Salvage Therapy for Ovarian Cancer

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Patients with epithelial ovarian cancer must receive optimal surgical care and state-of-the-art chemotherapy in the primary treatment setting. The salvage treatment of women with recurrent or persistent ovarian cancer remains a

Of the 28,000 patients diagnosed with epithelial ovarian cancer in 1997, nearly 70% presented with advanced disease. Through the use of primary taxane/platinum therapy, up to 50% of these patients achieved a complete clinical remission. Unfortunately, the majority of patients will have persistent disease after initial treatment or will relapse within the first 3 years. As a result, salvage therapy comprises the majority of patient encounters in the treatment of epithelial ovarian cancer.

Many treatment options are now available for patients with persistent or recurrent ovarian cancer; these include repeat treatment with a taxane and platinum compound or a choice from among a menu of new agents with activity in this disease. In addition to standard systemic drug strategies, proposed alternatives for salvage treatment include high-dose chemotherapy with stem-cell support, prolonged maintenance chemotherapy, intraperitoneal chemotherapy, hormonal therapy, secondary surgical cytoreduction, and radiotherapy.

Candidates for salvage therapy can be grouped into several different categories. These differences are more than semantic, in that they identify patients with markedly different prognoses and predict the likelihood of response to treatment. Because of the heterogeneity of these patients, they will be considered separately here.

The vast majority of patients with ovarian cancer respond to primary therapy. A small percentage of patients (< 20%) may have progressive tumor during primary treatment; this is defined as refractory disease. In general, these patients are considered to have a poor prognosis, and their poor performance status often precludes additional treatment.

A larger group of patients may show a partial clinical response to six cycles of therapy. A partial response is characterized by persistently elevated tumor markers or clinically evident disease at the conclusion of treatment; this is termed persistent disease. Despite a complete clinical remission, some patients may also have persistent disease documented only at second-look surgical assessment. This group can comprise up to 50% of patients with clinical complete remission. A final group of patients may initially respond completely to primary therapy but then relapse; these individuals are properly identified as patients with recurrent disease. If the disease recurs in < 6 months, it is defined as resistant to platinum (and taxanes) and requires alternative therapies. If the disease recurs ≥ 6 months following primary therapy, it may be termed sensitive, raising the potential for repeat treatment with platinum and taxane compounds administered on the same or different schedules.[1]

Primary Refractory Disease

As mentioned above, the outlook for the < 20% of patients whose disease progresses clinically during primary therapy with platinum- and taxane-containing regimens remains poor. No curative strategies are currently available for this group of patients, and any intervention must be considered palliative.

Patients with primary refractory disease are generally offered treatment with any of the various single-agent chemotherapies discussed below. No randomized trial of second-line therapy in this patient group has shown the superiority of one nonplatinum or nontaxane agent over another, and participation in clinical trials is particularly encouraged. Progress in testing new agents in this group is confounded by the small number of patients, as well as their often diminished performance status, which precludes additional chemotherapy following primary treatment failure. Additional surgical cytoreduction in patients with primary refractory disease has significant morbidity and has not altered the median survival of 12 months.[2]
Persistent Disease at Surgical Reassessment

Of all of the ovarian cancer salvage treatment groups, patients with persistent disease at second-look surgical assessment are the only group that appears to have the small possibility of achieving a cure with currently available treatment strategies. This possibility of definitive therapy provides a strong argument for accurate post-treatment assessment in patients with apparent complete clinical responses. Because of the limitations of computed tomography (CT) and available biochemical markers, an invasive second-look assessment remains the most accurate way to assess response to primary treatment.

Although the sensitivity and specificity of laparoscopic reassessment vs formal laparotomy are under investigation, second-look procedures have not been shown to prolong survival in previous comparative trials.[3] For example, a recent prospective trial randomized 102 patients in complete remission (as documented by clinical findings, CT, laparoscopy, and serum markers) to laparotomy or observation. Survival was not prolonged in patients who were surgically assessed. However, it must be noted that a positive outcome from any second-look procedure depends on the efficacy of salvage treatment, since the intent of surgical reassessment is primarily diagnostic rather than therapeutic.

No standard therapy currently exists for patients with persistent disease. Three forms of salvage treatment can be considered for these patients: prolonged chemotherapy with the same or different agents, intraperitoneal therapy, or high-dose therapy with hematopoietic support.

Prolonged Systemic Chemotherapy

Platinum Agents--In general, extended administration of platinum agents has shown no benefit in patients with persistent disease. Randomized trials of 6 vs 12 cycles or 5 vs 10 cycles of cyclophosphamide (Cytoxan, Neosar), doxorubicin, and cisplatin (Platinol) in advanced ovarian cancer demonstrated no survival advantage for the longer courses of treatment.[4,5] These observations are consistent with those seen in the treatment of Hodgkin’s disease or adjuvant breast cancer chemotherapy.

In contrast, a retrospective M. D. Anderson Cancer Center (MDACC) review of 116 optimally debulked patients investigated the relationship between duration of chemotherapy with platinum-based regimens and survival. Median progression-free survival of patients receiving 12 vs 6 planned cycles of therapy was 30 vs 15 months ($P = .0004$).[6] Thus, while additional cycles of platinum therapy may be considered for patients who may still be responding by CA-125 measurements, the preponderance of evidence does not support this "more of the same" strategy.

Paclitaxel--Recently, the addition of paclitaxel (Taxol) to primary therapy regimens has reopened the sustained chemotherapy question. No trials have compared longer courses of paclitaxel to the standard six cycles of treatment.

Inferential data can be gleaned from the large body of literature describing paclitaxel treatment of refractory patients. In 103 heavily pretreated (more than three prior regimens) patients receiving paclitaxel at Memorial Sloan-Kettering Cancer Center (MSKCC) who showed a minimal objective response rate of 4%, the 2- and 3-year survival rates were 18% and 11%, respectively. Of these patients, 21% received six or more courses of paclitaxel, and treatment-related disease stabilization may have had a greater impact on the natural history than is predicted by the response rate in these patients.

The concept of prolonged delivery of paclitaxel and other cell-cycle-specific cytotoxic agents remains to be tested in a randomized, prospective trial.[7]

"Consolidation" Treatment--The obvious alternative strategy is to select a different single agent or combination regimen for use as "consolidation" treatment. There is very little long-term information on such an approach, and no data exist regarding the impact of consolidation treatment on time to treatment failure or survival. However, the sequential administration of non-cross-resistant chemotherapy has been advocated by Norton and others.[8] Such sequential strategies are currently being tested in breast cancer and may be worthy of consideration in ovarian cancer as well.

Intraperitoneal Therapy

There is preclinical evidence of a cytotoxic dose-response curve with many chemotherapeutic agents, and the strategy of increasing drug delivery via the intraperitoneal route has been extensively studied and reviewed.[9-11] Several basic pharmacologic principles can be generalized to intraperitoneal regimens.

In a recent review, Dedrick and Flessner developed a spatially distributed pharmacokinetic model to
examine the two most common problems to be overcome when designing intraperitoneal regimens: (1) poor tumor penetration by drugs, and (2) incomplete irrigation of serosal surfaces by the drug-containing solution. The model predicts, in a mechanistic way, the characteristic penetration distance of a drug and the apparent permeability of a peritoneal surface. The goal is to provide insights into the expected effects of such procedures as pharmacologic manipulation or physical mixing.

To date, most of the information about intraperitoneal therapy has come from clinical studies with drug sampling and pharmacokinetic analysis. The pharmacokinetic advantages of intra-peritoneal drug delivery include the slow systemic uptake of drug from the peritoneal cavity and rapid subsequent drug clearance from the plasma. For hydrophilic drugs, passive absorption into peritoneal capillaries is directly proportional to the overall peritoneal surface area and inversely proportional to the square root of the molecular weight of the agent. As shown in Table 1, an increased mean peritoneal cavity/plasma concentration ratio has been demonstrated for many chemotherapeutic agents with known activity against ovarian cancer.

No randomized clinical trials of salvage intraperitoneal therapy have been conducted in patients with persistent ovarian cancer. The only available randomized data evaluating intraperitoneal therapy come from a study of patients with previously untreated stage III ovarian epithelial cancer conducted by Alberts et al. Among the 546 eligible patients in this study, estimated median survival was longer in the group receiving intraperitoneal cisplatin (49 months; 95% confidence interval [CI], 42 to 56 months) than in the group receiving intravenous cisplatin (41 months; 95% CI, 34 to 47 months). The effect of residual tumor size on predicting response to intraperitoneal therapy has been repeatedly demonstrated in the clinical arena, and the direct penetration of drug into tissue is limited, ranging from 1 to 3 mm. Small-volume disease, generally microscopic or < 0.5 cm is necessary for the rational application of this approach. The phase III randomized trial of intraperitoneal therapy by Alberts et al. in previously untreated patients with stage III ovarian cancer showed marked differences in survival based on tumor size at the initiation of intraperitoneal therapy: Median survival was 76 months in patients with microscopic disease; 42 months in those with < 0.5-cm disease; and 32 months in those with > 0.5- to 2.0-cm disease.

**Cisplatin**--Intraperitoneal cisplatin remains the most extensively studied agent in the setting of small-volume persistent disease after surgical reassessment. Overall, approximately 20% to 30% of patients with persistent ovarian cancer after initial chemotherapy have been shown to respond to intra-peritoneal cisplatin treatment. Surgically defined response (s-R) rates of 40% to 50% and surgically defined complete response (s-CR) rates of 25% to 35% have been reported in patients with small-volume residual disease (microscopic or all tumor nodules ≤ 0.5 cm in diameter) treated with a variety of regimens containing cisplatin.

Important predictors of response to intraperitoneal cisplatin include not only size of the residual tumor but also prior response to systemic cisplatin. In one series, even in the subset of patients with < 0.5-cm residual disease, only 9% of platinum nonresponders achieved a complete response (CR), as compared with 43% of such patients with a previously documented response to intravenous platinum.

In the MSKCC experience, a small (< 15%) group of patients achieve a pathologic CR after intraperitoneal cisplatin therapy and remain disease-free for more than 7 years of follow-up. If this experience can be duplicated by others, it may imply that salvage intra-peritoneal cisplatin therapy may be effective in a small number of patients with persistent disease.

Investigators at MSKCC have also recently reported preliminary data on the use of three cycles of intraperitoneal cisplatin and etoposide in patients with negative second-look surgical assessments. At 36-month follow-up, the median disease-free survival is 28.5 months in the untreated group (concurrent historical matched controls) and has not yet been reached in the treated group. The contribution of etoposide in this regimen is unknown. A phase II trial of intravenous cisplatin plus etoposide in 21 patients in complete clinical remission (10 of whom had minimal residual disease at second-look assessment) reported a median progression-free interval of 26 months, which is similar to data with cisplatin alone.

**Other Agents**--Numerous other agents have been evaluated for intraperitoneal administration, including paclitaxel, fluorouridine (FUDR), mitomycin (Mutamycin), carboplatin (Paraplatin), mitoxantrone (Novantrone), interleukin-2 (Proleukin), interferon-alfa (Intron A, Roferon-A), and interferon-gamma. Intrapertitoneal delivery of mitoxantrone is limited by chemical peritonitis, making this drug poorly tolerated and not recommended for this route of administration. Responses have been seen in some patients, however, including those who did not respond to intraperitoneal cisplatin.
New intravenous agents with activity in epithelial ovarian cancer that have recently been identified and tested largely in the advanced salvage setting include liposomal doxorubicin (Doxil), topotecan (Hycamtin), vinorelbine (Navelbine), docetaxel (Taxotere), and gemcitabine (Gemzar).[21-25] If intraperitoneal administration of cisplatin proves to be superior to intravenous administration for small-volume disease, an important question will be to identify which new agents may have a dose-response relationship and pharmacologic properties appropriate for possible intraperitoneal administration in combination.

**Summary**—With the exception of one published trial, data suggesting a benefit for intraperitoneal therapy come from nonrandomized phase II trials.[13] It is important to note that, although the response rates recorded in the various trials may be impressive, biases, such as treatment limited to patients with responsive tumors or those with very small residual disease, cannot be excluded or compared directly. Thus, intraperitoneal therapy remains an investigational approach at present.

**High-Dose Therapy**

Another approach that has been advocated in women with persistent disease is to increase drug delivery using high-dose treatment with stem-cell support as required. An original retrospective analysis by Levin et al suggested a statistically significant correlation between the dose intensity of cisplatin and both response rate and overall survival, although the evidence suggested a flattening of the dose-response curve above a cisplatin dose of 25 mg/m²/wk.[9]

**Moderately Increased Dose Intensity**—Table 2 lists the trials using modest increases in dose intensity that did not require stem-cell or bone-marrow support. Of these trials, only two[26,27] suggested a benefit of high-dose therapy, and both of these trials have serious flaws that undermine the results.

The trial by Kaye et al included 30% of patients with early-stage disease treated in the adjuvant setting, and despite this, the low-dose arm had markedly inferior results than those cited by other published salvage therapy trials. In addition, the reported benefit in the relative death rate for the high-dose arm was evident only during the first 2 years after the completion of therapy. At 4 years, only a 5% improvement in survival remained evident. In addition, the high-dose arm had substantial toxicity and was not ultimately recommended by the authors.[26]

The Ngan et al trial is difficult to interpret, as it randomized only 50 patients, and disease stage was not clearly defined.[27] In contrast, in a large prospective, randomized GOG trial of 485 suboptimal stage III and IV patients that compared cyclophosphamide and cisplatin given at standard and at double dose intensity but identical total doses, no differences in response rates or survival were shown with the modest increase of dose intensity.[59] This finding has been corroborated by others.[28] The trial by Conte et al increased not only dose intensity but also total dose without demonstrating an improvement in overall survival.

None of these trials without stem-cell or bone-marrow support achieved more than twice standard dose intensity, and it can be concluded that no study has shown a consistent benefit of modest increases in dose intensity in the salvage treatment of ovarian cancer.[29]

**High-Dose Therapy With Stem-Cell Rescue**—Several studies have recently been published using high-dose therapy with stem-cell rescue. In a trial by Legros et al, 53 patients were treated with either high-dose melphalan (Alkeran) or high-dose carboplatin plus cyclophosphamide.[30] At 5 years, the overall survival rate was 59.9% with a disease-free survival rate of 23.6%. The authors compared this selected population receiving high-dose therapy to historical controls with 5-year overall survival rates of 20% to 30%. Of note, the longest survival was found in the 19 patients with a pathologic complete response at second-look surgery prior to high-dose therapy; these patients had a 5-year overall survival rate of 74.2% and a disease-free survival rate of 32.8%.

Stiff et al reviewed 100 consecutive patients treated with one of several regimens. Median progression-free survival and overall survival durations for all 100 patients were 7 and 13 months, respectively. The best predictors of overall survival were tumor bulk (P = .0175), platinum sensitivity (P = .0330), and age (P = .0017). Median progression-free survival and overall survival durations for 20 patients with platinum-sensitive, ≤ 1-cm disease were 19 and 30 months, respectively.[31] Repeated studies have shown that platinum sensitivity and disease bulk are associated with outcome. In a phase I study of high-dose carboplatin with dose escalation of paclitaxel using...
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Peripheral blood progenitor-cell support, although not the objective of the trial, the overall response rate among 14 evaluable patients was 73% (33% [5 patients] with pathologic complete response and 43% [6 patients] with pathologic partial response). Of note, all of the patients with a pathologic complete response had optimally debulked disease on entry to the protocol.[32]
The trials of high-dose therapy with stem-cell rescue are not randomized and cannot be compared directly. These trials involve selected populations, who generally are compared to historical controls to demonstrate superior outcomes. Available data suggest that if high-dose therapy does have any benefit, it is not seen in older patients with cisplatin-resistant or large-volume disease. Despite these findings, it is unclear whether a true benefit exists in younger patients with chemosensitive, small-volume disease, as these patients also have the best responses to standard salvage regimens. An intergroup trial in the United States, based on the work of Stiff and co-workers, and an ongoing study in France have randomized patients with minimal or no residual disease and chemosensitivity to high- vs standard-dose therapy. This is a critical question in the treatment of ovarian cancer. The intergroup trial has been vigorously supported by the National Cancer Institute, the GOG, and the Southwest Oncology Group. These data are urgently needed to determine whether salvage high-dose therapy has any benefits over currently available standard therapy in patients with good prognostic features. At present, therefore, the role of dose-intensive therapy remains contested, and there is no place for such therapy in ovarian cancer outside of the setting of a clinical study.

**MSKCC Approach**—Each institution must formulate a systematic approach to patients with persistent disease. Our approach has been to recommend surgical reassessment to patients who complete six cycles of standard paclitaxel/platinum therapy. Patients with persistent disease who are willing to participate in clinical trials are enrolled in GOG 164 (the randomized high-dose chemotherapy trial) or offered investigational intraperitoneal therapy, depending on the clinical circumstances and the eligibility of the patient. Patients who are unable or unwilling to participate in clinical research are treated with five cycles of intra-peritoneal cisplatin (75 mg/m² every 3 weeks). Patients who have contraindications to intraperitoneal therapy may receive six additional cycles of paclitaxel if toxicity permits.

**Paclitaxel/Platinum-Sensitive Recurrent Disease**
In addition to chemotherapeutic agents, secondary surgical debulking is considered part of salvage treatment for patients who are sensitive to paclitaxel/platinum and whose disease recurs after a complete response to primary therapy.

**Secondary Surgical Cytoreduction**
Technically, secondary surgical cytoreduction has had varying rates of success, which have been as high as 84% in some series.[33] Secondary debulking has been employed at the time of second-look laparotomy, as well as in those patients with > 6-month disease-free intervals since primary therapy. No definitive randomized, prospective trials of secondary debulking have been performed. Hoskins et al described a series of 67 patients who, at second-look laparotomy, had microscopic (17 patients), < 2-cm (28 patients), or ≥ 2-cm (22 patients) disease. The 5-year survival rate of patients with microscopic disease (62%) at second-look laparotomy did not differ from that of patients rendered with microscopic disease (51%) by secondary debulking.[34]
Segna et al reported on a series of 100 patients, 73% of whom had a disease-free interval of 12 months or longer prior to secondary surgery. Median survival was 27.1 months in those with < 2 cm of residual disease after the cytoreduction attempt vs 9 months in those with ≥ 2 cm of residual disease ($P = .0001$).[35]
Vacarello et al studied 57 patients who relapsed a median of 33 months after a documented negative second-look laparotomy following primary treatment. Debubling surgery was performed in 23 of these patients and was considered optimal (< 0.5 cm of residual disease) in 14 (61%). Median survival in patients who were optimally debulked (41 months) was better than that in patients who were not explored (9 months) or in those who were suboptimally debulked (23 months; $P = .0001$ for both comparisons).[36]
In contrast, Morris et al showed no benefit in a group of 30 patients who underwent salvage cytoreductive surgery following a disease-free interval of at least 6 months after primary therapy. Among the 17 patients (57%) whose residual tumor volume was reduced to < 2 cm, median survival was 16.3 months; this did not differ significantly from the 13.3-month median survival irrespective of residual tumor size. It is noteworthy that only 11% of patients in this series responded to second-line therapy, despite the greater than 6-month interval from primary therapy; this may have contributed to the poor outcome in this group.[37]
In summary, although no randomized comparison data are available, secondary surgical debulking, particularly in patients with long disease-free intervals, may be of benefit if optimal debulking can be performed and effective second-line therapy applied.

**Chemotherapy**

**Treatment-Free Interval**—As mentioned above, patients whose disease recurs ≥ 6 months following initial treatment with a taxane and platinum-based regimen are considered to be platinum-sensitive. The response of patients with ovarian cancer to repeat treatment with cisplatin- or taxane-based regimens has been well described, and the magnitude of this response makes the determination of the treatment-free interval the first step in selecting a salvage treatment strategy. Markman et al defined the following overall response and surgically defined complete response (S-Cr) rates based on treatment-free intervals after cisplatin therapy: overall response and S-Cr rates in patients with a treatment-free interval of 5 to 12 months were 27% and 5%, respectively; in those with a treatment-free interval of 13 to 24 months, 33% and 11%, respectively; and in those with a treatment-free interval of more than 24 months, 59% and 22%, respectively. Patients who required no intervening treatment for more than 24 months from the completion of initial therapy had a 77% overall response rate and a 32% S-Cr rate.[38] Furthermore, Kavanagh et al demonstrated, in patients who initially responded to a platinum- and taxane-containing regimen, with at least a 12-month platinum-free interval, that carboplatin reinduction had a partial response rate of 21% (median duration, 7 months). Of note, no neuropathy was seen with this regimen, which was particularly well tolerated, making it a suitable choice for older patients with concomitant medical comorbidities or marginal performance status.[39] The effectiveness of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy likewise has been well established. In a review of 43 patients, Thigpen et al showed a 44% response rate in patients with a platinum-free interval of ≥ 6 months and a 33% rate in those who progressed during platinum treatment or had a platinum free interval of < 6 months.[40] Furthermore, 175 mg/m² of paclitaxel over 3 hours is equivalent to 135 mg/m² in the salvage setting.[63] Whereas 250 mg/m² of paclitaxel with granulocyte colony-stimulating factor (G-CSF [Neupogen]) support showed a slightly higher response rate when compared to 175 mg/m², overall survival duration with the two doses was similar (12.5 vs 11.9 months) and toxicity was increased at the higher dose.[41]

**Schedule of Salvage Therapy**—The effective treatment of late recurrences may hinge not only on the prior treatment-free interval but also on the schedule of salvage therapy. Fennelly et al demonstrated the feasibility and safety of weekly paclitaxel administration resulting in dose-intensive paclitaxel delivery in patients with advanced ovarian cancer. The rationale for this approach is based on the cell-cycle-specific cytotoxicity of paclitaxel and its effect on microtubule stability. Since only a small fraction of solid tumor cancer cells are actively dividing at any one time, prolonged exposure to the drug is theoretically appealing.[42] In the phase I trial by Fennelly et al, 18 assessable patients who had received a median of three prior regimens showed a partial response rate of 30% to weekly paclitaxel therapy; the phase II dose was determined to be 80 mg/m². Hematologic toxicity was dose limiting. Other toxicities included alopecia, and 3 of 18 patients had progressive neuropathy with no progression to grade 3. Of note, two patients who had progressed on a standard 3-week schedule of paclitaxel responded to weekly administration.

At MSKCC, a retrospective study of the cumulative experience with weekly paclitaxel administration as salvage therapy in ovarian carcinoma has been carried out, and preliminary findings from this retrospective analysis are summarized in Table 3.[32] Of note, this weekly regimen appears to spare platelets and allows the dose of dexamethasone premedication to be decreased to 8 mg orally prior to paclitaxel administration. Particularly noteworthy were the responses to weekly paclitaxel (partial response rate, 15%) seen in patients with a treatment-free interval of < 6 months after taxane therapy (patients who were previously termed “resistant”). This finding needs further evaluation. The next logical step is to determine the dose of carboplatin that can be administered with weekly paclitaxel. Phase I studies with this objective are currently underway.

The choice of therapy in this patient group depends on the patient and the institution. Patients with platinum-sensitive disease are an important group for the testing of new agents. In the absence of a clinical trial option, outpatient treatment with paclitaxel (175 mg/m² over 3 hours) and carboplatin (dosed to attain an area under the curve [AUC] of 5) is a manageable regimen with a high likelihood of response. Nonresponders will fall into the resistant group described below.
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Paclitaxel/Platinum-Resistant Recurrent Disease

In general, patients whose disease recurs < 6 months following initial platinum- and taxane-based therapy are considered treatment-resistant. Early data suggest that additional paclitaxel given on a weekly schedule may be considered in such patients, but the true response rate is unknown.[32] These patients, as well as those who have been retreated with platinum- and taxane-based regimens and again progress, require other second-line strategies. Options that have been considered include high-dose chemotherapy and a wide array of single chemotherapeutic and hormonal agents. Unfortunately, both the physician and patient must keep in mind the palliative nature of therapy in this setting.

High-Dose Chemotherapy

The use of high-dose chemotherapy in patients with platinum-refractory disease has been so disappointing that only carefully selected patients entering high-priority trials should receive high-dose treatment. In the trial by Stiff et al, among 66 platinum-resistant patients treated with a variety of high-dose regimens, the median overall survival was short at 9.6 months.[31]

Single Agents

Recent drug approvals have left the physician with difficult choices among single agents. The response data come largely from individual phase II trials, and direct comparisons are not meaningful. However, as shown in Table 4, there is a general similarity among the agents with respect to response rates and durations.

**Camptothecins**--Topotecan is the only agent that has received FDA approval for the treatment of platinum-refractory ovarian carcinoma. Overall, combining phase II trials by Creemers et al and Kudelka et al, topotecan shows a general response rate of 20% in platinum-sensitive patients and 14% in platinum-resistant patients.[25,43] In these trials, patients were categorized according to platinum sensitivity, but none had received prior paclitaxel therapy, which is not typical of most patients who receive salvage therapy today.

In the only randomized trial of topotecan, conducted by ten Bokkel Huinik et al, 226 patients with platinum-refractory disease received either paclitaxel (175 mg/m² over 3 hours) or topotecan (1.5 mg/m²/d) for 5 days every 21 days. Response rates for topotecan and paclitaxel were 13.3% vs 6.6% in platinum-resistant patients (P = .030) and 28.8% vs 20.0% in platinum-sensitive patients (P = .213). Median survival time was 15.2 months in the topotecan group and 10.7 months in the paclitaxel group (P = .515).[44] The differences in response and survival did not reach statistical significance. The authors noted that interpretation of the survival data is further complicated by the early crossover of patients to other treatments after the failure of initial therapy.

The conclusion that can be derived from the available data is that topotecan has activity similar to that of salvage paclitaxel in patients who have not received prior paclitaxel therapy and compares favorably to other salvage agents. Of note, an oral preparation of topotecan is entering phase II trials; diarrhea is the dose-limiting toxicity of this preparation.[45] Another camptothecin, irinotecan (Camptosar), has proved to be more active than topotecan in colorectal cancer. Single-agent trials of irinotecan in patients with epithelial ovarian cancer are ongoing.

**Etoposide**--In a phase II trial with 82 patients assessable for response, oral etoposide at a dose of 50 mg/m²/d for 21 days, produced a 26.8% response rate (7.3% complete responses, 19.5% partial responses) in patients with platinum-refractory disease, and a 34.1% response rate (14.6% complete responses, 19.5% partial responses) in platinum-sensitive patients. Of note, the number of patients in this trial is large, and 25 of the 41 platinum-resistant patients had also received prior paclitaxel therapy, which mimics usual practice. Hematologic toxicity was limiting, with grade 3 and 4 neutropenia occurring in 20% and 25% of patients, respectively, thrombocytopenia in 9%, and anemia in 13.4%.[46]

**Liposomal Doxorubicin**--In a study of 35 patients receiving liposomal doxorubicin, all of whom had progressed after at least one platinum- and taxane-based regimen, a clinical response rate of 25.7% (one complete response and nine partial responses) was noted, with a median survival of 11 months.[21] Notably, nausea, hair loss, and cardiac toxicity were not reported in this trial. Mucositis and hand-foot syndrome were the most significant toxicities, requiring dose reduction from 50 mg/m² every 3 weeks to 40 mg/m² every 4 weeks (the tolerated, currently recommended dose). Responses were seen after two or three treatments, which is 3 months into therapy for some patients. This phenomenon of delayed response may be related to liposomal pharmacology or to the biology of heavily pretreated ovarian carcinoma. A delay in time to response also has been seen with salvage paclitaxel, particularly when given weekly, and with topotecan.[21,25]
Docetaxel--A phase II trial of docetaxel (100 mg/m² every 21 days) by Francis et al in 25 patients with platinum-refractory disease, none of whom had received paclitaxel, reported partial responses in 35% of patients, with a median response duration of 5 months.[22] Of note, hospitalization for neutropenia was required in 12 (48%) of the patients. Granulocyte colony-stimulating factor was not given. Edema (> grade 1) occurred in 5 (20%) patients.[22] In a similar trial by Kavanagh et al, a partial response rate of 40% was reported with a median survival of 10 months.[47]

Vinorelbine--A phase II trial of vinorelbine (25 mg/m² weekly) in 33 patients with advanced ovarian cancer, the overall response rate (including stable disease) was 15% (95% CI, 5.1% to 31.9%). All 33 patients had received prior platinum-based therapy and 10 had received prior paclitaxel treatment; 24 patients were considered to be platinum-resistant. Of note, all of the responses (complete and partial responses) occurred in the platinum-resistant patients. Significant treatment delays were required for neutropenia and anemia, and worsening neuropathy (grade 3) developed in two patients.[23]

Gemcitabine--A phase II trial of gemcitabine in 38 patients whose disease progressed after platinum therapy and 27 patients who showed progression after paclitaxel therapy reported a response rate of 13% (partial responses). If stable patients were included, as defined by > 50% reduction in CA-125 for at least 3 months, 10 (32%) of 31 patients met these criteria. Uncomplicated neutropenia was the dose-limiting toxicity in this group of heavily pretreated patients.[24] In vitro and in vivo synergy between cisplatin and gemcitabine and the significant sensitivity of ovarian carcinoma to platinum-containing compounds makes this combination attractive. Trials of the combination are underway.[48]

Older alkylating agents--may also have a limited role in patients with cisplatin-refractory ovary cancer. Single-agent ifosfamide (Ifex), given at a dosage of 1.2 g/m²/d for 5 days with mesna, produced a 13.5% objective response rate with a median survival of 9 months. Of note, all of these patients, who were treated prior to the availability of paclitaxel, had received prior alkylating agent therapy with cyclophosphamide. Neurologic side effects were reported in 12% of patients.[49] A phase II trial of oral altretamine (Hexalen) included 71 patients, all of whom had an initial response to platinum lasting > 6 months and who, therefore, are considered to be platinum-sensitive. Patients were given 260 mg/m²/d of altretamine for 14 days each month. The overall response rate (complete plus partial responses) was 40% (95% CI, 25.4% to 54.6%) and response duration was 8 months. Of note, not only were these patients platinum sensitive, but also the median treatment-free period following initial chemotherapy was long (16.4 months), placing them in a group expected to have significant responses to salvage therapy.[50] Nausea was the most significant toxicity despite scheduled antiemetics. Grade 2 or 3 nausea occurred in 27 patients and grade 2 or 3 vomiting in 19 patients.

Hormonal Agents--The presence of estrogen and progesterone receptors on some ovarian tumors has prompted the evaluation of hormonal manipulation. A series of phase II trials has shown megestrol acetate and aminoglutethimide (Cytadren) to have minimal and no activity, respectively. Tamoxifen (Nolvadex) at 40 mg orally yields a response rate of approximately 13% if the results of multiple phase II trials are combined.[51] In a phase II GOG trial of 105 patients, the median duration of activity of tamoxifen was 7.5 months in those with a complete response and 3 months in those with a partial response, and the response rate was 17%. A consistent correla-tion between response proportion and estrogen-receptor status has not been demonstrated in ovarian cancer, as it has in other hormonally responsive malignancies.[52] Tamoxifen is a reasonable therapeutic choice, particularly in the asymptomatic patient with a rising CA-125. Although tamoxifen has a short duration of activity, it may serve to lengthen the interval before additional systemic cytotoxic therapy is required, and it may allow the sensitivity of other agents to return.

Summary--A variety of single agents appear to have limited efficacy in recurrent platinum-resistant ovarian cancer, ranging from 15% to 40% partial responses of modest duration in phase II trials. These trials use different definitions for platinum "resistance" and "refractoriness" and variably exclude paclitaxel as part of primary regimens. Furthermore, some assessments of overall response include stable disease while others include complete and partial responses only. Given this mixed population, the only conclusion to be drawn collectively is that the agents appear to be of similar marginal benefit and should be selected on the basis of route of administration and expected toxicity. The possible efficacy of these single agents applied in homogeneous populations earlier in the course of recurrent disease needs to be investigated.
Radiotherapy has been proposed for the palliative treatment of isolated symptomatic lesions and also has been delivered to the whole abdomen in patients with advanced disease. In a trial of 35 patients with persistent or recurrent disease (29 of whom received radiation to the pelvis; 5, to the retroperitoneum; and 1, to the vaginal cuff), the median dose delivered to the treatment field was 4,600 cGy. Of the 35 patients, 5 (14%) had grade 3 toxicity requiring a treatment break, and 3 (9%) developed late bowel complications. Median actuarial survival was 40 months, and 16 (62%) of 26 recurrences occurred in the treatment field.[53]

In a retrospective review of 41 patients treated with whole-abdominal irradiation (WAI), the 5-year actuarial survival rate in all patients was 47%. When patients were categorized according to disease size at the initiation of WAI, the 5-year disease specific survival rate was 53% for patients with tumors < 1.5 cm and 0% for patients with tumors ≥ 1.5 cm. Twelve patients (29%) did not complete therapy due to acute toxicity.[54]

Prospective, randomized data comparing salvage chemotherapy and radiation therapy are not available. The current practice at MSKCC is to reserve radiation therapy for the treatment of symptomatic isolated lesions in the salvage setting.

**Future Directions**

**New Combination Regimens**

Table 5 lists selected combination regimens that are currently used in the salvage treatment of ovarian carcinoma. Although it is impossible to compare regimens directly, no clear winner emerges when one reviews response rates, duration of response, or overall survival produced by these older agents. In addition, toxicity is generally increased with combination regimens, as compared with single agents. The noticeably higher response rates in platinum-sensitive patients is maintained (Table 5).

It is now important to begin testing doublets that include newer compounds that have nonoverlapping toxicities, different mechanisms of action, and reasonable phase II response rates as single agents. In vitro evidence of synergy, as in the case of the combination of gemcitabine and cisplatin, for example, should be exploited.[55]

Mechanistic advantages should also be considered when considering new combinations. For example, data suggest that administering a topoisomerase I inhibitor will upregulate topoisomerase II levels, thereby increasing the effectiveness of the subsequently administered agent.[56]

**Other Novel Approaches**

In addition to programs with new cytotoxic agents, other modalities have been proposed and are in varying states of development.

In the realm of gene therapy, in vitro and in vivo trials in mice have shown that ovarian cancer cells are readily transduced by recombinant adenovirus with the herpes simplex thymidine kinase gene, and will subsequently demonstrate significant cytotoxicity in the presence of ganciclovir (Cytovene). Other genes for delivery, such as the anti-erb-B2 single-chain antibody gene, are being investigated, and have shown reduced tumor burdens in xenograft models of erb-2-overexpressing ovarian carcinoma cells.

A recent review by Barnes et al summarizes currently approved gene therapy protocols in advanced or recurrent ovarian cancer.[57] Initial work has suggested a relationship between expression of the farnesyl transferase beta-subunit gene in human ovarian carcinoma and the K-ras mutation.[58] The role of farnesyl transferase and other signal transduction inhibitors in the treatment of ovarian cancer is also being explored.

Other ongoing trials are investigating immune strategies by using antibodies to a variety of targets, either alone or coupled to cytotoxic agents. At MSKCC, we are exploring the role of vaccine therapies in an active immunity approach targeted at ovarian cancer epithelial surface antigens, such as Lewis-Y.

Antiangiogenesis and antimetastatic agents are also being studied, but the effectiveness of these strategies in salvage therapy is unknown, and many may be more effective earlier in the disease course.

**Summary**

It is essential that patients with ovarian cancer receive both optimal surgical care and state-of-the-art chemotherapy in the primary treatment setting, since the salvage treatment of refractory, persistent, or recurrent epithelial ovarian cancer remains a discouraging and difficult task. Only a very small percentage of patients with platinum-sensitive, small-volume disease appear to
achieve prolonged disease-free survival. The treatment of patients with larger-volume (> 0.5-cm) disease or platinum-resistant disease remains largely palliative. The plethora of new agents has provided physicians with multiple options for salvage chemotherapy. Although cure in the salvage setting cannot be achieved currently, palliative treatment allows many of these patients to live pain-free, productive lives. New approaches with vaccines and other nonchemotherapeutic strategies are under investigation to supplement our resources. If we are to further improve the outcome of this devastating disease, the medical community will continue to depend on women with ovarian cancer for their continued selfless participation in clinical trials.

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