S, Gynecologic Oncology Group
L-PAM with G-CSF + PBSC support, followed by CBDCA + VP-16 + DHAD + TSPA + PBSC rescue with or without AutoBMT	Phase I (2/95) □ persistent or recurrent EOC		UNC-LCCC-9214, NCI-V94-0562 □ Shea TC, Lineberger Comprehensive Cancer Center UNC
TAX + CDDP + CTX + CYSF + PBSC rescue	Phase I (2/97) □ advanced cancer including Stage II, III or IV ovarian cancer	96-hour concomitant infusion of TAX + cisplatin + CYSF for 3 days, followed by CTX; 1/4 harvested stem cells given the next day followed in 2 days by the remaining 3/4; G-CSF support <i>bid</i>	CHNMC-IRB-95105, NCI-V96-1033 □ Doroshow JH, Beckman Research Institute of the City of Hope

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CDDP + TAX versus CBDCA + TAX	Phase III (6/97) □ Stage III EOC	CDDP + 24-hour continuous infusion of TAX versus CBDCA and 3-hour infusion of TAX	GOG-158 □ Ozols RF, Gynecologic Oncology Group
CTX + DHAD + CBDCA versus TSPA + CTX + CDDP, each with AutoBMT and/or PBSC support	Phase II (1/96) □ recurrent or persistent Stage III/IV EOC		SWOG-9106 □ Stiff PJ, Southwest Oncology Group
CBDCA + CTX with G-CSF, followed by standard-dose TAX versus high-dose TAX with G-CSF	Phase III (4/97) □ Stage III EOC		SWOG-9249 □ Alberts DS, Southwest Oncology Group
Sequential CDDP + CTX + VP-16 followed by IFF + CBDCA + TAX with PBSC support	Phase I (11/96) □ advanced cancers including Stage III/IV ovarian cancer	CDDP + VP-16 + CTX over 10 days, followed the next day by infusion of 1/4 harvested stem cells, with the remaining infused 2 days later; beginning no sooner than 14 weeks from the start of the first cycle of chemotherapy, stable and responding patients are treated with high-dose TAX + CBDCA + IFF over 5 days, followed 2 days later with 1/4 harvested stem cells, with the remaining infused the next day	CHNMC-IRB-94098, NCI-V96-1042 □ Raschko JW, Beckman Research Institute of the City of Hope
<b>Legend:</b>			
5-FU: 5-Fluorouracil, NSC-19893	DHAD: mitoxantrone, NSC-301739	MITO: mitomycin, NSC-26980	
AutoBMT: autologous bone marrow transplant,	DOX: doxorubicin, NSC-123127	PBSC: peripheral blood stem cells	
BU: busulfan, NSC-750	EOC: epithelial ovarian cancer	TAX: paclitaxel, NSC-673089	
CBDCA: carboplatin, NSC-241240	G-CSF: granulocyte-colony stimulating factor (Amgen), NSC-614629	TOPO: topotecan, NSC-609699	
CDDP: cisplatin, NSC-119875	IFF: ifosfamide, NSC-109274	TSPA: thiotepa, NSC-6396	
CTX cyclophosphamide, NSC-26271	IFN-α: interferon alpha (Schering), NSC-377523	TXT: docetaxel, NSC-628503	
CYSP: cyclosporine, NSC-290193	L-PAM: melphalan, NSC-8806	VP-16: etoposide, NSC-141540	

inum-sensitive patients and those with tumors <1 cm in size at time of transplant have the best outcome.

Clinical trials in patients with advanced stage ovarian cancer using transplants earlier in the course of treatment, when tumors are small, are underway. HDC with autologous cell support is also being explored in patients with Stage III and IV ovarian cancer as primary therapy following debulking surgery. Many studies are also exploring HDC/autoBMT in patients with positive second look laparotomy. Although no long-term results from randomized trials exist at this time, clinical responses have been documented in such cases that usually show no survival improvement when compared with conventional therapy. Evaluation of this approach, however, is hampered by the small number of patients enrolled in clinical trials and the heterogeneity of tumors, disease stage, histology, as well as the type, intensity, and clinical response to chemotherapy.

While it appears that results in ovarian cancer patients undergoing transplants may parallel those for lymphoma, testes cancer, and, possibly, breast cancer, there is substantially less published information for this tumor. Between 1989 and 1995, it is estimated that fewer than 1,000 autoBMT procedures were performed

world-wide in ovarian cancer but since then the pace has appeared to have increased. For a detailed review of HDC, see FO, pp 437-440.

### Drug Administration Routes

Regional administration of therapeutic agents is also being attempted to improve response and palliate symptoms of ovarian cancer. Two techniques, aortic infusional chemotherapy and intra-peritoneal (IP) chemotherapy, have been evaluated in clinical trials. Aortic infusional chemotherapy has resulted in some benefit in patients with advanced, progressive ovarian cancer (see FO, p 233). IP chemotherapy is associated with a pharmacokinetic advantage for certain chemotherapeutic agents. IP therapy can be used as consolidation therapy following a surgically defined complete remission, as primary therapy for early stage, high grade lesions or advanced disease and as salvage therapy in patients with tumors <0.5 cm. However, patients with adhesions, diffuse carcinomatosis, liver or lymph metastases, tumors >0.5 cm, or tumors resistant to IV platinum, are unlikely to benefit from IP. Approximately 20% of IP chemotherapy-treated patients can achieve a surgically defined CR. However, when IV and IP cisplatin were compared in newly diagnosed individuals, identical disease-free and overall sur-

vival were noted in the two groups (Kirmani S, et al, *Gynecol Onc*, 1994 Sep, 54(3):338-44).

Another management approach in advanced disease involves combination IV and IP chemotherapy. A prospective randomized phase III clinical trial of 6 courses of IV cyclophosphamide (600 mg/m<sup>2</sup>) plus IP cisplatin (100 mg/m<sup>2</sup>) versus IV infusion of both drugs, administered every 3 weeks, found that the IV/IP arm was superior to IV/IV, resulting in a median survival of 49 months versus 41 months (Alberts DS, ASCO95, Abs. 760:273). There was also reduced hearing loss and neutropenia.

IP interleukin-2 (IL-2) was also shown effective in heavily pretreated ovarian cancer patients, who had failed other therapies. In a phase I/II clinical trial, 43 patients were treated with IP IL-2 of various doses by intermittent or continuous infusion. Among 35 evaluable patients, overall response rate was 26.4% (7 CR and 2 PR). Remarkably, 6 responders survived for over 5 years (Edwards R, ASCO95, Abs. 997:333).

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## MEETING COVERAGE

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### ASCUS PATIENT MANAGEMENT IN CERVICAL CANCER SCREENING

FROM THE 45TH ANNUAL CLINICAL MEETING  
OF THE AMERICAN COLLEGE OF OBSTETRICIANS  
AND GYNECOLOGISTS  
LAS VEGAS, NV, APRIL 28-30, 1997

Information presented here is based on presentations at the educational symposium "Efficient ASCUS Patient Management: HPV Testing for Diagnostic Confidence."

#### SCREENING AND DIAGNOSIS OF CERVICAL CANCER

The screening standard for cervical cancer is the Pap smear test, a cytologic examination performed on a sample of cervical cells viewed under a microscope. It is estimated that over 50 million Pap smear tests are performed in the USA every year and an estimated 110 million worldwide. Approximately 3,500 laboratories perform Pap smear evaluations in the USA. Each Pap smear is classified according to the Bethesda System (TBS) for reporting cervical/vaginal cytologic diagnoses into the following categories:

- negative or normal
- atypical squamous cells of undetermined significance (ASCUS)/atypical glandular cells of undetermined significance (AGUS), or atypic/equivocal
- low grade squamous intraepithelial lesions (LSIL), or abnormal (borderline)
- high grade squamous intraepithelial lesions (HSIL), or abnormal
- carcinoma

One of the current challenges in mass screening for cervical cancer is the escalation of cost and morbidity associated with equivocal Pap smear testing that has not translated into a significant prevention benefit. The problems are twofold:

- sensitivity of Pap smear testing is estimated at 60% to 80%, resulting in 20% to 40% of false negatives; however, because cervical cancer grows slowly and women are encouraged to get a Pap smear test once a year, false negatives do not preclude the eventual diagnosis of cervical cancer in time for effective treatment
- low-grade lesions that are estimated to account for at least 5% of all Pap smear evaluations represent 2.5 million to 3.0 million cases annually that must be addressed; deciding on the management of women with ASCUS is particularly challenging because although few are eventually found to have cervical disease, many are treated as if they have abnormal Pap smears and undergo invasive procedures such as colposcopy, biopsy and even ablation (it is estimated that annually the cost of procedures to deal with equivocal Pap smears exceeds \$6 billion in the USA)

Numerous novel approaches to improve the accuracy and automate processing of Pap smears have been recently introduced or are in development (see Exhibit 7).

#### ROLE OF HUMAN PAPILLOMAVIRUS IN CERVICAL CANCER

There is little doubt that human papillomavirus (HPV) is the etiologic agent in cervical cancer. Recent studies have demonstrated that at least 93% of cervical cancers and high-grade cervical lesions contain one or more cancer-causing types of HPV. Earlier studies determined that there are several risk factors for cervical neoplasia including the number of sex partners, early age of first intercourse, low socio-economic status, and cigarette smoking. Today, however, it has become clear that the central risk factor is HPV infection; the number of sex partners, either of the woman herself or of her partner, increase the probability of acquiring such an infection.

Various studies, as well as consensus conferences held in 1996 by the National Institutes of Health and the World Health Organization, have all concluded that HPV is the etiologic agent in cervical cancer. Moreover, it has been shown that women without detectable cervical disease who test positive for one or more of the cancer-causing HPV types, have a high probability of developing cervical lesions over time. A recent prospective study conducted by the National Cancer Institute (NCI) on 21,000 women with a history of normal Pap smears, found that approximately 80% of those who tested positive for cancer-causing types of HPV developed clinically significant cervical lesions within four years.

**Exhibit 7**  
**Screening/Diagnostic Tests on the Market and/or in Development for Cervical Cancer**

<b>Supplier □ Affiliate(s)</b>	<b>Product</b>	<b>Status □ Description</b>
AccuMed International (was Alamar Biosciences, Manchester, MA) □ Olympus America (Western Hemisphere), Leica Microscopy and Systems GmbH (outside the Western Hemisphere)	AcCell Cytopathology Systems (2000 and 2001)	Introduced in May 1996, it is an automated slide handling and microscopy workstation to read Pap smear slides
	TracCell 2000	Specimen mapping workstation, which automatically pre-screens Pap smear slides to identify and create a computerized map of empty spaces and certain non-clinically relevant portions of the specimen to permit a more efficient analysis of the test slide; clinical trials have been completed and a PMA was filed in November 1996
AutoCyte (Burlington, NC), formed by Hoffmann-La Roche, Ampersand Ventures and the Sprout Group in November 1996 as a spin-off of Roche Image Analysis Systems (RIAS)	AutoSCREEN	Automated interactive cervical cancer screening system based on high resolution imaging already commercialized by RIAS
	AutoPREP	Monolayer slide preparation system; PMA to be filed in 1997
CompuCyte (Cambridge, MA)	Pathfinder System	Introduced in 1996, it is a microprocessor-based approach that uses sensors attached to a microscope that track the user's visual path in screening Pap smear slides and displays the screened area on a monitor; highlighting various aspects of image processing by the user to ensure quality
Cytec (Boxborough, MA)	Thin-Prep	Approved by the FDA in 1996, it is a fluid-based, thin-layer, slide preparation method
Digene (Silver Spring, MD)	Hybrid Capture HPV DNA	Approved by the FDA, it is a 14-probe DNA:RNA hybridization test for detection of high-risk human papillomavirus (HPV) types with high sensitivity and specificity
Denvu (Tucson, AZ)	EASY TRAK System	Patient tracking software that co-ordinates information on gynecological evaluations, including Pap smear tests and colposcopies
	DIMS Colposcopy System	Digital imaging and archiving system of colposcopy procedures; allows imaging in real-time; incorporates EASY TRAK System software
MatriTech (Newton, MA) □ Bayer (collaborator), Massachusetts Institute of Technology (licensor)		Discovery of three specific nuclear matrix proteins (NMPs) associated with cervical cancer (NMPs) was announced in August 1996; an automated diagnostic test in collaboration with Bayer is currently in development using these NMPs; a preliminary clinical evaluation was to begin in the second half of 1997
National Testing Laboratories (NTL; Fenton, MO)	Cervicography	A service that reviews enlarged photographs of the cervix
NeoPath (Redmond, WA) □ Nikon (marketing agreement for Japan entered 12/96)	AutoPap 300 QC System	Approved by the FDA in November 1995, it is an automated slide reader that uses an integrated high-speed video microscope, comprehensive image interpretation software to accurately analyze images and classify cells and slides, and high-speed custom field-of-view (FOV) computers to run the software at high speed to recognize and analyze cells from a Pap smear slide; designed to re-screen Pap smears that have been previously screened and classified as normal; regulatory approval to sell AutoPap System as a primary screener was obtained in Canada, Australia, New Zealand, the Netherlands and Japan (3/97)
	AutoPap Screener System	Designed to perform primary screening, as well as quality-control re-screening, it incorporates identical hardware as the AutoPap 300 QC System but has upgraded software features; on September 27, 1996 the Hematology and Pathology Devices Advisory Panel did not recommend approval of the supplemental PMA for use of the AutoPap Screener as a primary screener of Pap smear slides pending completion of additional studies

Neuromedical Systems (Suffern, NY)	Papnet Testing System	Approved by the FDA in November 1995 and launched in January 1996, includes two major sub-systems, the Papnet Scanning Station (and related equipment) located at Scanning Centers owned and operated by the company and the Papnet Review Station located at the customers' laboratories; the system is a computerized image processing service that uses neural network computing artificial intelligence technology to re-examine negative Pap smears; it is expected to increase detection of abnormal cells by 30% (Neuromedical Systems also re-scans negative slides at the request of the patient or physician); as of February, 1997, Papnet was available through 229 laboratories in the USA and in more than 20 countries worldwide
Trylon (Torrance, CA)	Pap Plus Speculoscopy (PPS)	Approved by the FDA in 1995 and launched in March 1997, this is a visual cervical abnormality screening test that uses acetic acid washing of the cervical mucosa, low-power magnification and a chemiluminescent (blue-white) light source to detect abnormalities in combination with a Pap smear; it is not recommended as first-line screening and does not replace colposcopy

According to Ralph M. Richart, MD, Professor of pathology in obstetrics/gynecology at Columbia University College of Physicians and Surgeons (New York, NY), findings have pointed out that the relative risk of having an abnormal Pap smear is 40 times greater if the patient is HPV DNA-positive. Furthermore, the attributable risk of HPV is 90% with nothing else having as much influence as a risk factor.

**Digene's Hybrid Capture HPV DNA Assay**

Early HPV detection methods produced flawed data because they were irreproducible from lab to lab and some were lacking sensitivity and specificity. There was a need for more sensitive technology and probes to identify additional HPV types. With the availability of new assay methods such as the Hybrid Capture HPV DNA Assay, developed by Digene, data has been generated that clearly and positively supports the role of HPV in the development of cervical cancer.

Digene's HPV test uses RNA probes to bind specific DNA sequences, creating DNA:RNA hybrids that are detected by chemiluminescence. To perform a test using the Hybrid Capture system, sample is mixed with RNA probes. Complementary DNA sequences in the sample bind to the RNA, creating DNA:RNA hybrids which are then captured on the surface of a specially coated polystyrene tube. All remaining DNA and specimen contaminants are removed by washing the tube. Captured hybrids are then reacted with a signal amplification system, which uses antibodies to detect any DNA:RNA hybrids bound to the tube. If DNA:RNA hybrids from the specimen are present on the surface of the tube, light is emitted, signaling a positive test result. The amount of DNA present in the sample is then rapidly and accurately quantified using standard laboratory luminometers. The entire test can be completed in four to six hours.

**DIAGNOSTIC TRIAGE USING HPV SCREENING**

Inclusion of HPV screening is expected to be a more effective means of identifying suspicious lesions. A diagnostic triage approach (see Exhibit 8) may provide a means of avoiding unnecessary procedures on patients with equivocal Pap smears and reduce morbidity and costs of Pap screening.

In a large-scale clinical trial, combination of HPV testing using the Hybrid Capture HPV DNA assay, in conjunction with the ThinPrep pap test supplied by Cytyc, provided a most efficient and cost effective approach for diagnostic triage of women with equivocal Pap smears. This conclusion is based on a study of 46,000 women conducted by Kaiser Permanente. Each woman had a conventional Pap smear, residual material was placed in PreservCyt solution, also supplied by Cytyc for the ThinPrep smear preparation, and a cervical specimen was placed in a specimen transport medium for the Hybrid Capture HPV DNA assay. In total, 999 ASCUS and 270 SIL lesions were detected from the total study population. Detection sensitivity for HSIL for all ASCUS smears was 75% for repeat Pap smears alone, compared to 88% for the HPV DNA assay plus the repeat Pap test. Furthermore, this approach could reduce the need for colposcopy by up to 70%, according to Michele Manos, MD, of Kaiser Permanente Northern California Region (Berkeley, CA).

Addition of HPV testing to ThinPrep cytology provides significant gains in diagnostic accuracy as compared with cytology augmented with chance testing. HPV DNA testing to triage inconclusive or low-grade Pap smear abnormalities seems to be a reasonable approach associated with potential cost savings because of the relative low rates of abnormal lesions among those diagnosed with ASCUS (73% false positives identified by colposcopy) and LSIL (48% false positives).

Using the triage method for managing ASCUS/LSIL, the HPV DNA assay can be administered in conjunction with ThinPrep cytology, eliminating the need for repeat patient visits to determine HPV status. According to Alex Ferenczy, MD, Professor of pathology at McGill University (Montreal, Canada), and Director of gynecologic pathology, cytology, and colposcopy at Mortimer B. Davis Jewish General Hospital (Montreal, Canada), high-risk HPV-positive patients should undergo colposcopy and then followed with increased vigilance, while, depending on the patient's history, low-risk and HPV-negative patients may be followed with routine repeat Pap smears. This approach is expected to significantly reduce the need (and added cost) for colposcopy for most ASCUS patients because only about 7% of women with ASCUS have HSIL and 18% of women diagnosed with LSIL will actually be diagnosed with HSIL by colposcopy.

## NEW DEVELOPMENTS IN THE TREATMENT OF GYNECOLOGIC CANCERS

FROM THE 21ST CONGRESS OF THE EUROPEAN SOCIETY OF MEDICAL ONCOLOGY VIENNA, AUSTRIA, NOVEMBER 1-5, 1996

### INVASIVE CERVICAL CANCER

Invasive cervical cancer is the fifth most common cancer and the second major cause of death in women, worldwide; nearly 450,000 women are diagnosed with cervical cancer annually around the world. In the last 15 years, significant advances have been made in the understanding of the etiology and patterns of spread of cervical cancer. Since the introduction of the Pap smear, death rate has decreased by as much as 70% in many developed countries. The five-year survival rate of any stage of cervical cancer, however, has not improved, and using presently available treatment modalities, no further improvement is to be expected. New agents or new therapeutic approaches or a better integration of the existing modalities in the primary treatment of poor-risk patients, those with locoregionally advanced disease or with involved lymph nodes, are urgently needed. For more on cervical cancer, see FO, pp 402-405.

### Metastatic Cervical Cancer

Patients with disease that has already spread to distant sites at first presentation (Stage IVB disease) or those whose disease recurred after prior local therapy and in whom salvage procedures such as radiotherapy failed, have a poor prognosis. Additional chemotherapy used in the latter group is merely palliative, used to produce an objective remission which, in most instances, is accompanied by some relief of symptoms.

With regard to palliative chemotherapy for cervical cancer, aggressive cisplatin-based combination chemotherapy regimens used in patients with recurrent and/or metastatic disease, may induce a higher response rate

than cisplatin alone, but at the cost of greater toxicity and with no survival benefit. As an alternative, these patients can be offered new drugs or new forms of treatment.

At present, none of the combined modality approaches (neoadjuvant chemotherapy prior to surgery or radiotherapy, and chemotherapy after surgery, or radiotherapy, or concurrently with radiotherapy) are considered standard treatment. Nevertheless, increased operability and survival, after a median follow-up of five years, observed in a randomized trial performed at the Buenos Aires University in Argentina in women with bulky Stage Ib squamous cell cancer who were treated by neoadjuvant chemotherapy [Sardi J, et al, *Int J Gynecol Cancer*, 1995; 5, suppl 1:15 (abstract)], is noteworthy and needs to be confirmed. Any treatment decision in this setting should be assessed against optimal supportive care, which may provide the best option for some patients with recurrent or metastatic disease (Vermorken JB, *Educational Book, ESMO96*, Pg 63-67).

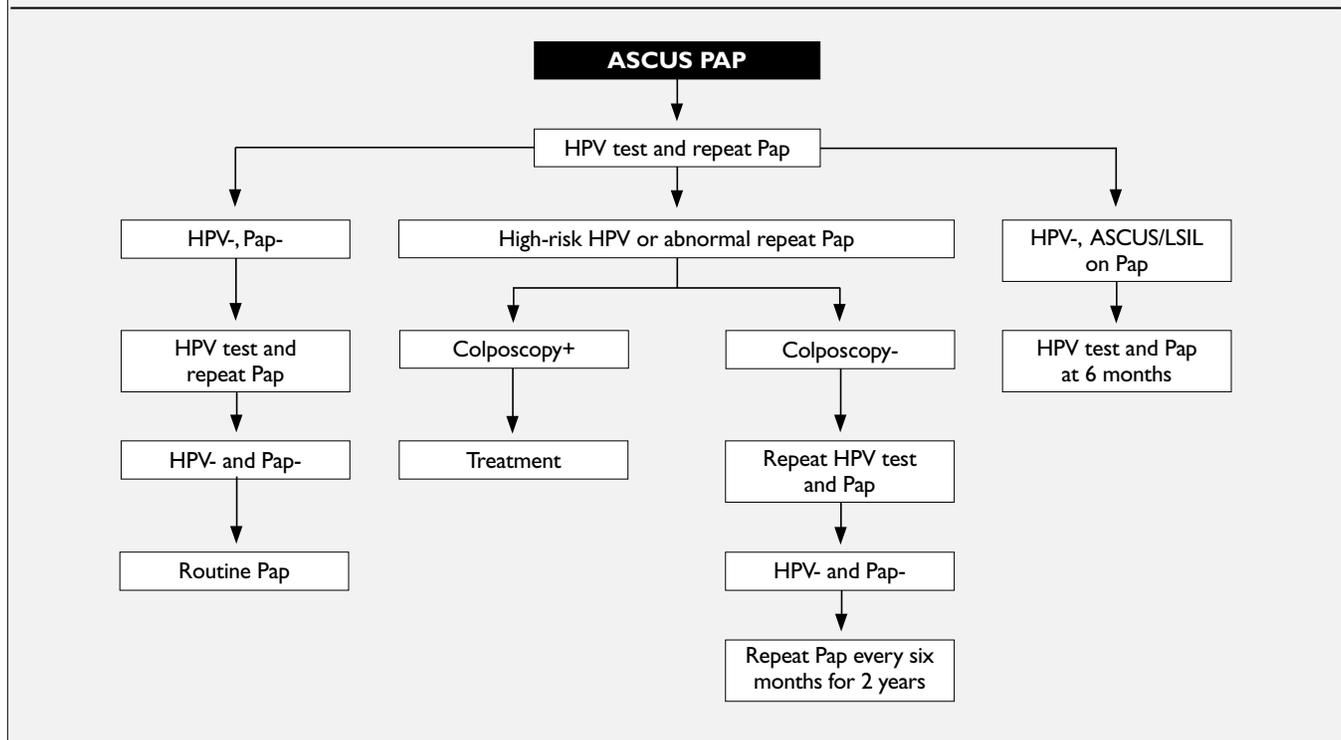
*HIV-related invasive cervical cancer* is occurring at a low rate in HIV+ patients in Italy, but there is a higher prevalence of carcinoma *in situ*, emphasizing the importance of integrating gynecological care into medical service for HIV+ women. From November 1986 to April 1995, 54 cases of HIV-related cervical cancer were retrospectively analyzed by the Italian Cooperative Group on AIDS and Tumors (GICAT). In this group, there were 35 (65%) carcinomas *in situ* and 19 (35%) invasive cervical cancers. Among patients with invasive cervical cancer, 63% had Stage I disease, 21% Stage II, and 16% Stage III/IV. Overall CR rate, after initial treatment for cancer, was 97% in women with carcinoma *in situ* and 81% in those with invasive cancer. Relapse rates were 13% and 20%, respectively (Vaccher E, et al, *ESMO96*, Abs. 354P:75).

### Combination Regimens in Invasive Cervical Cancer

*BEMP regimen*, consisting of bleomycin (Bleoxane; Bristol-Myers Squibb), vindesine (Eldesine) and mitomycin C (Mutamycin; Bristol-Myers Squibb), and cisplatin (BEMP), is associated with a higher response rate than cisplatin alone in patients with disseminated squamous cell carcinoma of the uterine cervix (SCCUC), but it is also associated with higher toxicity, and response rates do not translate into survival benefit. Therefore, cisplatin monotherapy remains the standard therapy of choice for women with SCCUC.

In a prospective, randomized, phase III trial (EORTC-GCCG protocol 55863), 287 chemotherapy-naive patients with SCCUC were treated either with bleomycin (15 mg/m<sup>2</sup>) as a 24-hour IV infusion on days 2-4, IV vindesine (3 mg/m<sup>2</sup>) on day 1, IV mitomycin C (8 mg/m<sup>2</sup>) on alternate cycles, and IV cisplatin (50 mg/m<sup>2</sup>) on day 1, or cisplatin alone (50 mg/m<sup>2</sup>). The first four cycles were administered every three weeks (induction) and subsequent cycles every four weeks (maintenance). Patients failing on cisplatin alone could be treated with BEMP.

**Exhibit 8**  
**Diagnostic Triage with Pap and HPV Testing**



Overall, there were 44 CR and PR (31%) with BEMP compared to 28 (19%) with single-agent cisplatin. However, BEMP was significantly more toxic, both in terms of hematologic and non hematologic toxicities. With a median follow-up of 6.1 years, survival curves (progression-free and overall) for each regimen were superimposable. Median overall survival was 10 months for BEMP versus 9.4 months for cisplatin alone (Vermorken JB, et al, ESMO96, Abs. 3180:67).

**Combination of cisplatin and vinorelbine** for metastatic cervical cancer is highly active, at least in terms of objective response against recurrent and/or metastatic adenocarcinoma of the uterine cervix, with acceptable toxicity. In a phase II trial, 21 consecutive chemotherapy-naïve patients were treated with IV infusion of cisplatin (80 mg/m<sup>2</sup>) and IV bolus vinorelbine (25 mg/m<sup>2</sup>), on days one and eight, every 21 days. Patients were restaged after three cycles. At time of presentation, in 17 evaluable patients, the overall response rate was 47%, with 2 CRs and 6 PRs; median duration of response was 6.0 months and 6.2 months, respectively. Disease stabilized for 4.0+ months in one patient and progressed in 7. Drug-related adverse events were manageable and toxicity of the combination was considered acceptable (Gebbia V, et al, ESMO96, Abs. 357P:76).

**Combination of cisplatin and paclitaxel** is moderately active in locally advanced cervical cancer (LACC), with an acceptable toxicity. To evaluate the response rate and safety of this combination as neoadjuvant treatment,

27 patients with LACC were treated with a 3-hour IV infusion of paclitaxel (175 mg/m<sup>2</sup>), followed by cisplatin (60 mg/m<sup>2</sup>), every 21 days. The combination was administered for four cycles provided there was no disease progression or unacceptable toxicity. Pelvic radiotherapy (external and intracavitary) was applied after chemotherapy. Among 24 evaluable patients (administered at least two cycles of the combination regimen), there was an overall response rate of 50%, all PR. In addition, disease stabilized in 7 women and progressed in 5. Among the 19 of 24 patients evaluated after radiotherapy, 9 (47%) were alive, with a median follow-up of 10.4 months. With regard to this combination's toxicity profile, 10 (40%) of 25 evaluable patients experienced Grade 3/4 gastrointestinal complaints, four (16%) Grade 3/4 neutropenia, four (16%) Grade 3 anemia, one (4%) Grade 3 mucositis, three (12%) Grade 3 myalgia and 23 (92%) Grade 3 alopecia. Three cases of hypertension, one severe bradycardia, and one ventricular tachycardia, also occurred (Costa MA, et al, ESMO96, 335P:71).

## OVARIAN CANCER

### Gemcitabine in Advanced EOC

Gemcitabine (Gemzar; Lilly) has moderate activity as a single agent in advanced epithelial ovarian cancer (EOC) with poor prognosis, without prejudicing subsequent response to platinum-based therapy. Thirty-five women with Stage IIIB (1), IIIC (10), and IV (23) disease and one unstaged, were administered gemcitabine (1250 mg/m<sup>2</sup>) weekly for three weeks, every four weeks. Toxicity

was mild; the major reason for dose reduction was leucopenia in 37 of 109 courses of treatment. Grade 3 neutropenia was seen in 10 women and Grade 4 in two, while two patients experienced Grade 4 thrombocytopenia. In 33 evaluable patients, the overall response rate was 24%, with one CR and seven PRs. Twenty-six of these women were treated with platinum-based regimens following gemcitabine. In 23 evaluable individuals (three were still too early to evaluate), the overall response rate was 52.2%, with three CRs and nine PRs; disease stabilized in three and progressed in eight (Underhill C et al, ESMO96, Abs. 324O:69).

### Marimastat for Advanced EOC

Marimastat (British Biotech), an oral matrix metalloproteinase inhibitor (MMPI), has shown activity in patients with advanced EOC. In a dose-ranging study, patients with progressive ovarian cancer, as documented by a rise in serum concentration of CA 125 of >25% over four weeks, were treated with marimastat for a period of 28 days at doses ranging from 5 mg once daily to 50 mg twice daily. Ten to 13 women were treated at each dose level. Patients whose rate of rise of CA 125 declined or demonstrated clinical signs of benefit, were eligible to continue treatment at the same dose level.

Marimastat was generally well tolerated at all doses over the initial 28-day study period, with musculoskeletal pain being the principal treatment-related side effect. Incidence and rate of onset of musculoskeletal pain were dose-related; none of seven patients treated with 25 mg twice daily experienced such symptoms while four of seven patients at the 50 mg twice-daily dose either withdrew from the study or had their dose reduced. Signs of biological activity were evident; serum CA 125 levels declined over the study period in 10 (45%) of 22 evaluable patients on doses of 10 to 50 mg twice-daily. Dose levels of 10 and 5 mg once-daily were less effective, with five (28%) of 18 patients experiencing a similar fall in CA 125. Several patients with clinical signs of stable disease have been treated for periods in excess of three months. Marimastat at a dose of 10-25 mg twice-daily is a reasonable regimen for further study (Poole C, et al, ESMO96, Abs. 322O:68).

### Paclitaxel and Ifosfamide in EOC

Combination of ifosfamide (Ifex; Bristol Myers Squibb) and paclitaxel appears to be active and well tolerated in platinum-pretreated ovarian cancer. Twenty-nine women with measurable or evaluable disease, who had been pretreated with at least one platinum analog (6 were primary platinum-resistant, 4 secondary platinum-resistant and 19 potentially platinum-sensitive) were administered ifosfamide (1.5 g/m<sup>2</sup>) IV on days one, two, and three, along with mense, and a 3-hour IV infusion of paclitaxel (135 mg/m<sup>2</sup>) on day three after ifosfamide. G-CSF (5 mg/kg) was administered daily subcutaneously

from day seven to eleven. Courses were repeated every three weeks for a maximum of six cycles.

Objective clinical response rate in 27 evaluable women was 48%, with four CRs and nine PRs. Response rates were higher in platinum-sensitive cases (63%) than in those with secondary platinum resistance (20%). Time to disease progression for responding patients was seven months, with a median follow-up of 13 months. Median survival had not been reached at time of presentation. Hematologic and non-hematologic Grade 3/4 toxicity included alopecia (90%), nausea and vomiting (27%), neutropenia (27%), anemia (15%), thrombocytopenia (7%) and neurotoxicity (3%). There were two episodes of febrile neutropenia but no treatment-related deaths (Dimopoulos MA, et al, ESMO96, Abs. 333P:70).

### PRIMARY FALLOPIAN TUBE CARCINOMA

In primary fallopian tube carcinoma (PFTC), a combination of surgery, post-operative radiotherapy and/or chemotherapy, may result in long-term survival. Because PFTC accounts for less than 2% (2.9 cases per million) of newly-diagnosed malignant gynecological tumors, experience with this malignancy is limited. At the Anti-Cancer Center Paul Strauss (Strasbourg, France), of 20 patients (6 Stage IA, 3 IC, 1 IIB, 6 IIC, 3 IIIB, and 1 IV) who presented with histologically proven fallopian tube adenocarcinoma, over a 25 year period (1972-1996), 17 underwent total hysterectomy and bilateral salpingo-oophorectomy extended by intracolonic omentectomy, and three salpingo-oophorectomy.

After surgery, 3 with Stage IA and one with Stage IIB disease were treated no further, while 3 Stage IA, 3 Stage IC, and 1 Stage IIB patients underwent post-operative irradiation. The 9 remaining patients (5 Stage IIC, 3 IIIB and 1 IV) were treated with chemotherapy (6 with doxorubicin, teniposide, cyclophosphamide, and cisplatin, and 3 with carboplatin and cyclophosphamide). Response to chemotherapy was evaluated by second look laparotomy. Five patients with pathologic CR were administered consolidation chemotherapy consisting of cyclophosphamide, methotrexate, and 5-FU. Three others with pathologic PRs were treated with whole abdominal irradiation. One case was too early for evaluation at the time of presentation. The overall survival rate, with a median follow-up of four years and seven months, is 60%. Median survival had not been reached at the time of presentation but 9 women (4 Stage IA, 1 IIB, and 4 IIC) were alive, disease-free, for a period exceeding seven years (Petit T, et al, ESMO96, Abs. 364P:77).

*Editor's Note: Next issue will cover development of novel agents for the treatment of ovarian cancer and include a comprehensive article on cell cycle regulation in cancer.*

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