Recent Progress in the Diagnosis and Treatment of Ovarian Cancer

Danijela Jelovac, MD[1]; Deborah K. Armstrong, MD[2]

Abstract

Epithelial ovarian cancer is the most lethal of the gynecologic malignancies, largely due to the advanced stage at diagnosis in most patients. Screening strategies using ultrasound and the cancer antigen (CA) 125 tumor marker are currently under study and may lower stage at diagnosis but have not yet been shown to improve survival. Women who have inherited a deleterious mutation in the *BRCA1* or *BRCA2* gene and those with the Lynch syndrome (hereditary nonpolyposis colorectal cancer) have the highest risk of developing ovarian cancer but account for only approximately 10% of those with the disease. Other less common and less well-defined genetic syndromes may increase the risk of ovarian cancer, but their contribution to genetic risk is small. A clear etiology for sporadic ovarian cancer has not been identified, but risk is affected by reproductive and hormonal factors. Surgery has a unique role in ovarian cancer, as it is used not only for diagnosis and staging but also therapeutically, even in patients with widely disseminated, advanced disease. Ovarian cancer is highly sensitive to chemotherapy drugs, particularly the platinum agents, and most patients will attain a remission with initial treatment. Recent advances in the delivery of chemotherapy using the intraperitoneal route have further improved survival after initial therapy. Although the majority of ovarian cancer patients will respond to initial chemotherapy, most will ultimately develop disease recurrence. Chemotherapy for recurrent disease includes platinum-based, multiagent regimens for women whose disease recurs more than 6 to 12 months after the completion of initial therapy and sequential single agents for those whose disease recurs earlier. New targeted biologic agents, particularly those involved with the vascular endothelial growth factor pathway and those targeting the poly (ADP-ribose) polymerase (PARP) enzyme, hold great promise for improving the outcome of ovarian cancer. **CA Cancer J Clin 2011;61:183–203. ©2011 American Cancer Society, Inc.**

Epidemiology and Risk Factors

Ovarian neoplasms are classified according to the tissue of origin, such as epithelium, stromal endocrine cells, and germ cells. Primary peritoneal cancer and fallopian tube cancer are managed similarly to epithelial ovarian cancer (EOC). EOC accounts for over 90% of all ovarian malignancies and is primarily a disease of postmenopausal women, occurring most commonly in sixth and seventh decades of life. In the United States, ovarian cancer is the second most frequent invasive malignancy of the female genital tract after cancers of the uterine corpus, with an estimated 21,880 cases diagnosed annually. Approximately 13,850 women die each year from ovarian cancer, representing the most common cause of death among women with gynecologic malignancies.[1] The lifetime incidence for ovarian malignancies is 1 in 72 (1.39%) and the lifetime risk of death from ovarian cancer is 1 in 96 (1.04%) for women living in the United States. The median age at diagnosis is 63 years.[2]

[1]Department of Oncology, The Johns Hopkins Kimmel Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD; [2]Associate Professor of Oncology, Associate Professor of Gynecology and Obstetrics, Director, The Johns Hopkins Kimmel Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD.

Corresponding author: Deborah K. Armstrong, MD, The Johns Hopkins Kimmel Cancer Center, The Johns Hopkins University School of Medicine, 1650 Orleans Street, Room 190, Baltimore, MD 21231; armstde@jhmi.edu

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Incidence rates have been declining by approximately 0.7% per year between 1985 and 2001, and by 1.9% per year from 2001 to 2007.

Although a clear etiologic factor responsible for the development of ovarian cancer has not been identified, the risk of the disease is inversely proportional to the number of lifetime ovulations. Thus, factors associated with suppression of ovulation, such as increasing numbers of full-term pregnancies, longer duration of lactation, and oral contraceptive use are associated with a decrease in ovarian cancer.[3,4] Factors associated with greater lifetime ovulation and/or greater lifetime estrogen exposure such as nulliparity, early age of menarche or late age of menopause, and use of hormone replacement therapy increase risk.[5-7] Furthermore, inflammatory conditions such as endometriosis appear to increase risk of ovarian cancer, whereas tubal ligation and hysterectomy reduce risk.[8,9] Ovarian cancer is more common in industrialized countries, and available epidemiologic data suggest that environmental factors may contribute to development of the cancer, although this remains uncertain. Cigarette smoking appears to increase the risk of some subtypes of EOC (mucinous), but not all EOC.[10] Incidence varies among races, and in the United States the delay-adjusted incidence rate is 52% higher for Caucasians than African Americans.[11] Although these hormonal, reproductive, environmental, and racial and ethnicity factors mildly alter ovarian cancer risk, genetic factors have the most potent impact.

Role of Genetic Mutations

Approximately 10% of EOCs are associated with inheritance of an autosomal dominant genetic aberration, which leads to cancer predisposition with a high penetrance.[12] Perhaps the most important new dimension in understanding the etiology of some cancers of the ovary was the discovery of the role of mutation in the BRCA genes. The *BRCA1* gene, located on chromosome 17q, and the *BRCA2* gene, located on chromosome 13q, function as an essential part of the normal mechanisms that repair double-strand DNA breaks (the main lesion after exposure to ionizing radiation and DNA cross-linking agents such as platinum agents) through recombination with undamaged, homologous DNA strands.[13] Because deleterious mutations interfere with their function, BRCA genes appear to act as tumor suppressor genes. The inherited (germline) mutation represents the first "hit" of Knudsen's 2-hit model of tumorigenesis. It is hypothesized that mutations interfere with the DNA repair function of the normal gene, thus resulting in the accumulation of chromosomal abnormalities and a propensity to develop malignancy. If the second allele of the gene develops a defect, the stage is set for the development of cancer.[14] Inheritance of a deleterious mutation in one of these BRCA genes is associated with a 45% to 80% lifetime risk of breast cancer and a 27% to 44% lifetime risk of ovarian cancer compared with 1.4% in the general population. The mean age of onset of ovarian cancer is significantly earlier in women with a *BRCA1* mutation, 45 years, compared with over 60 years of age for those with a *BRCA2* mutation.[15]

The exact cell of origin for BRCA-associated ovarian cancers has been recently called into question. This is based on the observation that the most common premalignant pathologic findings in risk-reducing salpingo-oophorectomy (RRSO) specimens from BRCA mutation carriers are in the distal, fimbriated end of the fallopian tube.[16] Even when no pathologic abnormality is found, increased background tubal proliferation, as measured by Ki-67 staining, and more p53 foci are identified in these specimens when compared with specimens from non-BRCA mutation carriers.[17]

The frequency of BRCA mutations, like other somatic genetic mutations, varies within populations. It is estimated that between 1 in 300 and 1 in 800 non-Ashkenazi Caucasian women harbor a BRCA mutation. However, the BRCA mutation carrier rate is higher in certain populations, most notably in the Ashkenazi Jewish population, in whom the carrier rate is 2.1%.[18] Specific founder mutations have been identified in some populations, including the Ashkenazi Jewish population. The majority of patients with a BRCA mutation will develop a serous adenocarcinoma, although it is more likely to be of higher grade than ovarian cancers in age-matched controls.[19] In spite of this, recent data suggest a more favorable outcome for patients with BRCA mutation-associated ovarian cancers. This has been attributed to the higher sensitivity to platinum-based treatment of these tumors relative to sporadic cases.[20-22]

In addition to mutations in the BRCA genes, a higher incidence of ovarian cancer is observed in women who are members of Lynch syndrome

TABLE 1. Risk Factors for the Development of Ovarian Cancer

INCREASED RISK	DECREASED RISK
Age	Multiparity
Nulliparity	Lactation
Early menarche or late menopause	Hysterectomy
Menopausal hormone replacement therapy	Tubal ligation
Endometriosis	Oral contraceptive use
BRCA1/2 mutation	
Lynch syndrome	

(hereditary nonpolyposis colorectal cancer [HNPCC]) families. The Lynch syndrome is caused by mutations in any of several DNA mismatch repair genes (human mutL homolog [hMLH] 1, human mutS homolog [hMSH] 2, hMSH6, human postmeiotic segregation increased [hPMS] 2, and other as yet unidentified genes). These families are characterized by a higher incidence and earlier onset of carcinomas of the colon, gastrointestinal (GI) tract, ovary, and uterus.[23] HNPCC carriers account for approximately 1% of ovarian cancer patients.[24] The estimated lifetime risk of ovarian cancer for carriers of HNPCC is 9% to 12%.[25]

A summary of the risk factors for ovarian cancer is shown in Table 1.

Screening

Screening the general population is currently neither cost-effective nor practical. However, certain subpopulations of patients (primarily those defined by the genetic risk factors described above) may be candidates for ovarian cancer screening. Three screening tests are currently employed: bimanual pelvic examination, cancer antigen (CA) 125, and transvaginal ultrasound. The pelvic examination does not add additional cost for women who are already undergoing regular gynecologic evaluation and is reliable when done by an experienced examiner, but it lacks adequate sensitivity and specificity as a screening test. It is estimated that physical examination detects only 1 in 10,000 ovarian carcinomas in asymptomatic women. The radioimmunoassay for CA 125, a tumor-specific antigen, is elevated in 80% of ovarian carcinomas, but only in 50% of women with cancer limited to the ovary. It may also be elevated in women with benign ovarian disease and in otherwise healthy women, which limits its specificity.

Ultrasound is not only expensive but also has limited specificity and sensitivity. In one published study, 4526 high-risk women underwent ultrasound every 6 months. There were 49 invasive surgical procedures: 37 for benign tumors and 12 for gynecologic malignancies. The detected malignancies were ovarian, peritoneal, or fallopian tube carcinoma in 10 women, all of which were stage III, and stage IA endometrial adenocarcinoma in 2 women.[26] The authors concluded that ultrasound was of limited value for the detection of early stage EOC in asymptomatic high-risk women.

Recently, the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) published data from a study of more than 200,000 postmenopausal women randomized 2:1:1 to a control, annual CA 125 with transvaginal screening (multimodal screening [MMS]) or annual screening with transvaginal ultrasound.[27] This initial report is a prevalence screen to evaluate the sensitivity and specificity of MMS and transvaginal ultrasound. No data are reported from the control group to avoid compromising the outcome of the screening trial. Ninety-seven of 50,078 women in the MMS group (0.2%) and 845 of 48,230 women in transvaginal ultrasound group (1.8%) underwent screen-directed surgical evaluation, and primary ovarian and tubal cancers were detected in 42 (MMS) and 45 (transvaginal ultrasound) women, including 28 borderline tumors (8 in the MMS group and 20 in the transvaginal ultrasound group). Of 58 invasive cancers, 28 (16 in the MMS group and 12 in the transvaginal ultrasound group) were stage I/II, with no difference in stage distribution between groups. The sensitivity of the MMS (89.4%) and transvaginal ultrasound (84.9%) screening strategy was encouraging, and specificity was significantly higher in the MMS group (99.8%) than in the transvaginal ultrasound group (98.2%), resulting in lower rates of repeat testing and surgery. This reflects in part the high prevalence of benign adnexal abnormalities and more frequent borderline tumor detection in the transvaginal ultrasound group. We await maturity of this trial with survival outcome. There is currently no recommended ovarian cancer screening for average-risk women.

Although no data demonstrate that screening reduces mortality of the disease even in the higher risk groups, women who are at the highest risk are recommended to have an annual bimanual pelvic

examination, assay for CA 125, and transvaginal ultrasound. RRSO is the most definitive risk reduction strategy for ovarian cancer and should be considered in women with a known BRCA mutation who have completed childbearing.[28]

Clinical Presentation

Early detection is the key to the successful treatment of ovarian cancer; however, EOC is rarely diagnosed at an early stage because the disease causes few specific symptoms when it is localized to the ovary. It is estimated that only 15% of ovarian cancer is localized to the ovary, 17% is regional, and 62% occurs as distant disease. Because of this, ovarian cancer has historically been called the "silent killer." With tumor spread into the pelvis and upper abdomen, patients often complain of pelvic or abdominal pain or pressure, abdominal swelling, dyspepsia, and early satiety. As the disease progress, patients can note weight loss and increasing pain, and they can develop bowel or ureteral obstruction. In retrospect, many patients will note a several-month history of vague abdominal discomfort that is generally very nonspecific and is initially not believed to represent serious underlying pathology.[29]

Although screening of asymptomatic women for ovarian cancer is not effective currently, knowledge of ovarian cancer symptoms may help identify patients at an earlier stage. Symptoms suggestive of ovarian cancer include pelvic/abdominal pain, urinary urgency/frequency, bloating, and early satiety, especially if symptoms are new (present for less than 1year) and frequent (occurring more than 12 days per month).[30] A positive symptom index (any of those 6 symptoms that occurred more than 12 times per month in less than 1 year) had a sensitivity of 56.7% for early stage disease and 79.5% for advanced disease. Specificity was 90% for patients older than 50 years and 86.7% for patients younger than 50 years. The presence of these symptoms should prompt consideration of ovarian cancer in the differential diagnosis and testing for the disease should be included in the workup.

The Ovarian Cancer National Alliance is working with Congress to increase funding for Johanna's Law, also known as the Gynecologic Cancer Education and Awareness Act, created under Johanna's Law (P.L. 109-475) and implemented by the Centers for Disease Control and Prevention. This law provides up to $16.5 million for awareness and education through a national public service campaign that would include written materials and public service announcements.

Diagnosis and Staging

Palpation of an adnexal mass during a pelvic examination commonly initiates a diagnostic evaluation for ovarian cancer. Ultrasound examination is the most useful noninvasive diagnostic test. Although most are benign, between 13% and 21% of women undergoing surgery for a suspicious adnexal mass will have an ovarian malignancy. Recommendation for surgery depends on the degree of suspicion that this mass may be malignant; factors that should be considered include age, menopausal status, family history, size and complexity of the mass, associated symptoms, CA 125, unilaterality versus bilaterality, and characteristics on ultrasound. Management may include observation with repeat examination, further radiographic imaging, and laparoscopy or laparotomy depending on the clinical circumstances.

The preoperative evaluation of a woman with suspected ovarian cancer includes measurement of CA 125, which is elevated in greater than 80% of patients with advanced EOC.[31] Sensitivity is lower for stage I disease (50%). It also varies according to histology: it is highest in serous and lowest in mucinous EOC. Moreover, CA 125 is not specific for EOC, and it can be elevated in nonmalignant conditions such as endometriosis and pelvic inflammatory disease, as well as in other malignancies including endometrial and pancreatic cancers.[32]

Surgery for EOC

Surgery is necessary for the diagnosis, staging, and treatment of EOC. Although ovarian cancer can spread hematogenously or via the lymphatic system, the bulk of the tumor will be found on peritoneal surfaces. This peritoneal disease results from shedding of ovarian tumor cells into the peritoneal cavity, circulation of these cells throughout the abdomen and pelvis, and eventual implantation onto peritoneal surfaces. The viability of these cells and successful tumor growth is further dependent upon the development of sufficient neovasculature to support cell survival and tumor growth.

This unique pattern of spread within the relatively accessible peritoneal cavity has led to attempts at surgical cytoreduction before the administration of chemotherapy. Dating back more than 30 years, nearly every study has demonstrated an inverse correlation between the volume of tumor remaining at the completion of initial surgery and overall survival (OS) for patients with ovarian cancer.[33] Although these data are almost exclusively retrospective, the consistency of the observation of improved outcome with surgical debulking has led to the goal of "optimal" tumor cytoreduction to no macroscopic visible disease with initial diagnostic surgery. The terms "optimal" and "suboptimal" refer to the diameter of the largest residual tumor nodule that remains after debulking surgery: 1 cm or less for optimal, and greater than 1 cm for suboptimal debulking. However, the goal of debulking surgery is to render the patient completely debulked and visibly with no evidence of disease. Patients who have their initial diagnostic surgery performed by a gynecologic oncology surgeon are more likely to be optimally cytoreduced. Patients who have had only a biopsy, paracentesis, or incomplete debulking should be referred to an experienced gynecologic oncologist for consideration for reoperation given the impact of initial surgery on clinical outcome. It should be recognized that it is unique among patients with solid tumors to attempt maximal surgical cytoreduction in the presence of widespread disease outside of the organ of origin.

The goals of initial surgery in ovarian cancer are thus to diagnose and stage disease and to provide therapeutic benefit with cytoreduction. Precise histologic diagnosis and accurate staging are required before systemic treatment because subsequent treatment, as well as prognosis, will be determined by the surgical stage of disease.

Ovarian malignancies are surgically staged according to International Federation of Gynecology and Obstetrics (FIGO) staging system, which is outlined in Table 2.[34] Staging laparotomy requires a thorough inspection of the peritoneal cavity, including the paracolic gutters, pelvis, and domes of the diaphragm; total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO); liver palpation and biopsy (if indicated); lymph node sampling; omentectomy; and peritoneal washings. The degree of surgical debulking should be reported, and if incomplete, the surgeon should describe the size, location, and extent of residual disease.

TABLE 2. FIGO Staging and Prognosis of Ovarian Cancer

FIGO STAGE	CHARACTERISTICS	STAGE DISTRIBUTION	10-YEAR SURVIVAL RATE
I	Disease confined to the ovaries	20%	73%
IA	One ovary, capsule intact, no ascites		
IB	Both ovaries, capsule intact, no ascites		
IC	Stage IA or IB plus ascites or washings, capsule ruptures, tumor on ovarian surface		
II	Disease spread confined to the pelvis	5%	45%
III	Disease confined to the abdominal cavity, including surface of the liver; pelvic, inguinal, or para-aortic lymph nodes; omentum or bowel	58%	21%
IIIA	Negative lymph nodes, plus microscopic seeding of peritoneal surface		
IIIB	Negative lymph nodes, peritoneal implants <2 cm		
IIIC	Positive lymph nodes and/or abdominal implants >2 cm		
IV	Spread to liver parenchyma, lung, pleura, or other extra-abdominal sites	17%	<5%

FIGO indicates International Federation of Gynecology and Obstetrics.

It should be noted that stage II disease is the least commonly diagnosed stage of ovarian cancer. This is likely because there is no anatomic boundary between the pelvis and upper abdomen. If disease has spread outside of the ovary to pelvic structures, it is also likely to spread to the upper abdomen. In the past, trials of the Gynecologic Oncology Group (GOG) have combined stages I and II as a definition of "early" ovarian cancer, with stages III and IV designated as "advanced" ovarian cancer. However, given the observed higher recurrence rate seen for stage II disease, the GOG is now including stage II in the category of advanced disease for trial purposes.

Histopathology

Ovarian cancer is heterogeneous disease, and it contains several histological subtypes.

TABLE 3. Pathology of Epithelial Ovarian Tumors

HISTOLOGIC TYPE	ANALOGOUS CELL TYPE
Serous (75%)	Endosalpingeal
Mucinous (10%)	Endocervical
Endometrioid (10%)	Endometrial
Clear cell	Mullerian
Transitional cell (Brenner tumor)	Transitional
Squamous cell tumor	Squamous
Mixed epithelial	Mixed
Undifferentiated	Anaplastic
Unclassified	Mesothelioma, etc

EOC accounts for over 90% of primary ovarian tumors and can be classified into distinct morphologic categories: serous, mucinous, endometrioid, clear cell, transitional cell (Brenner tumors), mixed, and undifferentiated type (Table 3).

Papillary serous histology accounts for 75% of ovarian cancers, and its histological pattern simulates the lining of the fallopian tube. High-grade, poorly differentiated tumors are the majority and are macroscopically indistinguishable from other epithelial tumors. This histologic variant is often associated with concentric rings of calcification known as psammoma bodies. Although no universal grading schema exists for ovarian serous carcinoma, a 2-tiered system (low-grade vs high-grade) has received increasing acceptance.[35,36] Histopathologic grade is of prognostic significance[35] and may also be of predictive value in that low-grade tumors appear less responsive to chemotherapy than high-grade tumors.[37-39]

Studies aimed at identifying a precursor lesion within the ovary have been largely unsuccessful. Based on the observation of a high rate of tubal intraepithelial changes (TICs) in high-risk women undergoing RRSO, it has been hypothesized that many apparent ovarian or primary peritoneal carcinomas may be of fallopian tube origin. Recent studies have documented that up to 59% of high-grade pelvic (nonuterine) serous carcinomas are associated with serous TICs. This is consistent with the hypothesis that the fallopian tube is the source of a majority of these tumors.[40]

There is increasing evidence that the pathogenesis of low-grade serous carcinomas and of serous tumors of low malignant potential (LMP; discussed later in this section) involves similar genes and pathways, and is distinct from that of high-grade serous carcinomas.[41-43] Low-grade serous carcinomas and LMP serous tumors are characterized by a young age at diagnosis and a prolonged natural history.[39] The clinical behavior of LMP tumors that recur as low-grade invasive serous carcinomas appears similar to that of newly diagnosed low-grade serous carcinomas.[37] Other studies have shown that LMP tumors often coexist with low-grade serous carcinomas, and when they recur, frequently do so as low-grade serous carcinomas.[44,45] These findings have led some to hypothesize that low-grade serous ovarian carcinomas represent the natural progression of an undetected serous ovarian tumor of LMP. However, there is no definitive evidence that low-grade serous carcinomas always arise from LMP tumors, and whether the 2 entities represent a continuum of tumor progression remains unproven. Although there are ongoing trials specifically for low-grade ovarian cancers, at present, low-grade and high-grade invasive serous ovarian tumors are treated similarly.

Mucinous tumors histologically resemble endocervical epithelium. They tend to be the largest epithelial ovarian neoplasms, with a median diameter of 18 to 20 cm, but tend to remain confined to the ovaries. Pseudomyxoma peritonei, a clinical syndrome characterized by accumulation of a gelatinous ascites, may be present. Furthermore, primary ovarian mucinous tumors can be difficult to distinguish from metastatic mucinous tumors from the appendix, colon/rectum, cervix, or pancreas. Primary tumors tend to be large and unilateral.[46] Platinum-based first-line chemotherapy seems to be less effective for mucinous compared with nonmucinous EOCs.[47-49] Current trials are examining whether chemotherapy regimens that include agents (such as capecitabine, oxaliplatin, and bevacizumab) with activity against GI cancers may be more effective in mucinous ovarian cancers.

Endometrioid tumors closely resemble the components of endometrial cancer and they appear to have an improved survival compared with serous adenocarcinoma, regardless of disease stage or response to platinum-based therapy.[50]

Patients with ovarian clear cell cancer frequently have a clinical history of endometriosis. Clear cell carcinomas tend to have a higher percentage of stage I disease than advanced stage disease. This suggests that clear cell carcinomas may have more symptoms

when confined to the ovary and are thus more easily diagnosed at an early stage, or that they have a lower propensity for spread. In support of the former theory, clear cell carcinomas may be associated with a large pelvic mass.[51,52] Recurrences are more frequent than with other histologies, and the response rate to platinum- and taxane-based regimens is lower.[47,52,53] Nevertheless, at this time, clear cell cancers are still treated similarly to other EOCs.

Brenner tumors can be benign or malignant. Benign Brenner tumors are small, solid masses comprised of nests of transitional epithelium within the fibrous stroma. Intermediate Brenner tumors are comprised of proliferating cells of LMP. These are generally unilateral and multicystic, with a good prognosis. Malignant Brenner tumors are comprised of frankly malignant cells with atypical features and invasive characteristics.

Transitional cell carcinomas represent less than 1% of ovarian cancers. Although some series have reported an improved outcome for ovarian transitional cell carcinoma, a recent Gynecologic Cancer Intergroup (GCIG) study reported that, when controlled for other prognostic factors, the outcome for patients with transitional cell carcinoma did not differ significantly from that for patients with serous carcinoma.[54]

Undifferentiated carcinoma refers to tumors with no discernible histologic differentiation or only minor areas of differentiation.

Mixed carcinomas are those containing 2 or more distinct histologic types of cancer, with each subtype involving at least 10% of the tumor mass. The presence of serous carcinoma or sarcoma as one of the components worsens the prognosis.[55]

Noninvasive borderline tumors or LMP tumors are a heterogeneous group of lesions defined histologically by atypical epithelial proliferation without stromal invasion and represent approximately 10% of ovarian epithelial tumors. The majority of borderline tumors are serous. Patients tend to be younger, and 75% have stage I disease. In general, these patients have an excellent prognosis, and the tumors can be treated conservatively in women who wish to preserve fertility or are pregnant at the time of diagnosis. The overall risk of recurrence after conservative surgery varies from 7% to 30%, and recurrences are typically again LMP, not invasive malignancies. TAH-BSO is recommended for women who are not planning pregnancy or have advanced disease and staging is recommended to rule out invasive implants. Use of adjuvant chemotherapy is controversial.

Primary peritoneal carcinoma (papillary serous carcinoma of the peritoneum) is closely associated with, but distinct from, EOC.[56–58] Histologically, this tumor is indistinguishable from papillary serous ovarian carcinoma, but morphologic distinctions have been described. The criteria established by the GOG to define primary peritoneal carcinoma are: 1) ovaries normal in size; 2) extraovarian involvement greater than ovarian involvement; 3) predominantly serous histology; and 4) ovarian surface involvement of less than 5 mm in depth and width. Primary peritoneal carcinoma is surgically staged according the FIGO/TNM staging system. The pattern of spread is similar to that in women with EOC.[59,60] Women with papillary serous carcinoma of the peritoneum are treated similarly to those with EOC. Optimal surgical cytoreduction may be more difficult to achieve in the setting of widespread peritoneal disease without a predominant ovarian or pelvic mass. Chemotherapy regimens and response rates are similar to EOC.[61]

Non-EOCs account for 3% to 7% and include germ cell tumors, sex cord-stromal tumors, carcinosarcoma (malignant mixed mullerian tumors), and small cell tumors. They differ from EOC in their biology and treatment. The ovary can also be involved by metastatic disease, especially from breast cancer or Krukenberg tumors (mucin-producing, neoplastic signet ring cells involving the ovarian stroma) from the GI tract.

Treatment

Treatment of Early Stage (Stages I and II) EOC

Specific ovarian carcinoma treatment recommendations are dependent on the stage of the disease and extent of surgical debulking. Approximately 25% of women with ovarian cancer have disease confined to one or both ovaries (FIGO stage I) or to the pelvis (FIGO stage II). Even among this good-prognosis group, the failure rate is high enough to warrant adjuvant chemotherapy in most patients.

Data from 2 parallel, randomized European clinical trials in early ovarian cancer, the International Collaborative Ovarian Neoplasm trial 1 (ICON1) and Adjuvant Chemotherapy in Ovarian Neoplasm

(ACTION), have been combined for analysis. Both trials compared a platinum-containing adjuvant chemotherapy regimen with observation after surgery. With over 4 years of median follow-up of over 900 patients, the hazard ratio for recurrence-free survival is 0.64 (95% confidence interval [95% CI], 0.50-0.82; $P = .001$) in favor of adjuvant chemotherapy, and the hazard ratio for OS is 0.67 (95% CI, 0.50-0.90; $P = .008$) in favor of adjuvant chemotherapy. A subgroup analysis suggested that the benefits of chemotherapy were primarily in nonoptimally staged patients, underscoring the prognostic importance and clinical relevance of surgical staging in early ovarian cancer.[62]

The GOG has attempted to precisely define the subgroups of patients with early ovarian cancer that would benefit from adjuvant therapy and determine the optimal form of therapy for these patients. Studies over the past 3 decades have shown that patients with stage IA or IB disease (limited to one or both ovaries with no ascites and negative peritoneal washings) and with well- or moderately differentiated histology have a 5-year disease-free survival (DFS) rate of 91% and a 5-year OS rate of 94% with surgery alone; thus, this subset of patients does well and is generally not treated with adjuvant therapy. It is, however, critical that these patients are fully staged. Studies have documented that almost one-third of apparent early stage patients will have more advanced stage disease when full staging is done. In contrast, chemotherapy improves progression-free survival (PFS) for patients with stage IA or IB poorly differentiated disease, stage IC, or stage II disease, and these patients should receive adjuvant chemotherapy.[63]

The rarity of early stage ovarian cancer has made it difficult to perform studies in this group of patients. The most recently reported phase 3 study in this population (GOG protocol 157) compared 3 versus 6 cycles of paclitaxel and carboplatin.[64] The 5-year probability of recurrence was 20.1% for 6 cycles versus 25.4% for 3 cycles, a 24% reduction in recurrence risk. However, the OS was similar for both regimens and the decrease in recurrence risk did not reach statistical significance. A subsequent unplanned analysis of patients from this trial showed that those with high-grade serous histology had a significantly lower risk of recurrence with 6 compared with 3 cycles. Based on these reports of this study, most recommend a minimum of 3 cycles of paclitaxel and carboplatin for patients with early stage disease who are treated with adjuvant chemotherapy and many recommend 6 cycles for those with high-grade serous cancers.

Treatment of Advanced Stage (Stages III and IV) EOC

Approximately 75% of women with ovarian carcinoma present with stage III or IV disease. As previously mentioned, prognosis correlates with the extent of residual disease after primary debulking surgery. Although this is best documented in patients with stage III disease, even patients with stage IV disease have an improved prognosis with optimal debulking (no residual implant greater than 1 cm). It is clear that this is a continuum, with those with the least tumor burden after surgery having the best prognosis and with prognosis worsening as the diameter of the smallest residual lesion increases.[33]

It has been recognized that not all patients can be optimally debulked at initial surgery. This has led to alternate approaches to achieve optimal surgical status. One of these is the administration of chemotherapy before definitive surgery, an approach referred to as neoadjuvant chemotherapy. A recent randomized trial compared primary debulking surgery followed by platinum-based chemotherapy with neoadjuvant platinum-based chemotherapy followed by interval debulking surgery in stage IIIC or IV EOC.[65] The findings from this trial were that neoadjuvant chemotherapy was not inferior to primary debulking surgery; however, the median OS of the 2 groups (30 months and 29 months, respectively) is inferior to the findings from GOG trials in this same population. Given the large body of literature demonstrating the survival benefit for cytoreduction, the inability to reliably predict preoperatively which patients will not be able to be cytoreduced, and the inferior outcome of both arms on this study, neoadjuvant chemotherapy remains controversial.

Treatment of Optimally Debulked Disease

The long-term OS rate for women with optimally debulked stage III disease is approximately 25%; thus, a small but appreciable cure rate is found in women treated with aggressive initial surgery followed by platinum-based chemotherapy. After surgery, all women should receive at least 6 cycles of

platinum-based therapy with either cisplatin or carboplatin in combination with a taxane, usually paclitaxel. If cisplatin is used, patients require careful monitoring of renal function, electrolytes, and neurologic status. Because nephrotoxicity and neurotoxicity are cumulative, cisplatin dosing should be modified early if there is an indication of renal dysfunction or progressive sensory neuropathy. Based on the results of GOG protocol 158, systemic treatment with carboplatin and 3-hour paclitaxel is equivalent to cisplatin and 24-hour paclitaxel, with an improved toxicity profile.[66] Carboplatin and paclitaxel thus have widespread acceptance as initial chemotherapy for ovarian cancer.

For women with optimally debulked ovarian cancer, a major controversy concerns the route, intravenous (iv) or intraperitoneal (ip), by which chemotherapy is optimally administered. Three randomized trials comparing iv with ip chemotherapy have shown a clinical benefit for use of the ip approach. The first trial, led by the Southwest Oncology Group, used iv cyclophosphamide in combination with cisplatin administered either ip or iv. This study showed a survival advantage for the group receiving ip cisplatin (49 months vs 41 months; $P = .02$; relative risk [RR] = 0.76), and there was a significant reduction in sensory neuropathy with ip therapy.[67] The second study compared a standard iv paclitaxel and cisplatin regimen with 2 cycles of high-dose carboplatin iv at an area under the curve (AUC) of 9 followed by 6 cycles of iv paclitaxel and ip cisplatin. This study showed an improvement in PFS (28 months vs 22 months; $P = .01$; RR = 0.78) and OS (63 months vs 52 months; $P = .05$; RR = 0.81) for the ip regimen.[68] The third study compared the same standard iv paclitaxel and cisplatin regimen with an intensive regimen of iv paclitaxel with ip cisplatin and ip paclitaxel. This study also showed an improvement in PFS (24 months vs 18 months; $P = .05$; RR = 0.80) and OS (66 months vs 50 months; $P = .03$; RR = 0.75) for the ip regimen.[69] The latter 2 studies showed increased toxicity for the ip regimen compared with the iv regimen and fewer patients were able to complete assigned ip therapy compared with those assigned to iv therapy. Current efforts are focusing on ways to improve the tolerability of ip administration using contemporary supportive care measures, modification of the treatment regimens, and use of carboplatin in place of cisplatin for ip administration. It should be noted that the use of ip therapy for suboptimally debulked and stage IV disease has not been widely accepted. Most such patients will still receive iv systemic therapy.

Treatment of Suboptimally Debulked Stage III and IV Disease

Women who have residual disease larger than 1 cm after initial debulking surgery have a substantially worse prognosis than those with optimally debulked disease. Nevertheless, a small proportion of these women will have long-term DFS. In contrast, women with disease outside the abdominal cavity or in the liver parenchyma, making them stage IV, have a worse prognosis and rarely have a long-term DFS. In addition to residual tumor volume, other factors associated with a poor prognosis include advanced age, mucinous or clear cell histology, and the presence of ascites.

Evidence clearly demonstrates that chemotherapy prolongs survival in women with stage III disease, whether optimally or suboptimally debulked, and possibly in stage IV disease. Thus, women in these disease categories should be encouraged to receive chemotherapy as a treatment option after surgery. Although there are many active agents for the treatment of ovarian cancer, the standard of care is combination therapy that includes a taxane and a platinum compound, usually carboplatin and paclitaxel.

Fifteen years ago, combination chemotherapy with paclitaxel plus cisplatin as administered in GOG protocol 111 became the standard of care for patients with advanced ovarian cancer.[70] The superiority of this regimen over the older cyclophosphamide and cisplatin regimen was confirmed in a European Organization for Research and Treatment of Cancer (EORTC) study.[71] The latter trial used 3-hour paclitaxel with cisplatin and demonstrated an increased incidence of high-grade neurotoxicity. Based on the notable differences in neurotoxicity between these 2 trials, the standard of care is to use a prolonged 24-hour paclitaxel infusion when combined with cisplatin to decrease neurotoxicity.

A subsequent study, GOG protocol 132, compared treatment with high-dose cisplatin (100 mg/m^2) as a single agent with high-dose paclitaxel (200 mg/m^2/24 hours) as a single agent, versus paclitaxel (135 mg/m^2/24 hours) followed by cisplatin (75 mg/m^2) (combination arm). All regimens were given every 3

weeks for 6 cycles to women with suboptimally debulked stage III or stage IV disease.[72] The results of this trial failed to demonstrate the same median PFS for the same population of women treated with the same combination arm in GOG protocol 111 (14 months vs 18 months). Furthermore, women who received cisplatin as a single agent or in combination with paclitaxel had no significant difference in PFS (16 months and 14 months, respectively), whereas women receiving paclitaxel alone had an inferior PFS (11 months). This is the only study in the current era using a non–platinum-containing treatment for newly diagnosed patients, and it demonstrates the superiority of platinum-based therapies. Interestingly, the survival of the 3 arms was similar. A possible explanation for this is that patients who discontinued treatment on the cisplatin arm (largely due to toxicity) went on to treatment with paclitaxel before disease progression, and patients on the paclitaxel alone arm who discontinued therapy (largely due to inferior disease outcome) went on to platinum therapy without disease progression. Although this was not specifically tested in this trial, this would suggest that "sequential" therapy may provide equivalent survival to combination therapy. It was noted that more patients in the combination arm were able to complete all 6 cycles of therapy and that toxicity in the combination arm was less toxic than cisplatin alone. Thus, the combination was considered the treatment of choice.

Docetaxel was examined as a replacement for paclitaxel in the Scottish Randomized Trial in Ovarian Cancer (SCOTROC) study. This study compared carboplatin at an AUC of 5 with either paclitaxel at a dose of 175 mg/m^2/3 hours or docetaxel at a dose of 75 mg/m^2/1 hour. There were no differences in PFS (14.8 months vs 15 months) or in 2-year survival (68.8% vs 64.2%) for paclitaxel/carboplatin compared with docetaxel/carboplatin, respectively.[73] There were more myelosuppression and hypersensitivity reactions on the docetaxel arm and more neurotoxicity and arthralgias/myalgias on the paclitaxel arm. The conclusion from the study was that docetaxel/carbopaltin was an alternative first-line chemotherapy regimen for ovarian cancer.

More recently, the GOG and the GCIG evaluated the addition of a third drug to the paclitaxel/carboplatin backbone for the initial therapy of ovarian cancer. More than 4000 women with newly diagnosed stage III or IV ovarian cancer were randomized to receive carboplatin/paclitaxel or 1 of 4 experimental regimens containing a third drug: a triplet of carboplatin/paclitaxel and gemcitabine, a triplet of carboplatin/paclitaxel and liposomal doxorubicin, a sequential doublet of carboplatin/topotecan followed by carboplatin/paclitaxel, or a sequential doublet of gemcitabine/carboplatin followed by carboplatin/paclitaxel. There was no difference in median PFS (range 15.3 months to 16.4 months) or median OS (range 39.1 months to 42.8 months) for any of the experimental regimens compared with carboplatin/paclitaxel.[74]

Some controversy exists regarding the appropriate doses of carboplatin and paclitaxel to use in this setting. The above trials have used carboplatin at an AUC ranging from 4 to 7.5 and paclitaxel at a dose of 150 to 175 mg/m^2 over 3 hours or 135 mg/m^2 over 24 hours. Although some argued that there is a dose-response effect of carboplatin, the overall comparable results from these trials argue against this point. Most now use an AUC of 6 for initial chemotherapy.

In a study from the Japanese GOG, dose-dense, weekly paclitaxel with every-3-week carboplatin has been shown to improve both PFS (28 months vs 17 months; $P = .0015$) and 3-year OS (72% vs 65%; $P = .03$) when compared with standard therapy given every 3 weeks.[75] However, the dose-dense regimen is more toxic, and patients discontinued dose-dense paclitaxel therapy more often than did those receiving standard therapy. This regimen is now being compared with an ip cisplatin regimen and an ip carboplatin regimen in GOG protocol 252.

A summary of preferred primary adjuvant chemotherapy regimens for EOC is shown in Table 4.

Maintenance Therapy

Although achieving a cure for advanced ovarian cancer is extremely rare, the majority of patients do achieve a complete clinical remission after initial cytoreductive surgery and combination chemotherapy. The ability to achieve a complete remission, which is uncommon in other advanced epithelial cancers, provides a unique opportunity to capitalize on this finite period with innovative consolidation and maintenance strategies. Clinical trials have studied consolidation therapies involving high-dose chemotherapy with stem cell transplantation and ip administration of antibodies conjugated with a variety of radioisotopes, while maintenance therapies

TABLE 4. Primary Adjuvant Chemotherapy for Epithelial Ovarian Cancer

Intravenous regimens	1) Paclitaxel (175 mg/m^2 over 3 h iv) followed by carboplatin (AUC 5-7.5 iv over 1 h) on d 1, every 3 wk for 6 cycles
	2) Docetaxel (60-75 mg/m^2 over 1 h iv) followed by carboplatin (AUC 5-6 iv over 1 h) on d 1, every 3 wk for 6 cycles
	3) Dose-dense paclitaxel (80 mg/m^2 iv over 1 h) on d 1, 8, and 15 plus carboplatin (AUC 6 iv over 1 h) on d 1, every 3 wk for 6 cycles
Intraperitoneal regimens	1) Paclitaxel (135 mg/m^2 iv infusion over 24 h) on d 1, cisplatin (75-100 mg/m^2 ip) on d 2, and paclitaxel (60 mg/m^2 ip) on d 8, every 3 wk for 6 cycles

iv indicates intravenous; AUC, area under the curve; ip, intraperitoneal.

have focused on the prolonged use of single-agent chemotherapy, ip chemotherapy, hormonal therapy, and vaccines. Thus far, none of these interventions has shown an improvement in OS.[66]

Results of a phase 3 trial led by the Southwest Oncology Group/GOG sparked controversy because it showed that a maintenance strategy of 12 monthly cycles of single-agent paclitaxel delivered to women who attained a complete response to primary platinum-paclitaxel chemotherapy significantly improved PFS, compared with delivery of 3 cycles of the same treatment regimen. The trial was unable to demonstrate an OS advantage, although a subset of the patients with a low CA 125 baseline did exhibit an improvement in survival.[68] Among the unanswered questions regarding this trial is whether the clinical benefit justifies the prolonged use of the agent with its inherent toxicities. Concerns about toxicity would lessen if a definitive OS benefit was shown.

Due to the promising results as a second-line treatment strategy (which will be discussed later), coupled with its favorable toxicity profile, the use of bevacizumab has emerged as an attractive choice as a maintenance strategy. Based on the results of prior single-agent phase 2 bevacizumab trials, the GOG performed a randomized, double-blinded, 3-arm phase 3 trial comparing the standard primary chemotherapy regimen of carboplatin/paclitaxel versus carboplatin/paclitaxel plus bevacizumab with chemotherapy versus carboplatin/paclitaxel plus bevacizumab with chemotherapy and bevacizumab continued for 1 year after the completion of chemotherapy. Results were recently presented and demonstrated that chemotherapy plus concurrent and maintenance bevacizumab prolongs PFS[76]; however, to date there is no survival difference between the 3 arms. We await mature survival data to determine if there is an impact of the addition of bevacizumab on survival.

There is a clear need for additional clinical trials to assess whether the clinical benefits such as quality of life, symptom control, and survival advantages outweigh the added exposure to the side effects of the agents or treatments used in the maintenance or consolidation setting.

Duration of Therapy and Evaluation of the Patient Receiving Therapy

Before treatment, levels of the ovarian tumor marker CA 125 should be measured and, if elevated, should be used as adjunctive evidence of response to therapy. Levels should be measured routinely during the course of treatment. A consistent rise in CA 125 can be used as a measure of failure of treatment in the absence of radiographic and clinical changes. Likewise, a linear fall in serum levels of CA 125 can be used as a measure of treatment success. Levels of carcinoembryonic antigen and CA 19-9 may be elevated in women with mucinous carcinomas and may be potentially useful in following the course of the disease.

Treatment should consist of 6 to 8 cycles of chemotherapy. Residual disease should be measured before beginning therapy by visual inspection at the time of surgery, by computed tomography (CT) scan if bulk disease remains, or by physical examination when appropriate. The role of positron emission tomography (PET) scanning is currently being investigated.

Recurrent EOC may be suspected by the development of new symptoms, the radiographic detection of an asymptomatic disease recurrence by CT scans, or a rising serum concentration of CA 125, which may predate radiographic disease progression by many months. Timing of second-line therapy is controversial. Immediate institution of therapy is indicated for symptomatic women, with the specific goal being symptom palliation. In contrast, the optimal timing of second-line therapy for an asymptomatic woman with recurrent disease (typically detected because of an asymptomatic rise in the serum level of CA 125) has been controversial.

This issue was directly addressed in a prospective trial of 1442 women with EOC in complete clinical

remission with a normal CA 125 level after surgical cytoreduction and first-line platinum-based chemotherapy.[77] Serum CA 125 levels were assayed every 3 months, but both patients and investigators were blinded to the results. Women who remained asymptomatic but whose CA 125 levels exceeded twice the upper limit of normal (n = 527) were randomly assigned to immediate treatment or to continued blinding of the CA 125 results with treatment delayed until the time of a clinical or symptomatic recurrence. Although chemotherapy was initiated a median of 5 months earlier in the immediate treatment arm, at a median follow-up of 57 months from randomization, this did not contribute to improved survival (hazard ratio for death with immediate vs delayed treatment, 1.00; 95% CI, 0.82-1.22) or a longer remission duration. Furthermore, immediate treatment had an adverse impact on quality of life. It should be noted that the median time to randomization of patients was approximately 9 months, indicating that this is an early recurrence population. It is not clear if patients with later recurrence might benefit from the earlier identification of recurrence that might allow for surgical cytoreduction of recurrent disease (see below) or more aggressive, multidrug therapies. Nonetheless, the value of routine monitoring of serum CA 125 levels in the follow-up of ovarian cancer patients is challenged by these results. Although the data from this trial provide reassurance that there is no apparent benefit to early detection and treatment of recurrence based upon intensive CA 125 surveillance, there may be specific subgroups of patients who might benefit. Thus, the impact of these results on clinical practice and on guidelines for post-treatment surveillance remain to be determined.

Treatment of Recurrent EOC

Once recurrent ovarian cancer is diagnosed, the goals of therapy should be carefully reviewed. In the recurrent setting, excessively aggressive therapy can limit future treatment options and impair quality of life. Patients may be under the impression that aggressive treatment can still result in cure. Unfortunately, the cumulative experience with recurrent ovarian cancer is that, although it is highly treatable, it is generally not curable. Patients with an early platinum-resistant recurrence rarely achieve a complete response from any therapy and will likely be on some type of treatment for the majority of their remaining life. Even patients who recur late and respond completely to second-line therapy will have a second remission that is shorter than the first in more than 95% of cases.[78] The goals of treatment of recurrent ovarian cancer are thus to prolong survival, to delay time to progression, to control disease-related symptoms, to minimize treatment-related symptoms, and to maintain or improve quality of life.

Patients with recurrent disease are commonly characterized as platinum sensitive or platinum resistant. Although this definition is useful for clinical trial purposes and to determine the optimal approach to treatment, it does have limitations. The definition of platinum-resistant disease includes patients who progress while receiving initial chemotherapy (sometimes called platinum-refractory) or within 6 months of completing initial platinum-based chemotherapy. This definition has been used to determine eligibility for clinical trials, most of which require disease that is measurable using traditional imaging modalities such as CT. Thus, most of the data regarding the efficacy of treatment in this group of patients are limited to those meeting these criteria. Patients who are determined to recur based solely on more sensitive criteria such as CA 125 or PET imaging generally have lower volume disease and may have different response characteristics than those with larger volume, traditionally measurable disease.

Treatment of Platinum-Sensitive Recurrent EOC

Platinum-sensitive patients are defined by recurrence 6 or more months after the completion of initial chemotherapy. Platinum-sensitive disease is a spectrum ranging from relatively less platinum-sensitive patients who recur shortly after the 6-month benchmark to those recurring more than 12 to 18 months after completing initial treatment. A common observation is that the response to platinum retreatment increases with a longer interval from prior platinum treatment. Because there are compelling data that cytoreductive surgery improves survival for patients with newly diagnosed ovarian cancer, the issue of surgery is appropriate to address in a highly platinum-sensitive recurrent patient with potentially resectable disease. The majority of ovarian cancer recurrences are within the abdomen and thus potentially amenable to cytoreductive surgery.

However, the benefit of secondary cytoreduction in women with a documented or suspected recurrence of EOC is unclear because of the lack of randomized trial data examining this issue.

Secondary cytoreductive surgery can be considered for patients who recur after an at least 6-month disease-free interval.[79] When selecting patients for secondary cytoreduction, the most significant preoperative factors are the disease-free interval and success of a prior cytoreductive effort. In general, patients who are further out from completion of their chemotherapy (more than 12 months) and who have limited sites of disease and an absence of signs of carcinomatosis on imaging are more likely to benefit from secondary cytoreduction. Once secondary cytoreductive surgery is attempted, the most important factor for improved survival is optimal cytoreduction. Review of outcomes after secondary cytoreductive surgery showed that the survival of patients with optimal debulking (less than 1 cm) was 16 to 61 months versus 8 to 27 months in those with suboptimal cytoreduction.[80,81] More recently, a retrospective analysis of 240 patients showed that only those with complete tumor resection, with no visible residual disease, had an improved outcome after secondary cytoreductive surgery.[82] Those with any visible residual disease fared no better than patients who did not have surgery. Secondary cytoreductive surgery for recurrent, platinum-sensitive ovarian cancer is being prospectively evaluated in 2 randomized trials: GOG protocol 213 and AGO-OVAR DESKTOP III.

Platinum-based combination therapy has become the standard of care for patients recurring more than 6 months after initial therapy, based on several recent phase 3 randomized trials comparing single-agent platinum agents with platinum-based combinations.

The first study, the ICON4/AGO-OVAR 2.2 trial, compared platinum without a taxane (largely single-agent carboplatin) with paclitaxel plus platinum (largely paclitaxel plus carboplatin) and showed an improvement in response rate (54% vs 66%), time to disease progression (9 months vs 12 months), 1-year PFS (40% vs 50%), median survival (24 months vs 29 months), and 2-year survival (50% vs 57%) for the combination arm.[83] Some question the results of this study because the majority of patients had not received a prior taxane with initial therapy.

A second study, AGO-OVAR 2.5, randomized platinum-sensitive patients to carboplatin (AUC of 4 on day 1) with gemcitabine (at a dose of 1000 mg/m^2 on days 1 and 8) or carboplatin alone (AUC of 5).[84] Compared with single-agent carboplatin, the combination arm had an improved response rate (31% vs 47%; $P = .0016$) and an improved PFS (5.8 months vs 8.6 months; $P = .0031$). However, there were no significant differences in OS for the 2 arms (17.3 months vs 18 months). The improved outcome for the gemcitabine and carboplatin arm provides an alternative to taxane/carboplatin therapy with less neurotoxicity and alopecia, toxicities that can negatively impact quality of life for many patients.

In CALYPSO, the GCIG compared paclitaxel (175 mg/m^2) and carboplatin (AUC of 5) every 3 weeks with pegylated liposomal doxorubicin (30 mg/m^2) and carboplatin (AUC of 5) every 4 weeks in patients with recurrent, platinum-sensitive ovarian cancer. The primary endpoint was PFS and the pegylated liposomal doxorubicin/carboplatin arm showed superiority compared with the paclitaxel/carboplatin arm (11.3 months vs 9.4 months; $P = .005$).[85] This study showed more myelosuppression, mucositis, and hand-foot syndrome in patients treated with pegylated liposomal doxorubicin/carboplatin and more alopecia, neuropathy, and hypersensitivity/allergic reactions in patients treated with paclitaxel/carboplatin. Overall, there were fewer drug-related adverse events and less early termination of therapy in the pegylated liposomal doxorubicin/carboplatin arm.

The development of carboplatin hypersensitivity reactions frequently occurs in patients receiving platinum-based therapy for recurrent disease. In a retrospective single-institution review, hypersensitivity reaction was reported in 24 of 205 (12%) patients with ovarian cancer treated with carboplatin.[86] Subsequently, multiple reports have been published documenting effective carboplatin desensitization protocols.[87-93] Several of these include the use of oral, nonsedating antihistamines; oral corticosteroids; and/or nonsteroidal anti-inflammatory drugs beginning 2 to 3 days before and continuing 2 to 3 days after carboplatin. In addition, iv H1 and H2 histamine blockers and corticosteroids are given before carboplatin, which is administered as a slow infusion with a gradually increasing rate, usually over 4 to 24 hours. The extra effort of desensitization should be limited to patients who are responding to

TABLE 5. Treatment Recommendations for Patients With Platinum-Sensitive Ovarian Cancer

Consider secondary cytoreductive surgery for appropriate patients
Platinum retreatment is the standard of care
Platinum-based combinations improve PFS and, in some cases, overall survival compared with platinum alone
Prior and persistent toxicities should be considered when choosing therapy

PFS indicates progression-free survival.

or who still have the potential for a significant response to carboplatin.

The recommendations for the treatment of patients with recurrent, platinum-sensitive ovarian cancer are summarized in Table 5.

Treatment of Recurrent Platinum-Resistant EOC

Most patients with recurrent ovarian cancer will eventually develop platinum-resistant disease. In general, platinum-resistant patients will be treated with sequential single agents rather than combination therapy. Table 6 lists common chemotherapy agents used in the treatment of recurrent platinum-resistant ovarian cancer.

Topotecan was first used as a "daily × 5" regimen using the drug for 5 consecutive days on a 3-week schedule.[94] This regimen, although effective, results in a high degree of myelosuppression and is poorly tolerated past second- or third-line therapy. More recently, weekly topotecan has been documented to be active in platinum-resistant disease, with response rates ranging from 9% to 20%.[95-97] The weekly topotecan regimen has much less myelosuppression and alopecia than the "daily × 5" regimen, and is better tolerated as treatment in more heavily pretreated patients. The weekly topotecan regimen has not been directly compared with the "daily × 5" regimen to formally compare efficacy; however, the improved tolerance of the weekly regimen has led to the more common use of this schedule and allows the use of topotecan in more heavily pretreated patients.

Pegylated liposomal doxorubicin also has documented efficacy, with response rates ranging from 12% to 26% in patients with recurrent, platinum-resistant ovarian cancer.[94,98-100] It has unique toxicities of hand-foot syndrome and mucositis, although these toxicities are not common and do not usually limit therapy. The convenience of the once-every-28 days treatment schedule and the relative lack of myelosuppression make this a favored regimen in the treatment of recurrent disease. Pegylated liposomal doxorubicin and topotecan have been compared in a randomized phase 3 trial and showed similar response rates in patients with platinum-resistant disease, with no significant differences in response, PFS, or OS.[94]

Gemcitabine has been studied as a single agent in platinum-resistant disease with response rates of 11% to 17%.[101-103] It has also has been compared with pegylated liposomal doxorubicin in a randomized phase 3 trial in patients who recurred within 12 months of the completion of initial chemotherapy.[100] In this trial, 56% of patients were platinum refractory, having developed disease recurrence within 6 months of completing initial chemotherapy. Compared with pegylated liposomal doxorubicin, the gemcitabine arm had an improved response rate (29% vs 16%); however, this did not reach statistical significance ($P = .06$). The median PFS was 20 weeks for gemcitabine and 16 weeks for pegylated liposomal doxorubicin ($P = .4$). In spite of the higher response rate and PFS for the gemcitabine arm, the pegylated liposomal doxorubicin arm had an improved median OS compared with the gemcitabine arm (55 weeks vs 60 weeks), which reached statistical significance ($P = .048$).

Oral etoposide has significant activity in platinum-refractory ovarian cancer, with documented response rates from 6% to 32%.[104-106] However, it is not commonly used, possibly because of secondary hematologic malignancies associated with its use.[107] In GOG trials, 3 of 150 patients treated with oral etoposide (2%) developed secondary myelodysplastic

TABLE 6. Common Chemotherapy Regimens in Recurrent Platinum-Resistant Ovarian Cancer

Topotecan daily × 5 d, every 3 wk
Topotecan wkly on d 1, 8, and 15, every 4 wk
Pegylated liposomal doxorubicin every 4 wk
Gemcitabine on d 1 and 8 every 3 wk OR d 1, 8, and 15 every 4 wk
Etoposide orally 14/21 d or 14-21/28 d
Paclitaxel wkly on d 1, 8, and 15 every 4 wk OR d 1, 8, 15, and 21 every 4 wk
Docetaxel every 3 wk

syndrome or acute myelogenous leukemia within 18 months of therapy.

Alternative taxanes have been shown to be active in platinum- and paclitaxel-resistant ovarian cancer. Weekly paclitaxel, docetaxel, and nanoparticle albumin-bound paclitaxel are all active.[108,109] This would indicate that resistance to the standard, every-3-weeks paclitaxel regimen does not necessarily confer resistance to paclitaxel administration, resulting in different exposures, or to an alternative taxane, docetaxel. Based on these studies, retreatment with an alternative taxane is reasonable to consider in platinum- and paclitaxel-resistant ovarian cancer.

Targeted Therapies

The major focus of current clinical trials for the treatment of recurrent ovarian cancer is the use of targeted biologic agents. Targeted agents that are documented to be effective in recurrent disease will then be candidates for study in front-line therapy. Although several families of agents have been studied in recurrent ovarian cancer, the greatest success to date has been with the use of agents that target the vascular endothelial growth factor (VEGF) pathway.

Bevacizumab

Bevacizumab is an anti-VEGF monoclonal antibody that inhibits activation of VEGF receptors (VEGF-R) through binding of their ligands. Angiogenesis, which is controlled by a myriad of proangiogenic factors, including VEGF, plays a central role in the physiologic function of the healthy ovary as well the malignant ovarian cancer cells.[110] Two studies using single-agent bevacizumab in recurrent ovarian cancer at a dose of 15 mg/kg iv every 3 weeks demonstrate the efficacy of this approach. The first study, conducted by the GOG, evaluated bevacizumab as a single agent in patients with 1 or 2 prior therapies who had recurred within 12 months of treatment with a platinum agent.[111] This phase 2 study demonstrated an overall response rate of 21%, with 52% of patients having stable disease as their best response and 40% remaining progression free at 6 months. It is notable that in most diseases with documented bevacizumab activity (colorectal cancer, non-small cell lung cancer, and possibly breast cancer), it has little single-agent activity; rather, bevacizumab was shown to increase the response to, or benefits of, chemotherapy. Thus, to date, ovarian cancer has the highest documented single-agent response to bevacizumab.

Another study using single-agent bevacizumab was a phase 2 trial that allowed a more heavily pretreated population. Patients demonstrated a response rate of 16%; however, the trial closed early due to an unexpectedly high incidence of GI perforation in 5 of 44 patients (11%).[112] A subsequent review of the available literature suggested that the incidence of GI perforation in ovarian cancer patients treated with bevacizumab is approximately 5.4%, which is approximately double the rate of 2.4% seen in colorectal cancer.[113] Hypotheses for this higher rate of bowel perforation, although not definitive, include a higher risk associated with heavily pretreated patients (greater than 3 prior regimens) and clinically relevant pretreatment bowel involvement, particularly if associated with bowel obstruction symptoms.

A third phase 2 study of bevacizumab in combination with oral, low-dose cyclophosphamide showed a response rate of 24% in patients with recurrent ovarian cancer.[114] The hypothesis in support of this combination is that the dose and schedule of cyclophosphamide used has antiangiogenic properties and thus, the combination may target sequential steps in the VEGF/angiogenesis pathway.

With the positive results from these bevacizumab trials in recurrent disease, major cooperative research groups worldwide began high-accruing, multiarm trials (eg, GOG protocol 218, GCIG-ICON7), with the focus on examining the use of bevacizumab in front-line therapy in combination and in varying doses with platinum-taxane combinations. These trials also include a bevacizumab maintenance component. Burger et al recently reported for the GOG the results of GOG protocol 218, a phase 3 trial of 1873 newly diagnosed patients with optimally and suboptimally debulked advanced ovarian cancer randomly assigned to carboplatin/paclitaxel/placebo (arm 1) versus carboplatin/paclitaxel plus bevacizumab followed by placebo (arm 2) versus carboplatin/paclitaxel plus concurrent and extended bevacizumab (arm 3).[76] The median PFS was significantly improved for arm 3 (14.1 months) compared with arm 1 (10.3 months) ($P < .0001$). The median PFS for arm 2 (11.2 months) was not significantly different from arm 1 and the median OS was comparable on all 3 arms (39.3 months, 38.7 months, and 39.7 months, respectively). This is the first study that demonstrates that a platinum doublet

plus concurrent and maintenance bevacizumab prolongs PFS. The GCIG randomized trial ICON7 compares carboplatin/paclitaxel with carboplatin/paclitaxel/bevacizumab (7.5 mg/kg) for 6 cycles followed by bevacizumab every 3 weeks for 12 cycles. It should be noted that this trial uses half the usual dose of bevacizumab.

As bevacizumab continues to be tested in settings of treatment-naive and recurrent ovarian cancer, both alone and in combination with other agents, many controversial aspects of its use will be better understood. The following pivotal questions will be answered: Will bevacizumab in combination with chemotherapy eventually yield better results than its single-agent use? Is the higher established dose of 15 mg/kg every 3 weeks the safest and most efficacious? Can statistically significant risk factors for bowel perforation be identified?

Aflibercept (VEGF Trap)

Aflibercept (also known as VEGF Trap) is a fusion protein that binds with high affinity to VEGF and functions as a soluble VEGF-R. Early results of a randomized phase 2 trial of 2 doses of aflibercept (2 or 4 mg/kg) administered iv every 2 weeks in patients with recurrent ovarian cancer were reported in 2007.[115] Of 45 patients, 5 had partial responses (11% response rate).

Sorafenib

Many small molecule inhibitors that target VEGF and other pathways have been and continue to be studied in ovarian cancer. Sorafenib is an oral tyrosine kinase inhibitor that targets Raf and other receptor kinases (eg, VEGF-R, platelet-derived growth factor receptor [PDGFR], fms-related tyrosine kinase 3 [FLT3], and c-Kit) and may have antiangiogenic activity through inhibition of VEGF-R. Sorafenib was studied by the GOG in ovarian cancer patients with 1 or 2 prior therapies who had recurred within 12 months of treatment with a platinum agent.[116] Although only 3% of patients with measurable disease had a documented response, 34% had stable disease and 27% were progression free by 6 months of therapy. Sorafenib has also been studied in combination with bevacizumab. In a phase 1 trial of the combination, 6 of 14 (43%) ovarian cancer patients had a partial response to therapy.[117] Based on these promising preliminary responses, a phase 2 trial of the combination is currently underway in ovarian cancer. Sorafenib is also being tested in combination with chemotherapy, both in recurrent disease and as initial therapy in newly diagnosed patients.

Sunitinib

Sunitinib is a multitargeted receptor tyrosine kinase inhibitor with activity against a number of targets, including VEGF-R and PDGFR. Early results from an ongoing phase 2 trial of sunitinib in recurrent disease showed a partial response in 2 of 17 patients with measurable disease, stable disease in 10 patients, and progression in 4 patients.[118] In addition, 6 of 11 patients evaluable by CA 125 levels responded to therapy. Treatment-associated effusions may have compromised the assessment of effect in some patients on this study, and the protocol treatment has been modified in an attempt to rectify this confounding factor.

Cediranib

Cediranib (AZD2171) is a selective oral tyrosine kinase inhibitor of VEGF-R1, VEGF-R2, VEGF-R3, and c-Kit. Two phase 2 trials of cediranib have been reported in recurrent ovarian cancer. In the first study of cediranib as second-line therapy, the clinical benefit rate (response plus prolonged stable disease) was 41% in platinum-sensitive patients and 29% in platinum-resistant patients.[119] In the second trial, which allowed 2 prior therapies, 19% of patients had a partial response to therapy and 13% had prolonged stable disease.[120]

Pazopanib is an oral angiogenesis inhibitor targeting VEGF-R, PDGFR, and c-Kit. In a phase 2 open-label trial, 11/36 patients (31%) had a CA 125 response while 18% of patients with measurable disease responded. The most common adverse events leading to discontinuation of the study drug were transaminase elevations.[121] Based on this activity, pazopanib is currently being tested in a randomized phase 3 trial of 12 months of maintenance after the completion of initial chemotherapy in ovarian cancer.

Targeting Folate Receptor Alpha

Another potential target in ovarian cancer is the folate receptor alpha (FRA). FRA is overexpressed in the majority of EOCs but is largely absent from normal tissue. MORAb-003 is a humanized monoclonal antibody to FRA. Binding of MORAb-003 to FRA blocks phosphorylation by Lyn kinase and produces cytotoxicity via antibody-dependent cellular cytotoxicity. Results of a recent phase 2 study of

MORAb-003 in combination with carboplatin and taxane therapy in platinum-sensitive ovarian cancer demonstrated that 89% of patients achieved normal CA 125 levels and more than 70% of patients responded to treatment with paclitaxel, carboplatin, and farletuzumab. In addition, 9 of 44 patients (20.5%) achieved a second remission that was of longer duration than the first remission.[122]

An alternate means of targeting FRA is through the use of folate-linked cytotoxic therapy. EC145 is a conjugate of folate and the vinca alkaloid desacetylvinblastine monohydrazide (DAVLBH). EC145 binds to the folate receptor, delivering DAVLBH into the cell via endocytosis. In the PRECEDENT study, liposomal doxorubicin alone was compared with liposomal doxorubicin plus EC145 in patients with platinum-resistant ovarian cancer. The combination demonstrated a superior overall response rate (29.6%) compared with liposomal doxorubicin alone (18.5%)[123]

Anti-Epidermal Growth Factor Receptor Agents

Although the epidermal growth factor receptor (EGFR) family is commonly overexpressed in ovarian cancer and has been associated with a negative prognosis, efforts to target the EGFR pathway have as yet not proven useful as therapy for ovarian cancer. For example, in a phase 2 trial, gefitinib was well tolerated in patients with recurrent ovarian or primary peritoneal cancer, but the agent showed minimal activity. Similarly, a phase 2 trial of erlotinib documented only a 6% response rate.[124] In a phase 2 trial of cetuximab in combination with carboplatin in platinum-sensitive recurrent ovarian cancer, 9 of 26 EGFR-positive patients (35%) responded to therapy, a response rate lower than that predicted for carboplatin alone.[125]

Poly (ADP-Ribose) Polymerase (PARP)

Poly (ADP-ribose) polymerase (PARP) is another target for developing agents in ovarian cancer. Repair of DNA damage is essential for the maintenance of genomic integrity. Distinct pathways exist for repair of single-strand and double-strand DNA breaks. The protein products of the *BRCA1* and *BRCA2* genes are critical cofactors in the repair of double-strand DNA breaks. Because loss of function of BRCA genes is common in ovarian cancer, these cells are more dependent upon single-strand DNA repair processes. Because PARP is critical to the process of single-strand DNA repair, PARP inhibitors could prevent cells with aberrant BRCA function from repairing chemotherapy-induced DNA damage, thus increasing cytotoxicity.[126] In a phase 1 trial of the oral PARP inhibitor AZD2281 (olaparib), 21 of 46 (46%) ovarian cancer patients with a BRCA mutation responded to treatment, including 8 of 10 (80%) platinum-sensitive patients, 11 of 25 (44%) platinum-resistant patients, and 2 of 11 (18%) platinum-refractory patients.[127] There is potential to combine these agents with chemotherapy, and several ongoing studies are investigating this possibility. A subsequent phase 2 trial of AZD2281 in BRCA-deficient advanced ovarian cancer showed an overall response rate of 33% to a dose of 400 mg twice daily and 12.5% to a dose of 100 mg twice daily.[128] More recently, 11 of 46 (24%) ovarian cancer patients unselected for the presence of a germline BRCA mutation responded to olaparib,[129] indicating that the PARP inhibitors may be beneficial for ovarian cancer patients in general, and that anticancer efficacy may not be limited to those with a germline BRCA mutation.

It is clear that targeted agents have a promising role in the treatment of ovarian cancer. Questions remain, however, about the requirement for documented single-agent activity of a given targeted agent before testing it in combination with chemotherapy or with other targeted agents. This is an issue not just in ovarian cancer but in cancer therapy overall.

Hormonal Therapies

Hormone therapy with tamoxifen, aromatase inhibitors (eg, letrozole), or fulvestrant is associated with low objective response rates (10%); however, occasional patients experience a dramatic tumor marker response, and some women have prolonged periods of stable disease. The efficacy of tamoxifen was explored in a Cochrane review that included 623 women from 11 nonrandomized series; 1 nonrandomized phase 2 study; and 1 randomized trial comparing tamoxifen alone, in combination with medroxyprogesterone, or with medroxyprogesterone alone in women with recurrent EOC.[130] Overall, 60 women (9.6%) achieved an objective response to tamoxifen alone, although the range within individual studies was 0% to 56%. An additional 32% achieved stable disease for periods of longer

than 4 weeks. When compared with chemotherapy (either weekly paclitaxel or pegylated doxorubicin), chemotherapy showed a small but statistically significant improvement in PFS.[131]

The aromatase inhibitor letrozole was studied in a phase 2 trial in women with estrogen receptor-positive EOC. In this trial, only 3 of 33 evaluable patients had a radiographic partial response, but 42% had stable disease for at least 12 weeks.[132]

The pure antiestrogen fulvestrant showed a modest degree of antitumor efficacy in a phase 2 trial in which 26 heavily pretreated women (median, 5 prior chemotherapy regimens) with estrogen receptor-positive EOC received fulvestrant. Half of the patients had stabilization of disease, but none had objective responses.[133]

Although there are no rigorous clinical trial data, there are anecdotal reports of increased response rates and prolonged responses of low-grade ovarian cancers to hormonal therapies.

Conclusions

Treating patients with recurrent ovarian cancer is challenging, and despite the many advances in therapeutic options for this disease, many controversies remain. Research findings continue to resolve many of these issues, including data from trials evaluating the role of secondary cytoreduction, maintenance therapy, and the prognostic significance of CA 125. Finding the optimal treatment paradigms for ovarian cancer patients will remain the goal for improving outcomes. ■

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