Epithelial Ovarian Cancer: Treatment Has Improved, But Not Enough

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With an estimated 19,000 new cases in 1987, ovarian cancer is now the second most common malignant disease of the genital tract of women in this country. About 1.4% or one of every 70 newborn girls will develop ovarian cancer during her lifetime. According to the American Cancer Society’s estimate, 11,700 women died as a result of ovarian cancer last year.

Epithelial ovarian cancer, the most common type, accounts for 85% of ovarian malignant tumors. Unfortunately, by the time it is diagnosed, about 75% of patients already have advanced disease with ascites and metastases in the upper abdomen.

Identify Tumor Markers

Although much valuable research has been done in the last two decades to identify tumor markers for this cancer, the ideal tumor marker is far from a reality. The potential benefits of having such a marker include the ability to detect the disease early in its course and to distinguish benign from malignant tumors before operations, to distinguish ovarian cancer from other cancers that have similar manifestations, monitor patients’ response during therapy and the maintenance of remission afterward, and possibly to replace second-look laparotomy in the standard management of this disease.

So far, the most promising serum tumor marker for epithelial ovarian cancer is CA-125, a murine monoclonal antibody that was raised against an epithelial ovarian cancer cell line and that binds to its antigen. A CA-125 marker is currently being used to monitor response in ovarian cancer patients undergoing therapy and to diagnose recurrence in patients after completion of therapy; it is also being studied as an alternative to second-look laparotomy. Unfortunately, CA-125 is not specific to epithelial ovarian cancer; it can be elevated in early pregnancy and a variety of benign diseases, including liver disease, acute pancreatitis, peritonitis, renal failure, endometriosis, and pelvic inflammatory disease. Furthermore, elevated CA-125 levels have been noted in other gynecologic cancers such as adenocarcinomas of the endometrium, endocervix, and fallopian tube, as well as nongynecologic cancers of the pancreas, colon, breast, and lung. Ultimately, ovarian cancer will probably be detected with a panel of monoclonal antibodies rather than a single one. Then, after a reliable preoperative diagnosis, patients who have the disease could be referred to gynecologic oncologists trained in aggressive cytoreductive surgical techniques.
Surgical Intervention Still Most Important

Surgery remains the cornerstone of epithelial ovarian cancer management. Primary surgical intervention enables physicians to confirm the diagnosis; determine the extent of disease precisely—that is, stage it—and perform maximum cytoreductive surgery in patients with advanced disease.

A meticulous, methodical approach is particularly critical for detecting occult or microscopic metastasis in patients with apparent early disease. Proper staging procedures include an adequate vertical midline incision, cytologic analysis of ascites or cytologic washings of the pelvis and bilateral paracolic gutters, and thorough inspection and palpation of all intraperitoneal contents. In addition to resection of the primary tumors, if the disease seems to be confined to one or both ovaries, the structures at risk—including the omentum and peritoneal surfaces of the pelvis and upper abdomen and the paraaortic and bilateral pelvic lymph-node-bearing areas—should be examined by random staging biopsies. Lymph nodes are involved more commonly in epithelial tumors than was previously thought, and several reports have documented occult metastasis in apparent stages I and II disease. Of all patients with so-called early ovarian cancer referred to major medical centers, about one-third are found by reexploration or other types of careful study to have more advanced disease.

Patients who complete initial surgery with minimal residual disease (2 cm or less) have a much greater chance of cure than patients who still have bulky disease after initial surgery. Cytoreductive surgery may, in addition to resection of the pelvic organs, include radical resection of the omentum, small-intestinal resection in about 10% of patients, and resection of the rectosigmoid colon in up to 30% of patients. When normal tissue planes in the pelvis are obliterated by tumor infiltration, a retroperitoneal approach avoids injuring the ureters and iliac vessels.

Although optimal cytoreductive surgery is possible in about 75% of patients, conservative surgery, that is, unilateral salpingo-oophorectomy, may be appropriate for young patients who want to have children and in whom the disease is apparently confined to one ovary; this is so especially for patients with borderline or other low-grade tumors. But even if a patient has bilateral tumors, hysterectomy is not always necessary. Preserving the uterus of a young patient undergoing bilateral salpingo-oophorectomy may enable the patient to undergo in vitro fertilization with donor oocytes, if she and her family so desire.

Postoperative Radiotherapy

Postoperative treatment in patients with epithelial ovarian cancer may be done with radioisotopes, external radiotherapy, and chemotherapy. The radiotherapy studies reported in the literature suffer from the same sorts of problems that plagued many early studies of ovarian cancer patients—poor study design, inadequate surgical staging, lack of uniform histologic analysis, and not the best statistical methods. Nevertheless, current evidence suggests that radiotherapy, if it has any role in primary postoperative therapy, is effective only in patients with minimal residual disease.

Interest in radiotherapy as part of multimodality treatment has grown recently, with abdominopelvic irradiation administered to patients who were found to have minimal persistent disease at second-look laparotomy, after primary cytoreductive surgery and combination chemotherapy. Preliminary results of these studies suggested, however, that these patients found radiotherapy difficult to tolerate because of myelosuppression, and that it resulted in a low salvage rate and in many patients injury of the small intestine. We are completing a study of the usefulness of radiotherapy in patients whose microscopic residual disease was discovered at second-look laparotomy after combination chemotherapy.

Chemotherapy: Some Progress

For most patients with epithelial ovarian cancer, the postoperative therapy is chemotherapy. Earlier, this involved single alkylating agents but by the mid-1970s changed to combination chemotherapy, when new active agents such as doxorubicin, hexamethylmelamine, and cisplatin were tested in clinical trials. In the last decade, some critical issues concerning combination chemotherapy have been at least partially resolved. Although the superiority of combination chemotherapy over single-agent therapy is still somewhat controversial, I believe that existing evidence favors the combination. In patients with advanced ovarian cancer, response rates to combination chemotherapy approximate 50% to 60%, and median survival periods range from 25 to 32 months. Many clinical trials have yet to produce mature data, but early results suggest that the five-year survival rates for patients with advanced disease treated with the best available combination chemotherapy are no better than 20% to 25%. 
Along the way, however, therapeutic methods have been refined in a number of ways. Despite some evidence to the contrary, most experts agree that cisplatin should be one of the major components of any combination chemotherapy regimen for this disease. Furthermore, accumulating evidence shows that two-drug regimens are much less toxic and just as efficacious as three- and four-drug regimens. When first introduced, combination chemotherapy was administered for 12 cycles, or one year. Current information suggests that a maximum of six to nine cycles is best for these patients. Now we also have much better antiemetic agents, including steroids and metoclopramide. Current standard postoperative chemotherapy for patients with epithelial ovarian cancer at UTMDAH includes the regimen of cisplatin and cyclophosphamide for six cycles, then second-look laparotomy.

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**Intraperitoneal Chemotherapy**

Dissatisfied with the ultimate results of combination chemotherapy, physicians and researchers have undertaken some new approaches, one of which is a new version of intraperitoneal chemotherapy. This method has been used in treatment of ovarian cancer since the 1950s but lost popularity as newer, more effective systemic chemotherapeutic agents were discovered. Intraperitoneal chemotherapy has several hypothetical advantages: (1) ovarian cancer is primarily confined to the peritoneal cavity; (2) most active agents against ovarian cancer can be safely infused into the peritoneal cavity; and (3) whereas the method achieves a drug concentration in the peritoneal cavity much higher than is achieved by systemic administration, drug levels in the systemic circulation are equal or lower, thereby allowing for free-surface diffusion of the drug as well as capillary flow. Indeed, there is now ample evidence that very high drug concentrations can be achieved in the peritoneal cavity along with acceptable systemic toxicity.

The rebirth of intraperitoneal chemotherapy was accompanied by two major advances in drug delivery. First, we now know that uniform distribution of drug in the peritoneal cavity requires large volumes of fluid. Second, safe and effective drug delivery systems were devised, including the Tenckoff catheter and Port-a-Cath. Yet these technical and pharmacologic advances do not necessarily translate into therapeutic advantages. Preliminary results suggest that intraperitoneal chemotherapy may be effective for some patients whose residual disease is minimal after remission induction with systemic chemotherapy. We hope that current clinical trials will elucidate the role of intraperitoneal chemotherapy in patients with minimal residual disease, the efficacy of multiagent intraperitoneal chemotherapy, and the role of intraperitoneal chemotherapy in previously untreated patients. In the meantime, this treatment remains experimental.

**High-Dosage Chemotherapy**

High-dosage or intensification chemotherapy to circumvent the problem of multidrug resistance is another area of exploration. The use of high-dose cisplatin in patients whom conventional doses of the drug failed to benefit has been reported. Unfortunately, the ototoxicity and neurotoxicity of this approach has been so prohibitive that we cannot currently recommend it. As for high doses of alkylating agents in conjunction with autologous bone marrow rescue, experience is scant. At UTMDAH, we are currently embarking on an intensification chemotherapy protocol combining etoposide, cisplatin, and cyclophosphamide with bone marrow rescue as first-line therapy for patients with bulky residual epithelial ovarian cancer.

Neurotoxicity is the major dose-limiting problem associated with cisplatin therapy. Considerable research has been done in the last few years to find an analogue of cisplatin that will have equivalent activity but less neuro- and nephrotoxicity. A number of reports documented the fact that the cisplatin analogue carboplatin is associated with much less renal, auditory, gastrointestinal, and neurological toxicity than cisplatin, but with more myelosuppression. Preliminary results suggested also that the activity of carboplatin is equivalent to that of cisplatin. Perhaps the analogue will eventually replace cisplatin in combination therapy, although results of further phase III trials will have to be evaluated with regard to its activity and myelotoxicity. The data so far indicate little non-cross-resistance between cisplatin and carboplatin.

**Biologic Response Modifiers**

Among other interesting experimental approaches is therapy with such biologic response modifiers as the interferons, recombinant interleukin 2 (IL 2) and lymphokine-activated killer (LAK) cells, and monoclonal antibodies. Preliminary data from phase I and II trials suggested that

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Hematopoiesis in Myelodysplastic Syndromes Improves with Granulocyte-Macrophage Colony-Stimulating Factor

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The myelodysplastic syndromes, a group of stem-cell disorders arising from cell maturation defects, are characterized by defective hematopoiesis in all marrow cell lineages, refractory cytopenias, functional abnormalities of mature cells, and a substantial risk of leukemic transformation. Most patients affected by these disorders are elderly, and many succumb to complications related to bone marrow failure whether the defect evolves into acute leukemia or not.

Providing effective treatment for these disorders remains a difficult problem. Most attempts to stimulate hematopoiesis with androgen hormones, steroids, and hematinc agents have been unsuccessful. Several differentiation-inducing agents including retinoids, vitamin D, and low doses of cytarabine have been used to treat these patients, with disappointing results. Toxicity has been high, the response rate low, and the survival rate not significantly higher. Palliative therapy with blood products has therefore been an essential ingredient of treatment for this disease.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a T cell-derived lymphokine with a broad range of biologic activities. The rationale for using GM-CSF in treating patients for myelodysplastic syndromes is that it stimulates hemopoietic progenitor cells to proliferate and differentiate, and it enhances the functional activities of mature cells such as neutrophils, monocytes, and eosinophils.

The recent cloning of the gene for human GM-CSF made it possible to assess the role of GM-CSF in therapy for myelodysplastic syndromes. As part of a broad phase I study of patients with cancer or bone marrow failure, or both, we administered recombinant human GM-CSF to eight patients who had myelodysplastic syndrome. The objectives were to stimulate hematopoiesis in these patients, improve their blood counts, and thus reduce their risk of infection and hemorrhage. The treatment was administered by continuous intravenous infusion daily for two weeks. After a two-week rest period, the treatment cycle was repeated.

Clinical Characteristics

Most of the patients we studied (Table 1) were advanced in age and had a poor prognosis because of excess blasts in bone marrow, chromosomal abnormality, previous exposure to chemotherapy, and the presence of other malignant conditions. Although preleukemic syndrome lasts a highly variable period of time, the presence of cytogenetic abnormalities and records of previous exposure to mutagens portended poor prognoses for these patients, including shorter survival and a higher likelihood that the disease would progress to acute leukemia. Furthermore, as the data in Table 1 show, seven of our eight patients had pancytopenia, four patients required platelet transfusions, and all needed red-cell transfusions before the GM-CSF treatment.
Hematologic Response to GM-CSF Treatment

In all patients the treatment was associated with marked increases in white blood-cell and granulocyte counts (Figure 1). The elevation in white counts seemed to be dose-dependent, with increases up to 30,000/mm$^3$ at lower doses (120 µg/m$^2$ or less) and up to 100,000/mm$^3$ at higher doses (250 µg/m$^2$ or more). Although increases in neutrophilic granulocytes were the predominant response, significant increases were observed also in eosinophils, monocytes, and lymphocytes.

In addition to a rise in white blood cells, three of the eight patients experienced multilineage responses characterized by two- to tenfold increases in platelet counts and responses in red cells that freed two of the three patients from red-cell and platelet transfusions for 20 and 40 weeks, respectively.

Other Clinical Benefits

Among the clinical benefits was a reduced rate of infection. In the three months preceding GM-CSF treatment, five patients had had 12 febrile episodes for which they required intravenously administered antibiotics. While in this study, in contrast, three patients required antibiotic treatment on three occasions. Furthermore, three patients previously considered poor risks for surgery grew healthy enough to undergo operations for their underlying illnesses.

Figure 2 shows the hematologic benefits of GM-CSF treatment in a patient who had had hypoplastic bone marrow for three months after low-dose chemotherapy. During this period the patient had required frequent red-cell and platelet transfusions and antibiotics for recurrent infections. Treatment with GM-CSF improved the patient’s bone marrow function and increased his blood counts; the increase in granulocyte rendered him free of infections. This is the patient who did not require red-cell and platelet transfusions for more than 40 weeks.

Reasons for Response

We were interested in understanding the biologic basis for these patients’ response. The rapid increase in white cells, for example, suggested that the response begins with the release of mature cells from the bone marrow. The fact that the white-count elevation was sustained (Figure 2) indicated the second component of the response to be at the stem-cell level. Our observations of a higher number of bone-marrow stem cells in the proliferative cycle and of increased bone-marrow cellularity after GM-CSF treatment support this notion. These findings also explain why in some patients the baseline granulocyte counts improved with repeated treatment cycles.

In treating patients for myelodysplastic syndromes, the ultimate goal is to prevent evolution of the disease in acute leukemia and to restore the patients’ normal hematopoiesis. Because 15% to 40% of these patients develop acute leukemia, treatment with antileukemic agents seems a logical approach. Yet, even at low dosages, these agents are often poorly tolerated because the patients have low bone-marrow reserve and profound cytopenias. One intriguing approach, therefore, would be to eradicate the abnormal

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No disease diagnosis arouses as much fear and dread as cancer, which one of three Americans experiences directly and which causes almost 450,000 deaths a year. Hearing this diagnosis, a person’s first response may be a feeling of acute emotional turmoil, of shock and disbelief. Anxiety and depression often follow, but these may abate as the patient begins to accept the information and to participate actively in his or her treatment. The next challenge is coming to grips with issues that concern the threat of recurrence after treatment and the possibility of diminished life span. These worries are realistic. Most patients struggle with them, and unless recognized and acknowledged, they may interfere with the patient’s compliance and response to treatment.

At the same time, differences in symptomatology, personality, age, social status, and support systems inevitably make each patient’s reactions unique. No patient’s case is typical, and each has its own agonies and ironies. Because age makes a crucial difference, we pay attention to when in the patient’s life cycle the disease has occurred. Older people who may have cancer at more advanced stages tend to experience deeper depression than younger patients, whereas younger ones may express more resentment and be less cooperative as an expression of their anger.

Identifying the Profoundly Troubled Patient

Early identification of the individuals who are likely not to cope well with their illness and treatment is essential to treatment planning. These patients have often had difficulties in handling other crises in their lives. The unusually troubled patient may generally be identified by symptoms of anxiety and agitation, unrealistic perception of the illness, and extreme behavior. Feelings of worthlessness and guilt are particularly sharp indicators of potential emotional crises. Profoundly upset, such a patient may express suicidal thoughts. The social work practitioner will focus on the patient’s support system of family, friends, religious, and work groups to encourage continuing contact and support. Besides simply being available when needed, social workers may help to provide transportation and financial assistance. Without this support, troubled patients may become isolated, withdrawn, noncompliant with treatment, and unable to mobilize enough energy and determination to fight their disease.

Deal with Sexual Problems Early

Fears and misunderstandings about cancer may also lead to impotence and frigidity. Whether a patient’s sexual impairment is organic or psychological, both patient and partner should participate in counseling early in the treatment process. Such a problem can often be identified and dealt with successfully before it becomes integrated into the patient’s lifestyle and accepted as a normal byproduct of cancer and its treatment.
Emotional Support

By virtue of their relationship, family members play two distinct and potentially contradictory roles in the patient’s treatment and recovery process. They function as the patient’s first line of emotional support and are so perceived and encouraged by health professionals. Simultaneously, health professionals view them as equally in need of attention and support, and varying in ability to cope with the impact of a cancer diagnosis.

Both patients’ and relatives’ scores on various questionnaires and tests have been found to be significantly correlated with the patients’ medical condition. Stress and anxiety scales related to cancer diagnosis and administered to patients and families reveal equally elevated scores—often as much as twice as high as those of the general population. Understanding this interrelationship is of fundamental importance in caring for patients with cancer. A supportive family environment is believed to enhance the capacity to adapt to illness and treatment.

Toughest Problems

Cancer patients find it particularly hard to cope with pain, manage uncertainty, modify the reality of their lives, and redefine time. Chronic, unrelenting pain is the most disturbing—a private experience no machine or instrument can quantify. At M. D. Anderson Hospital, the Pain Service provides specialized treatment when this becomes a significant and unresolved problem.

Because survival rates vary widely for the various types of cancer, a growing number of men and women in our country now live with cancer and the uncertainty of recurrence. As cancer has become more treatable and more patients survive the illness longer, quality of life and total care have become central issues. To lessen patients’ uncertainty about their illness, physicians now commonly explain the nature of the illness to patients, describing findings, treatment, and prognosis. This contrasts sharply with prevalent attitudes 20 years ago, when 90% of doctors reported in a 1961 survey that they did not tell cancer patients their diagnosis. Our current belief is that the more patients know and understand, the more certain and secure will they feel.

Once diagnosed, cancer becomes a part of these patients’ lives, forcing them to alter their sense of reality because the disease changes family relationships, puts friendships on trial, and may even cost a patient his or her job. The patient’s ultimate balancing of the realistic or unrealistic fears associated with cancer diagnosis and adjustment to the psychosocial stress of the treatment process itself depends on many of the factors discussed. Those who make a good adjustment demonstrate resilience, adaptability, and resourcefulness under severely difficult circumstances, a self-contained capacity to cope with problems, and the supportive and enhancing effects of patient-family-friends relationships.

Mobilizing emotional and financial resources to fight this disease over months and years is difficult for most people. Suddenly the patients’ lives are redefined in terms of treatments and remissions. Rather than plan several years in advance, patients must focus on living day-to-day, week-to-week; the uncertainty is with them constantly, as may be their pain and discomfort. The world of patients, revolving around the medical system and its time frame, takes on a different meaning and dimension. Time is very different in this new reality of cancer and cancer treatment.

A comprehensive approach to cancer care requires, therefore, awareness and consideration of the psychosocial factors associated with the illness. At our hospital, we are fortunate to have one of the best patient-to-social worker ratios in Texas, so the team approach is an essential part of care and reflects this reality. Increasing recognition of these psychosocial factors is reflected by patients’ improved treatment compliance, their enhanced responsiveness to treatment, and an improvement in the quality of their lives.

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intrapertitoneally administered interferon and intraperitoneal or systemic IL-2 with LAK cells achieve antitumor activity in ovarian cancer patients. Several clinical trials of these agents as well as of monoclonal antibodies linked to drugs, toxins, or radionuclides are under way; results should become available in the next few years.

Hope for Next Decade

Our hope for the next 10 years or so is that innovative methods like intraperitoneal chemotherapy, intensification chemotherapy, and multimodality therapy will raise our patients’ survival rates. Therapy with biologic response modifiers, although in its infancy, will also be studied carefully and will, we hope, assume its proper role in the armamentarium against epithelial ovarian cancer. Meanwhile the search continues for more active agents against this disease. The ultimate hope lies in the early detection of ovarian cancer with a reliable serum tumor marker.

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clones with chemotherapy and then stimulate normal elements with GM-CSF. As is illustrated by the clinical course of one such patient (Figure 2), GM-CSF might be effective in restoring normal hematopoiesis in patients rendered hypoplastic by chemotherapy.

The patients, who were treated as outpatients, tolerated the therapy well. The few side effects they experienced included flulike symptoms and bone pain.

Our findings demonstrated that GM-CSF stimulates hematopoiesis significantly in humans. Treatment with this hormone may benefit patients with myelodysplastic syndromes and cytopenias by improving blood elements and thus reducing the morbidity related to infections, hemorrhages, and transfusions. The long-term impact of GM-CSF treatment on the natural history of myelodysplastic syndromes, including its effect on leukemic transformation and survival, needs to be learned from controlled clinical studies.

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