

# The Treatment of Epithelial Ovarian Cancer

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## Introduction

Epithelial ovarian cancer is the most common lethal malignancy of the female genital tract. In 1995 it is estimated that 26,600 new cases will be diagnosed and 14,500 deaths will occur from ovarian cancer in the United States.<sup>1</sup> Survival is directly correlated with stage, and treatment is also stage dependent. Thus, a basic understanding of the staging of ovarian cancer is essential (Table 1).

The high mortality is largely related to absence of symptoms during early-stage disease (stage I and II), with 76 percent of patients having disease discovered when it has spread beyond the ovaries to involve the abdominoperitoneal cavity, liver parenchyma, and/or pleural cavities (stage III or IV).<sup>2,3</sup> The role of early diagnosis and screening has been discussed elsewhere in this issue,<sup>4</sup> but at a recent consensus conference on ovarian cancer, the panel recommended screening only those patients with some form of hereditary ovarian cancer,<sup>5</sup> which accounts for less than 10 percent of all epithelial ovarian malignancies.<sup>6</sup>

Even within the category of early-stage disease, five-year survival ranges from 50 to 95 percent depending, in large measure, on the intactness of the ovarian

capsule and the degree of tumor differentiation and, less clearly, on treatment.<sup>7</sup> Advanced-stage ovarian cancer is responsive to multiple cytotoxic drugs. Nevertheless, less than 25 percent of these patients are alive and free of disease at the fifth year after diagnosis. This is primarily due to drug resistance, both intrinsic and acquired. Thus, there is ready justification for the intensive research that is attempting to find new drugs, identify new drug combinations, abrogate drug resistance of active agents, and increase the intensity (anticipating an increase in efficacy) of currently used drugs. In this review we will discuss current and experimental approaches to the treatment of all stages of ovarian cancer.

## Surgery and Staging For Ovarian Cancer

Ovarian cancer requires an exploratory laparotomy at the time of presentation for diagnosis; staging; and, frequently, tumor debulking. Staging accuracy is dependent on how aggressively the surgeon looks for disease. Ovarian cancer frequently spreads to the upper abdomen, forming implants on Glisson's capsule and the diaphragm. Spread into retroperitoneal lymph nodes is also common, especially nodes in the paraortic chain. In a study by Young of 100 patients referred for treatment of early-stage ovarian cancer, 24 percent were found to have upper abdominal disease at re-exploration laparoscopy or laparotomy, and 75 percent

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of the patients were referred with an incision that did not allow adequate evaluation of the upper abdomen.<sup>8</sup> McGowan et al reported that 52 percent of patients evaluated by general obstetricians and gynecologists and only 35 percent of patients operated by general surgeons were adequately evaluated compared with 97 percent of patients operated by gynecologic oncologists.<sup>9</sup> More recently the effect on outcome of the primary surgeon was demonstrated in a study by Nguyen et al<sup>10</sup> where a survey of 12,316 patients from 904 hospitals revealed inferior survival in all patients except those with stage I disease when primary surgery was carried out by a general surgeon compared with a gynecologic oncologist or obstetrician-gynecologist ( $P < .004$ ).

Once a diagnosis is made, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial omentectomy

### Management of Early Ovarian Cancer

Because only 20 to 25 percent of women with ovarian cancer present with early-stage disease, clinical research in this area has been very cumbersome due to low patient numbers. Additionally, many of these patients typically present with premenopausal adnexal masses, are operated by nongynecologic oncologists, and are not offered protocol therapy.

Patients with stage I and II ovarian cancer comprise a diverse group of patients with quite variable prognosis depending on stage, grade, intactness of the ovarian capsule, and presence of ascites. Despite investigations in this area over the past three decades, many questions remain unanswered for four major reasons. Some studies included patients with borderline tumors (with very good prog-

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are usually performed along with a careful examination of all serosal surfaces, biopsies of grossly involved areas, and a collection of ascites or peritoneal washings for cytologic studies. Appropriate removal of large tumor masses is also associated with improved survival, especially when the largest residual is 1 cm or less. This will be discussed in more detail later. If the disease appears to be limited to the ovary or if all intraperitoneal macroscopic disease can be resected, the retroperitoneal lymph nodes are also examined, because evidence of lymphatic involvement alters the stage and postoperative treatment approach. Also important in the early-stage patient is assessment of upper abdominal tumor by cytologic washings from diaphragm and Glisson's capsule.<sup>11-14</sup>

nosis), leading to possible overestimation of outcome. Some studies lacked rigid staging (particularly of the upper abdomen and retroperitoneal nodes), resulting in possible inclusion of cryptic stage III patients and underestimation of outcome. Some studies lacked control arms, raising questions about the actual value of any therapeutic approach. Finally, many studies had small sample sizes, resulting in low statistical power of any observed differences in therapy. Currently, the approach to treatment of early-stage disease focuses on which prognostic variables identify patients where risk of relapse after primary surgery is great enough to recommend no therapy and what is the most-effective, least-toxic therapy, if any, that should be used for high-risk patients.

**Table 1**  
**FIGO Staging of Ovarian Cancer**

<b>Stage I</b>	Growth limited to ovaries
Stage IA	Growth limited to one ovary; no ascites. No tumor on external surfaces; capsule intact
Stage IB	Growth limited to both ovaries; no ascites. No tumor on external surfaces; capsule intact
Stage IC	Stage IA or IB with tumor on surface of one or both ovaries; or capsule ruptured; or malignant ascites present or malignant washings present
<b>Stage II</b>	Growth involving one or both ovaries with extension to pelvic structures
Stage IIA	Extension and/or metastases to uterus and/or tubes
Stage IIB	Extension to other pelvic structures
Stage IIC	Stage IIA or IIB with tumor on surface of one or both ovaries; or capsule ruptured; or malignant ascites present or malignant washings present
<b>Stage III</b>	Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal nodes
Stage IIIA	Tumor macroscopically confined to the pelvis and negative retroperitoneal nodes with microscopic disease in the abdomen except liver parenchyma
Stage IIIB	Tumor macroscopically involving the abdomen but no single nodule measuring greater than 2 cm. Nodes are negative
Stage IIIC	Abdominal implants greater than 2 cm or retroperitoneal or inguinal node involvement
<b>Stage IV</b>	Extra-abdominal disease or parenchymal liver disease. Pleural effusions must be cytologically positive to assign this stage

FIGO = International Federation of Gynecology and Obstetrics

The first study of the Gynecologic Oncology Group (GOG) focused on patients with stage I disease.<sup>15</sup> Eighty-six patients were randomized to observation, pelvic irradiation to 55 Gy, or 18 months of melphalan (0.2 mg/kg daily for five days every 28 days). No difference in survival was noted among the three arms. The group receiving radiation therapy had the poorest outcome, and the group receiving chronic chemotherapy did significantly better than the other two groups combined. This study, conducted in the early 1970s, has been criticized for its lack of uniform staging criteria and because many of the patients were ultimately excluded from evaluation because of protocol violations (particularly in the radiation arm). The most important findings from this study were higher relapse rates for patients with poorly differentiated (grade 3) tumors and a relatively good prognosis for patients with low-grade tumors confined to the ovary (greater than 90 percent disease-free survival at five years).

A subsequent GOG study confirmed the importance of both grade and stage in identifying patients who do not require additional postoperative therapy.<sup>16</sup> Eighty-one patients with grade 1 or 2, stage IA or IB tumors were randomized to observation or 12 cycles of melphalan (0.2 mg/kg daily for five days every four to six weeks for 12 cycles). All patients in this study underwent rigorous surgical staging. The actuarial five-year, disease-free survival for patients on both arms of the study was greater than 90 percent, and the conclusion was that surgery alone was adequate therapy for this group of patients, particularly if one considers the three deaths from alkylating-agent-induced acute nonlymphocytic leukemia in the treatment arm.

Another nonrandomized study conducted in Italy reported a disease-free survival of greater than 94 percent at three years and disease-free survival of 90 percent at five years when women with

stage IA and IB disease were followed without treatment,<sup>17</sup> further demonstrating the inherent good prognosis of low-stage/low-grade ovarian cancer. Contemporary studies have generally excluded these low-risk patients from therapeutic trials due to their inherently good prognosis.

One multivariate analysis of prognostic variables revealed residual disease and high grade to be the most negative prognostic variables, followed by increasing stage, increasing age, and certain histologic types (clear cell and solid adenocarcinoma).<sup>18</sup> Another comprehensive analysis of prognostic factors in stage I patients found grade followed by dense adhesions and large-volume ascites to be powerful predictors of relapse and poor prognosis.<sup>19</sup>

In more advanced early-stage disease (stage IA or IB/grade 3, stage IC, or stage II/all grades), a recent Ovarian Can-

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cer Study Group and GOG collaborative trial<sup>16</sup> compared oral melphalan (0.2 mg/kg every day for five days every four to six weeks for 12 cycles) and intraperitoneal <sup>32</sup>P (15 mCi as a single application). Both arms had a similar disease-free survival and overall survival of 80 percent, but this study included a number of borderline tumors (17 percent). Exclusion of these patients from both arms reduces the survivals to 76 percent without significant differences between the two arms. As mentioned previously the risk of leukemia related to melphalan favored use of intraperitoneal <sup>32</sup>P therapy.

For the past two decades, cisplatin has been considered the most active drug against advanced epithelial ovarian can-

cer and therefore potentially useful in the adjuvant setting. Only recently has it been used in this setting. In a study from the Norwegian Radium Hospital, 347 patients with completely resected stage I to stage III disease of any grade were randomized to six cycles of intravenous cisplatin (50 mg/m<sup>2</sup> every three weeks) or intraperitoneal <sup>32</sup>P (7 to 10 mCi).<sup>20</sup> Seventeen percent of patients randomized to <sup>32</sup>P received whole abdominal irradiation instead because of extensive peritoneal adhesions. Five-year, disease-free survival (75 percent for cisplatin and 83 percent for <sup>32</sup>P) and overall survival (81 percent for cisplatin and 83 percent for <sup>32</sup>P) were not significantly different. Because significantly more late bowel complications were seen in the <sup>32</sup>P arm, the authors recommended cisplatin as standard therapy for future studies. Noteworthy is the observation that most of the late bowel complications were in patients treated with whole abdominal irradiation due to technical difficulties with administration of intraperitoneal <sup>32</sup>P.

Studies from the Princess Margaret Hospital have attempted to define the role of external-beam radiation therapy

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given to the whole abdomen in patients with early-stage disease. One study in stage I patients showed that adjuvant pelvic irradiation decreased pelvic relapses without significant impact on survival.<sup>21</sup> Another study<sup>22</sup> randomized patients with stage IB, II, and asymptomatic and primarily completely resected stage III disease to pelvic irradiation (50 Gy), pelvic irradiation plus chlorambucil (6 mg per day for two years), or pelvic irradiation plus whole abdominal irradiation.

An analysis of 132 completely resected patients showed a survival of 78 percent for patients receiving pelvic irradiation plus whole abdominal irradiation compared with 51 percent for the other two arms combined. This study had several problems, including the fact that patients were inadequately staged, patients with residual disease were included (in whom there was no benefit for pelvic irradiation plus whole abdominal irradiation), and the chemotherapy used in the adjuvant setting was inadequate to control unirradiated disease.

Conversely, a Danish study<sup>23</sup> compared whole abdominal irradiation with pelvic irradiation plus cyclophosphamide (200 mg/m<sup>2</sup>/day for five days every 28 days for 12 cycles). This study included stage IB, IC, and II disease, and meticulous surgical staging was performed. No significant difference was found in disease-free survival (55 percent) or overall survival (63 percent) between the two arms at four years. This study failed to confirm the superiority of whole abdominal irradiation over pelvic irradiation plus chemotherapy for preventing relapse in early-stage patients.

Similarly, another study by National Cancer Institute of Canada<sup>24</sup> comparing whole abdominal irradiation, melphalan, and intraperitoneal <sup>32</sup>P in patients initially treated with pelvic irradiation did not report any significant difference in overall survival between the whole abdominal irradiation and melphalan (<sup>32</sup>P stopped early due to excessive toxicity) with disease-free survival favoring patients receiving melphalan (P=.015). This study included patients with stage IB and any IC, II, and IIIA and IIIB disease confined to the pelvis.

Because, historically, women with high-risk stage I and II disease have had relapse rates of 35 to 60 percent after surgery alone,<sup>25,26</sup> investigators have been reluctant to include an observation arm in adjuvant studies. Therefore, while comparisons are often made between non-

prospective adjuvant therapies for low-stage, high-risk patients, the overall contribution to survival of any of these therapies remains unproved without prospective comparison to surgery alone.

One interesting study partially addressed this issue. An Italian group<sup>27</sup> randomized moderately and poorly differentiated stage IA and IB patients (n=90) to cisplatin (50 mg/m<sup>2</sup> intravenously every 28 days for six cycles) or observation. Those patients with poorly differentiated lesions would not have been included in a no-treatment control arm in the United States. Five-year, disease-free survival was 85 percent in both arms. Stage IC patients (n=182) were randomly allocated to cisplatin as above or a single treatment with intraperitoneal <sup>32</sup>P. Five-year, disease-free survival was 82 percent in the cisplatin arm and 70 percent in the <sup>32</sup>P arm (P=.006), suggesting that cisplatin may be superior to the current standard for this group in the United States (i.e., <sup>32</sup>P). Survival data are not significantly different.

Conversely, however, a Norwegian study<sup>28</sup> suggests that cisplatin is no better than <sup>32</sup>P. In that study 340 patients (stage

In summary, good-risk patients, that is, patients with stage IA and IB who have well or moderately differentiated cancers, should be treated with surgery alone. For stage IA and IB poorly differentiated tumors and stage IC and stage II disease of any grade that have a high risk of relapse, postoperative adjuvant chemotherapy<sup>29</sup> should be considered although the benefit of such therapy is not proven. Ideally, these patients should be entered into clinical trials designed to assess the impact of treatment on survival and to assess the toxicity of specific regimens. When a decision is made to treat a patient outside of a clinical trial, a regimen with the lowest potential for late toxicity should be selected because the inherently good survival of these patients puts them at risk for such toxicity.

### **Treatment of Advanced-Stage Disease**

Current trials in advanced ovarian cancer usually subdivide stage III patients by the amount of postoperative residual disease that is prognostic for outcome in multiple studies and multivariate analyses per-

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*For the past 20 years, cisplatin has been considered the most active drug against advanced epithelial ovarian cancer.*

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I to IIIA) were randomly assigned to cisplatin or <sup>32</sup>P as above. With five years of median follow-up, there are no differences in either group with survival of 85 percent in both. These authors concluded that future studies in early ovarian cancer should have a control group.

The current GOG study of high-risk patients compares either a single dose of <sup>32</sup>P or three cycles of high-dose cyclophosphamide and cisplatin (1,000 mg/m<sup>2</sup> and 100 mg/m<sup>2</sup>, respectively). The results of that study are too immature for analysis.

formed on large populations.<sup>30</sup> Although it has not been proven in randomized trials that "debulking" improves survival, there is significant evidence that patients with low-volume disease at the end of surgery have better outcomes than those with high-volume disease. How much surgical expertise compares with biologic characteristics of the tumor in allowing for optimal debulking is a matter of continued debate. Additional factors found to be favorable prognostically for outcome include low tumor grade,<sup>31</sup> younger

age, good performance status, absence of ascites, cell type other than mucinous or clear cell, and treatment with cisplatin.<sup>32-34</sup>

Contemporary studies use residual mass size of 1 cm as the breakpoint between optimally and suboptimally cytoreduced patients within stage III, while studies prior to 1985 usually used 2 to 3 cm as a breakpoint. This fact and any effect it may have on outcome must be considered when attempting to compare studies. By definition, patients with optimally debulked stage III disease rarely have measurable tumor at the completion of staging laparotomy. With the exception of the occasional patient who progresses during therapy, determination of response is currently dependent on second-look laparotomy, although there re-

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***Patients with stage IA and IB well or moderately differentiated cancers should be treated with surgery alone.***

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mains significant controversy regarding its value outside a research study.<sup>30,35</sup> Interested readers are referred to a recent discussion of this topic.<sup>36</sup> Nevertheless, as in most tumors, it is the attainment of a pathologic complete response that generates "cures" in advanced ovarian cancer. Patients with persistent disease following primary therapy are rarely alive three years later. Other endpoints of treatment efficacy have been used, e.g., progression-free survival or survival, but these endpoints are variably influenced by salvage therapies (particularly as more effective salvage therapies have been developed recently). Whether salvage therapy has an impact on survival and a detailed discussion of what constitutes acceptable salvage therapy are beyond the scope of this article.

#### SINGLE-AGENT CHEMOTHERAPY FOR ADVANCED OVARIAN CANCER

Ovarian cancer is highly sensitive to chemotherapy, and single agents active in ovarian cancer include classic alkylating agents (most commonly cyclophosphamide, melphalan, and chlorambucil), the platinum coordination compounds (cisplatin and carboplatin), anthracyclines (doxorubicin, epirubicin, and mitoxantrone), etoposide, hexamethylmelamine, mitomycin C, methotrexate, 5-fluorouracil, and the taxanes (paclitaxel and taxotere). Tamoxifen and progestational agents have a low level of activity in patients with detectable cytoplasmic steroid receptors.<sup>37</sup> This subject has been reviewed extensively in the recent past.<sup>38,39</sup>

#### COMBINATION THERAPY FOR OVARIAN CANCER

The past two decades of research have reasonably established that cisplatin-based combination therapy is more effective than single-agent alkylating agents<sup>40</sup> or combinations without cisplatin.<sup>41,42</sup> This improved efficacy, however, applies only to response rates and, possibly, disease-free survival because no large impact on survival has been noted. This may be due to the frequent use of platinum compounds as salvage therapy in patients failing nonplatinum regimens. It is clear that some 30 to 40 percent of patients with disease refractory to standard alkylating agents will respond to cisplatin, often for long periods with prolongation of survival. When alkylating agents or nonplatinum combinations were used in advanced ovarian cancer, the anticipated response rate was, on average, 40 percent (complete pathologic response of 10 to 20 percent) with median survivals of 12 to 15 months. Frequently, such studies did not subdivide patients by postoperative tumor bulk, making it somewhat difficult to compare those results with more contemporary ones in which platinum com-

pounds are incorporated into primary therapy.

In the era of primary therapy with cisplatin combinations, the response rates have generally risen to 70 to 80 percent (complete pathologic response of 20 to 50 percent) with the greatest activity noted in those patients who were optimally cytoreduced.<sup>43</sup> A recent retrospective study from the Netherlands found that patients diagnosed with ovarian cancer between 1981 and 1985 had better survival than a similar group of patients diagnosed between 1975 and 1980. The two major reasons proposed for this finding were the more routine use of aggressive surgical cytoreduction and cisplatin-based therapy, thus further suggesting that incorporation of cisplatin into initial therapy may have also improved survival, although no single small study demonstrates this convincingly.<sup>44</sup>

To date there has also not been a definitive prospective study comparing cisplatin as a single agent with a cisplatin-containing combination in advanced ovarian cancer. Some investigators argue that single-agent cisplatin or carboplatin alone is just as effective as platinum-based combinations, has less toxicity, and is less likely to lead to secondary tumors. Nevertheless, a recent meta-analysis of more than 8,000 cases of advanced ovarian cancer (greater than 6,500 deaths) suggested very strongly that platinum-containing combinations were statistically superior to single-agent cisplatin.<sup>45</sup>

#### THE ROLE OF CARBOPLATIN

Many studies suggest that carboplatin can be substituted for cisplatin in combination regimens with equivalent end results<sup>46-48</sup> and that both agents are equivalently active as single agents.<sup>49</sup> Carboplatin is much easier to administer (outpatient without hydration) and appears to have less gastrointestinal toxicity. It is also devoid of renal and neurologic ad-

verse effects in clinically relevant doses. The dose-limiting toxicity is myelosuppression, especially thrombocytopenia. Equivalent efficacy, however, is predicated on maintaining an adequate dose of carboplatin. Because both carboplatin and alkylating agents have dose-limiting hematologic toxicity, there is a temptation to reduce carboplatin dose (and subsequent efficacy) when toxicity occurs.<sup>50</sup> This outcome was demonstrated when a group at the Mayo Clinic treated patients with high-dose cyclophosphamide (1,000 mg/m<sup>2</sup>), necessitating reduction of the carboplatin dose to 150 mg/m<sup>2</sup>. Their results with this combination were significantly inferior to cisplatin and cyclophosphamide (60 mg/m<sup>2</sup> and 1,000 mg/m<sup>2</sup>, respectively).<sup>51</sup>

There are now several studies in which carboplatin has been substituted for cisplatin in various combination regimens in the treatment of ovarian cancer, with only the Mayo study showing results with carboplatin that were clearly inferior to those with cisplatin. Nevertheless, a recent long-term follow-up of data from the Netherlands comparing cisplatin-based and carboplatin-based combination therapy demonstrated a survival advantage favoring use of cisplatin in those patients who started with low-volume disease.<sup>52</sup> This effect was not appreciated until the fourth posttreatment year, demonstrating the real need for long-term follow-up in such studies.

#### SALVAGE CHEMOTHERAPY

Treatment of platinum-resistant tumors remained ineffective after platinum coordination complexes were incorporated into primary therapy. The most active agents, hexamethylmelamine, etoposide, ifosfamide, fluorouracil, and doxorubicin, have response rates of 15 to 25 percent in an unselected population, but when cisplatin-resistant patients are evaluated, the response rates are typically in the range of 12 to 15 percent with brief dura-

tion and questionable impact on survival. Furthermore, cisplatin-resistant patients respond poorly to salvage therapy with cisplatin or carboplatin. This topic has been extensively reviewed recently.<sup>53</sup>

#### DOSE INTENSITY

Although retrospective analysis suggested a steep dose-response relationship between platinum coordination complexes and ovarian cancer,<sup>54</sup> clinical results are conflicting. A Scottish study<sup>55</sup> showed improved outcome when higher-dose therapy was used, while two other studies<sup>56,57</sup> were unable to verify this finding. A recent, unpublished update of the Scottish study has shown the apparent benefit of the high-dose therapy to be disappearing as data mature. Thus, dose-intense chemotherapy including very high-dose therapy and autologous bone marrow

The effect on long-term survival is unknown. A nationwide study is currently comparing primary therapy with cyclophosphamide and cisplatin in optimally cytoreduced stage III patients where randomization is to intravenous or intraperitoneal cisplatin. The results of that study are too immature for reporting, but unless there is some benefit in this "good prognosis" group of patients, it is unlikely that intraperitoneal approaches will be continued because they are associated with significant technical difficulties.

#### PACLITAXEL-BASED CHEMOTHERAPY

Paclitaxel, a unique antimicrotubule agent, has emerged as the most active agent since cisplatin for patients with ovarian cancer,<sup>59,60</sup> with an overall response rate of 30 percent in previously treated patients, equivalent to cisplatin

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***Dose-intense chemotherapy including very high-dose therapy and autologous bone marrow transplantation must be considered experimental.***

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transplantation must be considered experimental at present.

#### INTRAPERITONEAL CHEMOTHERAPY

For the past decade, intraperitoneal chemotherapy has been evaluated in patients with advanced ovarian cancer. To date there are no published prospective, randomized studies to clearly identify the role of intraperitoneal therapy as part of primary therapy. The role of intraperitoneal chemotherapy in the salvage setting has been reviewed recently.<sup>58</sup> At best this technique is applicable to a small subset of patients with microscopic disease or very small (less than 0.5 cm) macroscopic disease, where third-look laparotomy demonstrates complete pathologic response in some 30 percent of patients.

when it was first tested in the phase II setting<sup>61</sup> a decade ago. Response rates for other salvage agents, including all drugs evaluated in the last 17 published GOG phase II trials, have been no greater than 20 percent. In the setting of these dismal results, the development of paclitaxel, the first of a new class of antineoplastic agents, has been associated with significant optimism.

Paclitaxel is a natural product isolated from the bark of the Pacific yew, *Taxus brevifolia*, but it can now be semi-synthesized. It promotes the assembly and stabilization of microtubules, thus working on the mitotic spindle in a unique way different from the vinca alkaloids or the podophyllotoxins. This topic has been extensively reviewed recently for those interested in a more detailed

**Table 2**  
**Outcome in 100 Hypothetical Consecutive Patients**  
**With Ovarian Cancer**

Stage/Grade	Number of Patients	Primary Therapy	Salvage Therapy	Expected Five-Year Survival (No. of patients)
I/1 and 2	5	None	Chemotherapy	5
I/3	15	<sup>32</sup> P/Cisplatin/None	Chemotherapy	13
II/All	5	<sup>32</sup> P/Cisplatin/None	Chemotherapy	3
III Optimal/All	25	Cisplatin or Carboplatin and Cytoxan or Taxol	Investigational	10
III Suboptimal/All	35	Cisplatin or Carboplatin and Taxol	Investigational	4
IV/All	15	Cisplatin or Carboplatin and Taxol	Investigational	1
				36

discussion of preclinical data.<sup>62</sup>

Paclitaxel was first identified as an active agent in a phase II study from Johns Hopkins where 47 women with advanced epithelial ovarian cancer received paclitaxel.<sup>60</sup> Starting doses were 200 or 250 mg/m<sup>2</sup>, but these were reduced over the course of the study in this group of heavily pretreated patients due to severe myelosuppression. All patients had received prior cisplatin, and 25 of the 40 patients evaluable for response had platinum-resistant disease. The dose-limiting toxicity was myelosuppression, with 40 of 41 experiencing at least one episode of grade IV neutropenia. Other toxicities included peripheral neuropathy, alopecia, mucositis, arthralgias, and myalgias. There were 12 responses (30 percent), including one pathologic complete response, and the activity in platinum-resistant disease was nearly as great as in

platinum-sensitive disease. Additional phase II studies followed and confirmed this level of activity.<sup>59,63</sup>

The demand for paclitaxel in the salvage setting prior to drug approval by the Food and Drug Administration led the NCI to sponsor the Treatment Referral Center Protocol.<sup>64</sup> This large study again demonstrated the activity of paclitaxel and verified the safety of the drug when administered in multiple hospital settings with variable experience with the drug.

The observation that the dose-limiting toxicity of paclitaxel in these early studies was neutropenia led investigators at the NCI to study dose escalation with hematopoietic growth factor support. Those studies have demonstrated that doses of 250 mg/m<sup>2</sup> can be given with granulocyte colony-stimulating factor support,<sup>65</sup> with dose-limiting toxicity becoming a stocking-and-glove sensory pe-

ripheral neuropathy associated with impaired proprioception and abnormal nerve conduction. Because of these results, 47 women with recurrent disease were treated at the 250 mg/m<sup>2</sup> dose level in a subsequent phase II trial.<sup>66</sup> More than 75 percent of the patients in this study had received two or more prior regimens, and 89 percent were platinum resistant.<sup>67</sup> The authors observed a response rate of 48 percent, higher than that seen in prior studies in similar patient populations, although survival was not clearly better than in studies using lower doses of paclitaxel.

In addition to the role of dose intensity, the optimal schedule of paclitaxel administration has been explored. A study coordinated by the National Cancer Insti-

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***Paclitaxel has emerged as the most active agent since cisplatin for patients with ovarian cancer.***

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tute of Canada Clinical Trials Group randomized 407 patients treated with one or two prior regimens to one of two doses of paclitaxel (135 or 175 mg/m<sup>2</sup>) by one of two schedules (three- or 24-hour infusions).<sup>68</sup> The overall incidence of hypersensitivity reactions was 1.3 percent and not significantly different between the four groups. Neutropenia was significantly more common with the 24-hour infusion. The overall response rate for 382 evaluable patients was 17 percent with no significant differences between treatment arms. Although a modest prolongation of progression-free survival was noted in women receiving 175 mg/m<sup>2</sup> (amounting to a five-week delay in time to progression, P=.02), no differences in median or overall survival were seen. It appears, therefore, that paclitaxel can be administered as a short infusion on an outpatient

basis with equal safety and efficacy compared with prolonged infusions in the salvage setting.

The excellent response rates seen with paclitaxel as a salvage agent, particularly in patients with platinum-resistant disease, have spurred investigators to explore its use in primary therapy. The observation that paclitaxel can be successfully combined with cisplatin<sup>69</sup> generated a GOG trial in which 394 patients with suboptimally debulked disease were randomized to cisplatin plus paclitaxel (75 mg/m<sup>2</sup> and 135 mg/m<sup>2</sup> every three weeks for six cycles) or cisplatin plus cyclophosphamide (75 mg/m<sup>2</sup> and 750 mg/m<sup>2</sup> every three weeks for six cycles). At an interim analysis,<sup>55</sup> response rates in 209 evaluable patients were significantly higher in the cisplatin and paclitaxel group (77 percent versus 64 percent for cyclophosphamide, P=.02). A trend was also noted toward more negative second-look laparotomies in the paclitaxel group (26 percent versus 19 percent for cyclophosphamide, P=.08) and no evidence of macroscopic disease in the paclitaxel group (40 percent versus 22 percent for cyclophosphamide, P<.001). There was also a reduction by 33 percent in the relative risk of progression or death in a unit of time for the paclitaxel group as compared with the cyclophosphamide group (similar to or better than what cisplatin accomplished in this population two decades ago).

Paclitaxel and one of the platinum coordination complexes has now been accepted by most in the United States as the new standard of care for advanced ovarian cancer, though trials to replicate the above study are just beginning. Further, the role of paclitaxel in earlier disease and whether paclitaxel and carboplatin will be equivalent to paclitaxel and cisplatin remain to be determined by ongoing trials. Additionally, further study of the proper dose and schedule of paclitaxel administration continues.

The role of paclitaxel in the management of epithelial ovarian cancer contin-

ues to evolve. In the salvage setting, patients with disease progression more than six months after responding to a cisplatin-containing regimen should be retreated with a platinum compound because they may still be platinum sensitive. Paclitaxel is the most active agent in platinum-resistant disease and should be considered first-line salvage therapy in this population. In the salvage setting, three-hour infusions appear as safe and effective as 24-hour infusions. Until the mature results of ongoing clinical trials are available, the use of more expensive and potentially more toxic high-dose, paclitaxel-containing regimens with growth factor support should be reserved for patients entering clinical trials of this approach in primary therapy, because it has not been shown to improve survival in the salvage setting and is costly and more toxic. Paclitaxel plus cisplatin is more active than cyclophosphamide plus cisplatin as primary therapy for women with suboptimal disease. Ongoing clinical trials should define the role of paclitaxel in optimal disease.

It is certainly hoped that paclitaxel with its significant activity will translate into further long-term survival benefit for all patients with invasive ovarian cancer. The next decade of research should answer that question.

Other investigational drugs have already been identified with some significant activity in ovarian cancer, including topotecan,<sup>70</sup> gemcitabine,<sup>71</sup> and pyrazolo-

acridine. These and other agents need to be evaluated in combination in advanced ovarian cancer, as well, in the next decade, which may further complicate the evaluation of paclitaxel. This is a rather happy state of affairs, however, because never before have so many agents been available to tackle this difficult disease.

## Conclusion

The next decade holds great promise for the treatment of ovarian cancer due to the identification of paclitaxel as an active agent that appears to improve survival when combined with cisplatin. Additionally, with the plethora of new agents that appear in early clinical trials to have activity in ovarian cancer, it is our hope that we will, in fact, be able to improve cure rates in this disease. Whether that promise is met will depend largely on the proper design of and accrual to important clinical trials. All oncologists are encouraged to submit their patients to these studies.

Table 2 summarizes the current approach to ovarian cancer by looking generically at treatment and outcome in 100 hypothetical patients based on incidence and expected outcome. It is hoped that the overall five-year survival of 36 percent will improve in the next decade as we learn how better to use old drugs and incorporate the plethora of new ones entering clinical trials. CA

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