Chapter 156: Ovarian Cancer

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KEY CONCEPTS

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1. Ovarian cancer is denoted “the silent killer” because of the nonspecific signs and symptoms that contribute to the delay in diagnosis. The few patients who present with disease still confined to the ovary will have a 5-year survival rate greater than 90%, but most patients present with advanced disease and have a 5-year survival rate around 30%.

2. Ovarian cancer is a sporadic disease with less than 20% of cases of ovarian cancer attributed to heredity. However, a history of two or more first-degree relatives with ovarian cancer increases an individual’s risk of developing ovarian cancer by greater than 50%.

3. As there are currently no effective screening tools for early detection of ovarian cancer, considerable education efforts have been made to identify patients with the persistence (ie, greater than 2 weeks) of nonspecific presenting symptoms of ovarian cancer including: abdominal pressure/pain, difficulty eating or feeling full quickly, urinary urgency/frequency, change in bowel habits, or unexplained vaginal bleeding.

4. Serum cancer antigen 125 (CA-125) is a nonspecific antigen used as a tumor marker for diagnosing and monitoring epithelial ovarian carcinoma. If CA-125 is positive at the time of diagnosis, changes in CA-125 levels correlate with disease response and progression.

5. Although most patients will achieve a complete response to initial treatment, more than 50% of patients will have recurrence within the first 2 years. If recurrence occurs less than 6 months after completion of chemotherapy, the tumor is defined to be platinum-resistant. The antitumor activities of second-line chemotherapy regimens are similar, and the choice of treatment for recurrent platinum-resistant ovarian cancer depends on residual toxicities, physician preference, and patient convenience. Participation in a clinical trial is also a reasonable option for these patients.

6. Ovarian cancer is staged surgically with the International Federation of Gynecology and Obstetrics (FIGO) staging algorithm. Tumor-debulking and total abdominal hysterectomy–bilateral oophorectomy surgery are the primary surgical interventions for ovarian cancer. After the completion of the staging and primary surgical treatment, the current standard of care is six cycles of a taxane/platinum-containing chemotherapy regimen.

7. Neoadjuvant chemotherapy is intended to reduce tumor burden in preparation for surgery and should be used in patients who are poor surgical candidates because of comorbidities or bulky tumors. The goal of neoadjuvant chemotherapy is to improve the likelihood of optimal tumor debulking.

8. A platinum-containing doublet chemotherapy regimen is the standard of care for the first recurrence of platinum-sensitive ovarian cancer.

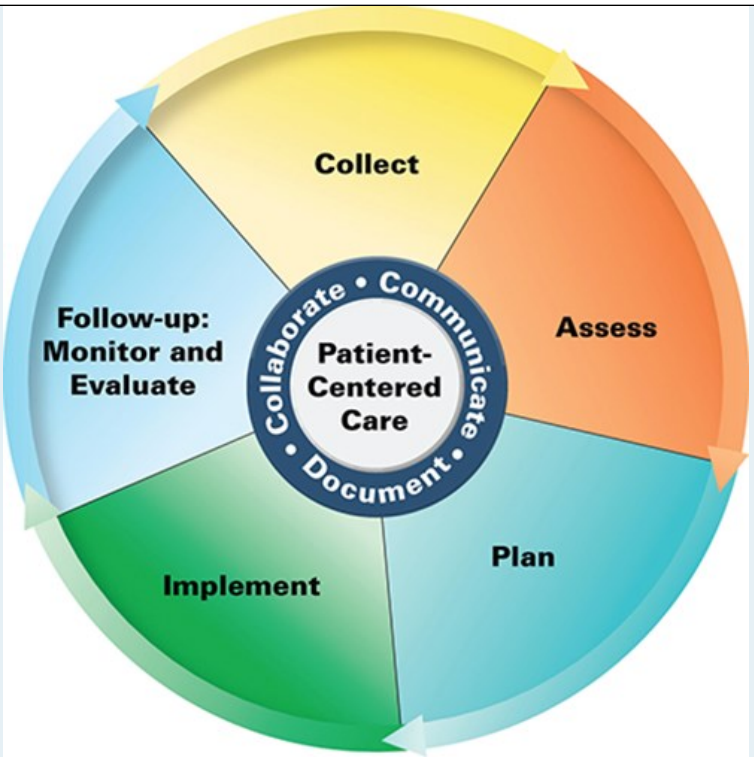
9. Despite recent advances, enrollment in an investigational study is still the primary treatment recommendation for patients with recurrent platinum-resistant ovarian cancer.

10. Poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors cause double-stranded DNA breaks that cannot be repaired in cancer cells with homologous recombination deficiency, such as those with *BRCA1/2* mutations.

11. Patients receiving a platinum or taxane-containing regimen should be monitored for signs of hypersensitivity or infusion-related reactions.

PATIENT CARE PROCESS

Patient Care Process for Ovarian Cancer



Collect

- Patient characteristics and medication history, including any allergies
- Medical history, family cancer history, and physical assessment findings
- Patient-specific factors, tumor-specific factors, and laboratory information that may influence chemotherapy selection and drug dosing
- Lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care

Assess

- Goal of therapy defined by prognosis-based stage of disease and patient preferences
- Medication profile to identify agents that may worsen the patient's symptoms, potential interactions, duplicate therapies, or unnecessary medications. Determine need for symptomatic supportive care medications including antiemetics or pain medications
- Medical and family history to determine whether the patient has compelling indications or contraindications for specific chemotherapy and if additional genetic testing is recommended
- Relevant laboratory tests (eg, CBC, electrolytes, complete metabolic panel to determine liver and hepatic function, tumor markers [eg, CA-125, CEA, and CA19-9 as part of differential], tumor genetic profile) that may impact drug selection or dosing
- Potential appropriate chemotherapy regimens and the related toxicities; review chemotherapy history to determine potential for platinum sensitivity/resistance and consider genetic mutation status in selection of treatment options

Plan*

- Recommendations for any medications or supplements that need to be held temporarily before surgery (eg, anticoagulants, nonsteroidal anti-inflammatory agents, omega 3 fatty acids, etc.)
- Anticancer therapy order with dosages based on organ function and patient characteristics (calculate body surface area), list of drug

interactions and possible adverse drug reactions from the regimen

- Determine whether patient has insurance coverage for planned anticancer therapy regimen and supportive care medications as indicated; consider institution's formulary if applicable
- Recommendations for lifestyle modifications that may assist in symptom and disease management and supportive care options
- Counseling for potential adverse drug reactions of the regimen and management strategies

Implement

- Patient education treatment plan
  - Patients undergoing surgery: use of low-molecular weight heparin for postoperative clot prevention, list of medication to stop prior to surgery and when to resume, plan for postoperative pain
  - Patients undergoing anticancer treatment: anticancer therapy agents including timing of administration, expected adverse drug reactions and prevention and management of these toxicities (nausea, infection, neuropathy, alopecia, electrolyte disturbances), necessary laboratory monitoring and follow-up visits; help patient set realistic expectations during treatment

Follow-up: Monitor and Evaluate

- Patients undergoing surgery (2-3 weeks postoperative): evaluate symptom management including nausea, pain control, and determine if adjuvant anticancer therapy is required
- Patients undergoing anticancer therapy:
  - CBC with differential should be obtained prior to each anticancer therapy dose
  - Complete laboratory values should be obtained with each cycle
  - Adjust doses based on unacceptable toxicity or organ dysfunction when indicated
  - Tumor markers obtained with each cycle: consider reevaluating therapy if a 50% increase or consistent trend upwards
  - Radiographic scan (CT scan/MRI/PET) once every 3 months: assess tumor response, following current RECIST criteria

**Collaborate with patient, caregivers, and other healthcare professionals.*

BEYOND THE BOOK

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Pair up with a classmate and create flashcards of treatment regimens for ovarian cancer on one side and the appropriate line of therapy (first-line following primary surgery, consolidation/maintenance therapy following a complete response with first-line therapy, treatment for relapse greater than 6 months from last platinum therapy, treatment for relapse less than 6 months from last platinum therapy) and common adverse drug reactions of that treatment on the other side. Present your partner with the treatment and have them recommend a patient scenario when that would be an appropriate therapy based on the line of treatment and describe the adverse drug reactions of that regimen. Discuss supportive care interventions to prevent or minimize common adverse drug reactions from the chemotherapy. Compare and contrast your recommendations and discuss other possible situations when the treatment may be considered or any patient-specific factors that may cause you to consider an alternative therapy or recommend dose modifications (eg, avoid bevacizumab in a patient with recent bowel surgery).

INTRODUCTION

Ovarian cancer is a gynecologic cancer that usually arises from the disruption or mutations in the epithelium of the ovary. It is associated with the highest mortality among the gynecologic cancers, primarily because most patients present with advanced disease. Ovarian cancer is denoted “the silent killer” because of the nonspecific signs and symptoms that often lead to a delayed diagnosis. Ovarian cancers often metastasize via the lymphatic and blood systems to the liver or lungs. Common complications of advanced and progressive ovarian cancer include ascites and small bowel obstruction. Patients who present with disease still confined to the ovary will have a 5-year survival rate greater than 90%, but most patients present with advanced disease and have a 5-year survival rate around 30%.[1] Primary treatment includes tumor-debulking surgery followed by six cycles of a taxane-platinum chemotherapy regimen. Although 70% of patients achieve an initial complete response to chemotherapy, most of these patients will have recurrence within the first 2 years from diagnosis.[2]

EPIDEMIOLOGY

In this chapter, the term “woman” is used to reflect the gender identified in previous research studies and other literature on ovarian cancer and to recognize the biological sex of individuals at birth. In doing so, we recognize that not all patients with ovarian cancer identify as females at the time of diagnosis and treatment of this condition. It is estimated that 19,880 new cases of ovarian cancer were diagnosed and 12,810 women died of the disease in 2022.[1] Unfortunately, despite clinical advances over the past two decades, the overall mortality rate for ovarian cancer is an estimated 60% and has not changed over the past two decades. Ovarian cancer is still associated with the highest mortality rate among the gynecologic cancers and is the fifth leading cause of cancer-related deaths in women. The high mortality rate is related to the insidious onset of nonspecific symptoms and the lack of adequate screening tools, which allows the disease to go undiagnosed until it has progressed beyond the pelvic cavity.

ETIOLOGY

As with many other cancers, the risk of ovarian cancer increases with increasing age. A woman’s risk increases from 2.9 to 41.2 per 100,000 as their age advances from less than 40 to 75 years or more, and the median age at diagnosis is 63 years.[3] Most cases of ovarian cancer are diagnosed during the peri- and postmenopausal phase of individual’s reproductive life span.

Heredity accounts for approximately 20% of ovarian cancer cases.[2] Family history of ovarian or breast cancer is an important risk factor in the development of ovarian cancer. If a first-degree relative has a diagnosis of ovarian cancer, the associated lifetime risk is increased by 50%. An individual’s risk of ovarian cancer is increased by 10% if a first-degree relative has a diagnosis of breast cancer.[4] Risk is greatest in individuals with multiple family members with ovarian cancer and in those with family members who were diagnosed at an early age.[5]

Breast cancer activator gene 1 *(BRCA1)* and breast cancer activator gene 2 *(BRCA2)* are tumor suppressor genes thought to be involved in one or more pathways of DNA damage recognition and repair. The *BRCA1* gene is located on chromosome 17q12–21 and the *BRCA2* gene is located on chromosome 13q12–13. Both *BRCA1* and *BRCA2* mutations are associated with ovarian cancer. However, *BRCA1* is more prevalent and is associated with 90% of inherited and 10% of sporadic cases of ovarian cancer.[6] Patients with *BRCA1*-associated ovarian cancer are usually considerably younger than patients with *BRCA2* mutations, with a mean age of 54 years.[6] Patients usually present with advanced stage at diagnosis, and the *BRCA1*-linked ovarian cancers are more aggressive tumors that typically are serous histology, moderate-to-high grade. As *BRCA1* and *BRCA2* are thought to be involved in DNA damage or repair, their mutations may be associated with an increased resistance of ovarian cancer cells to cytotoxic agents.

Hereditary breast and ovarian cancer syndrome is one of the two different forms of hereditary ovarian cancer that are associated with germline mutations in *BRCA1* and *BRCA2.* The hereditary nonpolyposis colorectal cancer or Lynch syndrome is a familial syndrome with germline mutations causing defects in enzymes involved in DNA mismatch repair, which is associated with 10% to 15% of hereditary ovarian cancer cases.[7] This syndrome is associated with mutations in DNA mismatch repair genes such as *MSH2, MLH1, PMS1*, and *PMS2* and leads to microsatellite instability.

Hormone exposure, specifically estrogen, and reproductive history is also associated with the risk of developing ovarian cancer. Conditions that increase the total number of ovulations in individual’s reproductive history, such as nulliparity, early menarche, or late menopause, are associated with an increased risk for epithelial ovarian cancers.[7] Conversely, those conditions that limit ovulations are associated with a protective effect. Each

time ovulation occurs, the ovarian epithelium is broken, followed by cellular repair. According to *incessant ovulation hypothesis*, the risk of mutations and, ultimately, cancer increases each time the ovarian epithelium undergoes cell repair.

Finally, ovarian cancer is associated with certain dietary, lifestyle, and environmental factors. A diet that is high in galactose, animal fat, and meat may increase the risk of ovarian cancer, whereas a vegetable-rich diet may decrease the risk of ovarian cancer.[5] Although controversial, exogenous factors such as asbestos and talcum powder use in the perineal area are also associated with an increased risk of ovarian cancer.[5] Obesity has also been associated with an increased risk of low-grade ovarian cancer in some studies.[5]

PATHOPHYSIOLOGY

Ovarian carcinomas can be separated into three major entities: epithelial carcinomas, germ cell tumors, and stromal carcinomas. Most ovarian tumors (85%-90%) are derived from the epithelial surface of the ovary.[2] The classification of common epithelial tumors has been developed by the World Health Organization and FIGO.[2] The nomenclature considers cell type, location of the tumor, and the degree of the malignancy, which ranges from benign tumors to tumors of low malignancy to invasive carcinomas. Epithelial tumors classified as low malignancy ("borderline malignancy") are characterized by epithelial papillae with atypical cell clusters, cellular stratification, nuclear atypia, and increased mitotic activity, and have a much better prognosis than those classified as invasive carcinomas. Malignant tumors are characterized by an infiltrative destructive growth pattern with malignant cells growing in a disorganized manner and dissection into stromal planes.

Invasive epithelial adenocarcinomas are characterized by histologic subtype and grade, which measures the degree of cellular differentiation. Although the histologic type of the tumor is not a significant prognostic factor, with the exception of clear cell, the histopathologic grade is an important prognostic factor. Undifferentiated tumors are associated with a poorer prognosis than those lesions that are well or moderately differentiated. A universal grading system for ovarian cancer was developed that combines mitotic score, nuclear atypia score, and architectural score based on the histologic pattern.[8]

The histologic subtypes of ovarian epithelial tumors include serous, mucinous, endometrioid, clear cell, Brenner tumors, mixed epithelial, and undifferentiated carcinomas.[2] High-grade serous carcinoma is the most common type of epithelial ovarian cancer and accounts for about 70% to 80% of cases.[9] The peak age of diagnosis ranges from 55 to 64 years with 63 years as the median age of diagnosis.[3] Endometrioid carcinomas are seen in individuals 40 to 50 years of age and comprise about 8% of ovarian carcinomas, of which about 6% are surface epithelial neoplasms.[10] Endometrioid tumors are usually diagnosed as stage I disease and have a better prognosis than tumors with serous histology. Mucinous carcinomas occur in individuals between 40 and 70 years of age and account for about 36% of all ovarian cancers. The overall prognosis for mucinous carcinoma is better than for serous carcinoma because most patients present with stage I disease. Clear cell carcinoma comprises about 3% of ovarian carcinomas in individuals, with a mean age of 57 years. Although clear cell carcinoma is the least common ovarian neoplasm, it is most commonly associated with paraneoplastic-related hypercalcemia.

Germ cell tumors of the ovary, including malignant teratoma and dysgerminomas, are rare, comprising about 2% to 3% of all ovarian cancers in Western countries with an increased incidence in Black and Asian individuals.[9] These tumors are highly curable and affect primarily young individuals. In contrast to epithelial tumors, about 60% to 70% of germ cell tumors are stage I at diagnosis, which is related to earlier detection and response to symptoms in this younger patient population.[9] Serum markers (human β-chorionic gonadotropin and α-fetoprotein) are helpful to confirm the diagnosis and monitor response to treatment.

Finally, ovarian sex cord-stromal tumors account for 7% of all ovarian cancers and tend to be diagnosed at an early stage.[9] Sex cord-stromal tumors are associated with hormonal effects, such as precocious puberty, amenorrhea, and postmenopausal bleeding. Because these tumors are rare, the optimal treatment of ovarian sex cord-stromal tumors is not clear. The current recommended standard of care is surgery followed by treatment with a platinum-based chemotherapy regimen.

Ovarian cancer is usually confined to the abdominal cavity, but can spread to the lung, liver, and, less commonly, the bone or brain. Direct extension, peritoneal seeding, lymphatic dissemination, or blood borne metastasis spreads disease. Lymphatic seeding is the most common pathway and frequently causes ascites.

SCREENING AND PREVENTION

Screening

3 Ovarian cancer is an uncommon disease with no known preinvasive component, which has made it difficult to detect early disease. In addition, the risk factors for developing ovarian cancer are not well understood, which also makes it difficult to identify a high-risk group of individuals. At the present time, there are no effective screening tools for early detection of ovarian cancer. However, considerable education efforts have been made to identify patients with the persistence of nonspecific presenting symptoms of ovarian cancer including abdominal pressure/pain, difficulty eating or feeling full quickly, urinary urgency/frequency, change in bowel habits, or unexplained vaginal bleeding.

Pelvic examinations are noninvasive and may be able to detect large tumors; however, routine pelvic examinations are not an effective screening tool and do not decrease overall mortality because pelvic examinations cannot detect minimal or microscopic disease.[11]

Transvaginal ultrasound (TVUS) creates an image of the ovary by releasing sound waves. It can be used to evaluate the size and shape and to detect the presence of cystic or solid masses or abdominal fluid. Transvaginal ultrasound can also evaluate blood flow within an ovarian mass. Transvaginal ultrasound is sensitive in identifying ovarian lesions and abnormalities, but its use as a routine screening test is limited by a lack of specificity and an inability to detect peritoneal cancer or cancer in normal-size ovaries.[11]

Serum CA-125 is a nonspecific inflammatory antigen that can be elevated in numerous conditions associated with inflammation in the abdominal cavity. CA-125 has been extensively studied as a potential tumor marker for ovarian cancer based on the observation that CA-125 levels in an individual without ovarian cancer tend to stay the same or decrease over time, whereas levels associated with malignancy tend to gradually increase over time.[11] However, CA-125 is a nonspecific test that can be elevated in a number of benign conditions, including other gynecologic conditions, such as endometriosis, and many nongynecologic conditions, such as diverticulitis and peptic ulcer disease. Because of these limitations, CA-125 levels are not recommended as a routine screening test for detection of ovarian cancer. Numerous other serologic markers such as carcinoembryonic antigen and lipid-associated sialic acid have been evaluated but cannot be recommended for routine screening for ovarian cancer.

The United States Preventive Services Task Force found fair evidence to support screening with CA-125 or TVUS and concluded that earlier detection would likely have a small effect, at best, on mortality from ovarian cancer.[12] Unfortunately, because of the low prevalence of ovarian cancer and the invasive nature of diagnostic testing after a positive screening test, the Task Force also found fair evidence that screening could likely lead to important harms. The United States Preventive Services Task Force concluded that the potential harms outweigh the potential benefits and recommended against any form of routine screening with CA-125 or TVUS for ovarian cancer for asymptomatic individuals who do not have a high-risk hereditary cancer syndrome.

In high-risk individuals, as defined by family history, most clinicians use a multimodality approach for ovarian cancer screening that includes an annual TVUS in combination with a CA-125 blood test every 6 months. Changes in CA-125 are monitored over time, and changes such as a persistent elevation or consistent increases in CA-125 levels in conjunction with TVUS abnormalities are evaluated further.

Prevention

It is difficult to make recommendations for prevention for the general population because ovarian cancer is a sporadic disease with no established risk factors. Noninvasive measures, such as chemoprevention, can decrease the risk of developing ovarian cancer. Ovulation itself is considered a potential insult to the ovarian epithelium, increasing its susceptibility to damage and, ultimately, to cancer. Interventions or reproductive conditions associated with decreasing the number of ovulations, including multiparity, may have a protective effect for the prevention of ovarian cancer. However, the more invasive prevention interventions, such as prophylactic surgery and genetic screening, should be reserved for those individuals identified to be at high risk based on their inherited risk for developing ovarian cancer.

Although a number of agents have been investigated as chemoprevention of ovarian cancer, including oral contraceptives, aspirin, nonsteroidal anti-inflammatory agents, and retinoids, none of these agents is currently accepted as a standard treatment for the prevention of ovarian cancer. Oral contraceptives may be considered for patients at high risk of ovarian cancer as they inhibit ovulation, which reduces the potential for damage to the ovarian epithelium. When taken for longer than 10 years, oral contraceptives decrease the relative risk to less than 0.4.[13] Because oral contraceptive use has been associated with an increased risk of breast cancer, individuals with a family history of breast cancer should carefully consider the use of

oral contraceptives as chemoprevention of ovarian cancer, though modern oral contraceptives are far less likely to increase the risk of breast cancer than those used prior to 1975.[13]

Prophylactic Surgery

Prophylactic surgical interventions for the prevention of ovarian cancer are reserved for patients with a significant family history or known genetic mutations such as *BRCA1* and should be postponed until after childbearing is completed, preferably between the ages of 35 to 40 years.[14] The goal is to remove healthy, at-risk organs before any carcinogenic activity is initiated, ultimately reducing the risk of developing cancer. These surgeries include prophylactic oophorectomy or bilateral salpingo-oophorectomy and tubal ligation. These procedures cause surgical menopause, which can be associated with severe hot flashes, vaginal dryness, sexual dysfunction, and increased risk for development of osteoporosis and heart disease. Because of the potential impact on quality of life and increased health risks, prophylactic surgery is not recommended as a general prevention intervention.

Although prophylactic surgical interventions are the most effective way to reduce the risk of developing ovarian cancer in high-risk populations, patients who choose to have a prophylactic oophorectomy/bilateral salpingo-oophorectomy need to be informed that complete protection is not guaranteed.[13-15] Although a 67% risk reduction has been shown, a potential 2% to 5% risk of primary peritoneal cancer remains.[15] Primary peritoneal cancers have identical histology of ovarian tumors with diffuse involvement of peritoneal surfaces. Primary peritoneal cancers can often result from "seeding" during the prophylactic surgery. It is recommended for peritoneal washings to be completed during the prophylactic surgery to check for the presence of tumor cells on peritoneal surfaces. If positive, then prophylactic surgery would change to staging and treatment surgery to determine extent of disease and remove any other possible lesions.

Tubal ligation is another procedure that can reduce the risk for developing ovarian cancer. In a case-control study, Narod and colleagues[16] reported that tubal ligation in *BRCA*-positive patients was associated with a 63% reduction in risk of developing ovarian cancer. However, it is not recommended as a sole procedure in prophylaxis. The mechanism for its protective effect is not clear, but it has been proposed that tubal ligation may limit exposure of the ovary to environmental carcinogens.

Genetic Screening

Genetic screening should be considered for all individuals who are suspected of carrying a BRCA mutation, based on family history or young age (less than 50 years old) at diagnosis and a high-grade serous tumor. Patients should be evaluated for the presence of genes such as *BRCA1*, *BRCA2*, or other genes such as those associated with hereditary nonpolyposis colorectal cancer or the hereditary breast ovarian cancer (hereditary breast and ovarian cancer syndrome) syndrome.[16] Prior to genetic screening, appropriate patient/family counseling and genetic counseling should be available to help individuals prepare and deal with the health and psychosocial implications of the genetic screening results.

CLINICAL PRESENTATION

Patients with early ovarian cancer are often asymptomatic and the ovarian mass is detected incidentally during an unrelated surgery, procedure, or imaging. Patients with ovarian cancer often present with nonspecific, vague symptoms such as abdominal bloating, pressure or pain, indigestion, or change in bowel movements.[2] These symptoms can easily be confused with symptoms of common benign gastrointestinal disorders. Patients will often not seek medical attention until these symptoms become unrelenting and bothersome, which allows the disease to progress undetected. Patients with advanced disease may report symptoms such as pain, abdominal distension, and ascites.[2]

Several groups have partnered together to educate individuals about early signs and symptoms of ovarian cancer. Goff and colleagues[17] developed a symptom index, based on a comparison of symptoms experienced in patients with ovarian cancer and a matched control group. Symptoms that were correlated with ovarian cancer include persistent or recurrent bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary symptoms (either urgency or frequency). The Gynecologic Cancer Foundation, Society of Gynecologic Oncologists, and American Cancer Society recommend that individuals who have any of those problems nearly every day for more than 2 weeks should see a gynecologist, especially if the symptoms are new and quite different from the usual state of health. Furthermore, healthcare professionals should keep ovarian cancer in the differential for patients presenting with these persistent symptoms.

The diagnostic workup for suspected ovarian cancer includes a careful physical examination including a Papanicolaou, or Pap, smear and a pelvic and rectovaginal examination.[18] The presence of a pelvic mass that is unilateral or bilateral, solid, irregular, fixed, or nodular is highly suggestive of ovarian cancer. Unfortunately, by the time a pelvic mass can be palpated on physical exam, the disease would have already advanced beyond the pelvic cavity. A detailed family history should be taken, especially noting the number and pattern of first-degree relatives with malignancies. All patients with suspected ovarian malignancies should be referred to a gynecologic oncologist for evaluation as survival is increased when primary assessment and surgery is performed by a specialist.[19]

4 A complete blood count, chemistry profile (including liver and renal function tests), and CA-125, carcinoembryonic antigen, or CEA, and cancer antigen 19-9, or CA19-9, levels should be performed. Although CA-125 is a nonspecific antigen, it is the best current tumor marker for epithelial ovarian carcinoma.[18] A normal CA-125 value is less than 35 units/mL (kU/L). If the CA-125 is elevated at the time of diagnosis, changes in CA-125 levels correlate with tumor burden. Rising CA-125 levels are often associated with disease progression, but CA-125 can be elevated in various other conditions such as different phases of the menstrual cycle, diverticulitis, endometriosis, as well as other nongynecologic cancers. When a patient presents with an abdominal mass, it is important to rule out other cancers in the abdominal cavity. Carcinoembryonic antigen and CA19–9 are markers for other gastrointestinal cancers and may be helpful in the differential diagnosis.

Other diagnostic tests should include a TVUS or abdominal ultrasonography, chest radiography, computed tomography, magnetic resonance imaging, or positron emission tomography scan. An upper gastrointestinal series, intravenous pyelogram, cystoscopy, proctoscopy, or barium enema is sometimes indicated to confirm diagnosis and extent of disease.

CLINICAL PRESENTATION: Ovarian Cancer

General

- Ovarian cancer is sometimes referred to as “the silent killer” because of the vague nonspecific signs and symptoms that contribute to the delay in diagnosis.

Symptoms

- The patient may complain of abdominal discomfort, nausea, dyspepsia, flatulence, bloating, fullness, early satiety, urinary frequency, change in bowel function (diarrhea or constipation), weight change, and digestive disturbances.

Signs

- Abdominal or pelvic mass may be palpable.
- Lymphadenopathy may be present.
- Vaginal bleeding may be irregular.
- Patient may have signs of ascites (abdominal distension, shifting, and dullness to percussion—may present like “pregnant abdomen”).

Laboratory Tests

- CA-125 may be elevated (normal level is <35 units/mL [kU/L]).
- Abnormalities in liver function tests may suggest hepatic involvement.
- Abnormalities in renal function tests may suggest compression of the renal system by the tumor.

TREATMENT

Desired Outcomes

The goals of treatment of ovarian cancer depend upon the FIGO stage at diagnosis. While ideally "treatment for cure" is desired, it is important to set realistic expectations for the patient. Most patients will achieve a complete response to the initial multimodality treatment, but over 75% of these patients will have disease recurrence.[20] Although overall survival has not significantly changed for ovarian cancer patients, progression-free survival has improved, which translates to less time on chemotherapy and overall improvement in quality of life for these patients.

In patients who present with metastatic disease or are not surgical candidates, the goal of treatment is to alleviate symptoms and prolong survival as long as quality of life is acceptable. In the setting of recurrent platinum-resistant ovarian cancer, the treatment goal is also to alleviate symptoms and prolong survival as long as quality of life is acceptable.

General Approach

5 A multimodal approach that includes comprehensive surgery and chemotherapy is used for the initial treatment of ovarian cancer with curative intent. Although most patients will initially achieve a complete response, more than 50% will recur within the first 2 years.[21] A clinical complete response to treatment is defined as no evidence of disease by physical examination or diagnostic tests and a normal CA-125 level.

Chemotherapy regimens for ovarian cancer have evolved over the past several decades to the current standard of care for first-line treatment that includes a taxane- and platinum-based regimen. Certain subgroups of patients have a better or worse response to chemotherapy. The histologic subtype of the tumor is a prognostic factor; clear cell histology is more likely to be poorly differentiated, faster growing, and have intrinsic drug resistance.[2,9] However, the extent of residual disease, size larger than 1 cm, and tumor grade are better predictors of response to chemotherapy and overall survival.[2] In general, younger patients have a better performance status and tolerate chemotherapy better than older adult patients. For unknown reasons, white women tend to have a worse prognosis and response to therapy as compared with women of other ethnic backgrounds.[2]

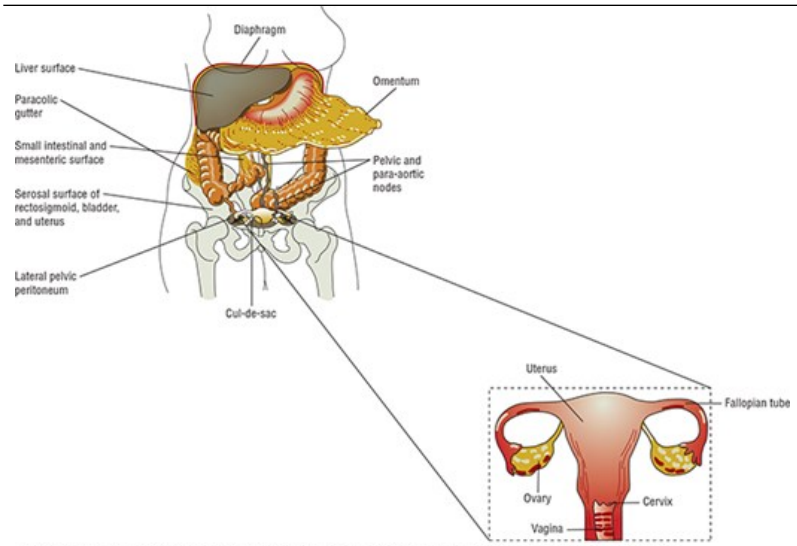
In patients with recurrent ovarian cancer, the goals of treatment are to relieve symptoms such as pain or discomfort from ascites, slow disease progression, and prevent serious complications such as small bowel obstructions.

Surgery

Surgery is the primary treatment intervention for ovarian cancer.[22-24] Surgery may be curative for selected patients with limited stage IA disease. Primary surgical treatment includes a total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO), omentectomy, and lymph node dissection (Fig. 156-1).[22-24] The primary objective of the surgery is to optimally debulk the tumor to remove all gross disease.[18] Long-term follow-up studies confirm that residual disease smaller than 1 cm correlates with higher complete response rates to chemotherapy and longer overall survival as compared to patients with bulky residual disease (>1 cm).[23]

FIGURE 156-1

Staging laparotomy for ovarian cancer with diagram of female reproductive tract (uterus, fallopian tubes, ovaries, and vagina). Dashed line box outlines what is removed during the TAH/BSO. *(Data from References 22-24.)*

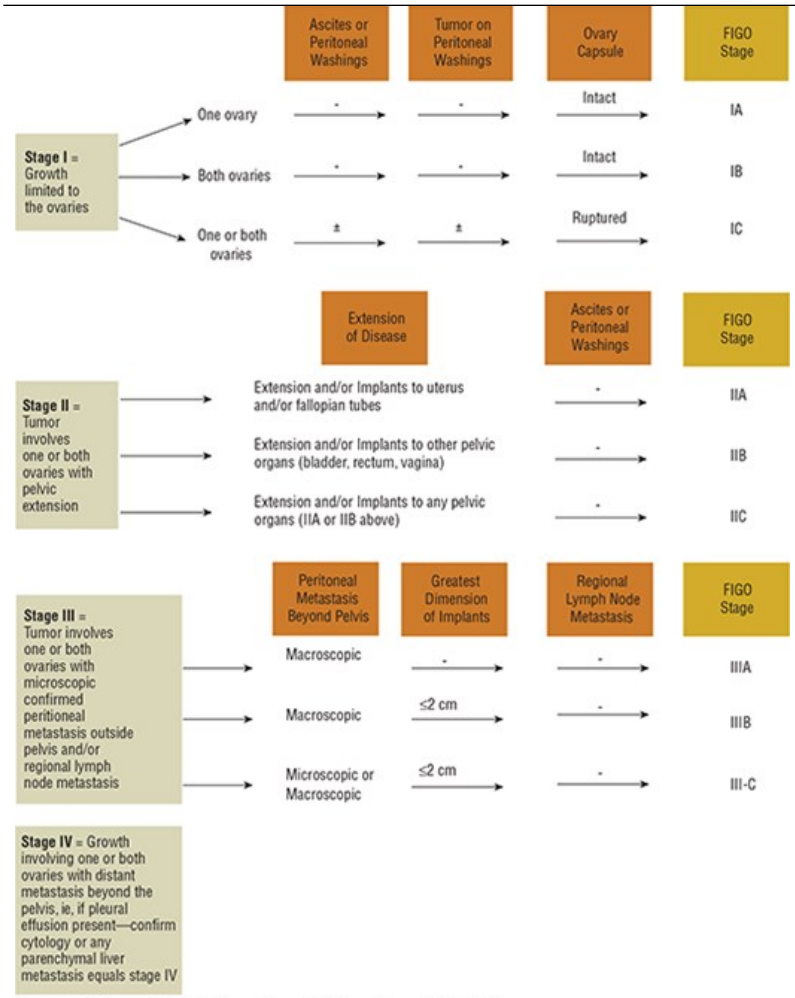


Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

A comprehensive exploratory laparotomy is vital for the accurate confirmation of diagnosis and staging of ovarian cancer.[22,23] Unlike other cancers that are typically diagnosed by biopsy or laboratory results and clinically staged by results from imaging tests, gynecologic cancers are surgically diagnosed and then staged according to the FIGO staging algorithm (Fig. 156-2). The FIGO staging system requires an extensive surgery by an experienced gynecologic oncologist. The training and skill of the surgeon has a significant effect on prognosis, with definitive benefit of a trained gynecologic oncologist performing surgery as compared with a gynecologist or general surgeon.[19,25] The reasons for this approach include (a) pelvic tumors cannot be readily biopsied without risk of "tumor seeding," which can increase the risk of recurrence, and (b) surgical staging takes into account the presence of microscopic disease in samples obtained by pelvic washing and lymph node dissection and read by a pathologist during the surgical procedure. It is recommended that the initial surgical staging and tumor-debulking surgery be completed by a trained gynecologic oncology surgeon when ovarian cancer is suspected to prevent understaging and to optimize overall outcome.[18,19,22,26]

FIGURE 156-2

FIGO staging algorithm.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Secondary cytoreduction or interval debulking is when surgery is performed after completion of some or all chemotherapy to remove residual disease. Some protocols include additional cycles of chemotherapy after the surgical procedure. The importance of cytoreduction before, during, or after chemotherapy is still controversial, but it has been recommended to facilitate response to chemotherapy and improve overall survival.[18] Randomized trials of secondary surgical cytoreduction have reported conflicting results. In a study of 550 women with stage III or IV disease treated with primary cytoreductive surgery and three cycles of paclitaxel and cisplatin, patients randomized to receive secondary cytoreductive surgery followed by three more cycles of chemotherapy had similar progression-free survival and overall survival as compared with those randomized to receive three more cycles of chemotherapy alone.[27]

The overall effect of interval debulking is influenced by several factors, including initial response to chemotherapy, the amount of residual disease before and after second-look surgery, and the presence of microscopic residual disease. The results of recent trials suggest that secondary surgical cytoreduction does not prolong survival in patients who are treated with maximal primary cytoreductive surgery followed by appropriate postoperative chemotherapy.[28]

"Second-look surgery" is an elective surgical procedure performed in patients who achieve a clinical complete response after primary chemotherapy to determine if any visible or microscopic disease is present in the peritoneal cavity. The benefit of "second-look laparotomy" to evaluate residual disease after completing chemotherapy remains controversial because it has been difficult to establish any impact on overall survival. It has questionable benefit because about 50% of those with a negative second look still relapsed.[27] If visible or microscopic disease is detected during second look, then the clinician may decide to give additional chemotherapy. But if no visible or microscopic disease is detected during second look, the clinician may decide to observe and monitor the patient. Use of laparoscopic surgical techniques is controversial for initial surgery but is sometimes

considered in debulking of recurrent or advanced disease when the intent is palliative rather than curative.[24] In patients with recurrent disease, the goal of debulking surgery is to relieve symptoms associated with complications such as small bowel obstructions and to improve the patient's quality of life.

Radiation Therapy

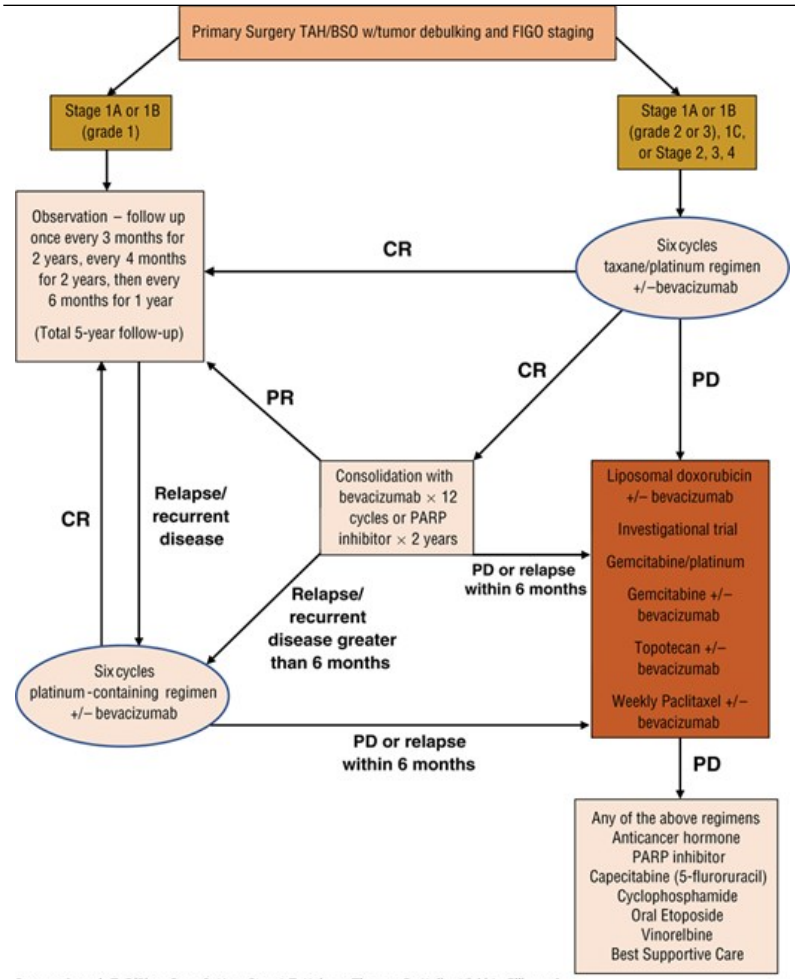
Radiation therapy has a limited role in the management of ovarian cancer. Use of radiation therapy for treatment of early stage disease has no impact on overall survival.[29] Radiation therapy is most beneficial for palliation of symptoms in patients with recurrent pelvic disease, often associated with small bowel obstructions. The two forms of radiation therapy used in ovarian cancer are external beam whole-abdominal irradiation and intraperitoneal isotopes such as phosphorus-32, or ^{32}P. Alleviation of symptoms with external beam whole-abdominal irradiation is associated with a significant improvement in the patient's quality of life. The recommended dose ranges from 35 to 45 Gy (3,500-4,500 rad), depending on the treatment history and ability to tolerate radiation treatments.

First-Line Chemotherapy

The mainstay of ovarian cancer treatment is chemotherapy. It is used as a component of first-line treatment after completion of surgery and is the primary modality of treatment for recurrent ovarian cancer. Systemic chemotherapy with a taxane and platinum regimen following optimal surgical debulking is the standard of care for treatment of epithelial ovarian cancer (Fig. 156-3).[18] Table 156-1 summarizes the chemotherapeutic regimens used as the initial treatment of newly diagnosed epithelial ovarian cancer. More than 60 randomized controlled clinical trials have evaluated combination chemotherapy regimens for the treatment of advanced ovarian cancer, and a meta-analysis of these trials confirms the efficacy of platinum and taxane regimens over other regimens.[30]

FIGURE 156-3

Management of newly diagnosed, refractory, and progressive epithelial ovarian cancer. (CR, complete response; PD, progression of disease; PR, partial response; TAH/BSO, total abdominal hysterectomy/bilateral salpingo-oophorectomy).



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

TABLE 156-1

Initial Chemotherapeutic Regimens of Epithelial Ovarian Cancer

Regimen	Initial Dose(s)/Usual Range	Cycle Frequency
Paclitaxel + carboplatin	Paclitaxel 175 mg/m^2 IV (3-hour infusion) day 1	Every 21 days
	Carboplatin AUC 5–6 IV day 1	
Paclitaxel + carboplatin + bevacizumab	Paclitaxel 175 mg/m^2 IV (3-hour infusion) day 1	Every 21 days
	Carboplatin AUC 5-6 IV day 1	
	Bevacizumab 7.5-15 mg/kg IV on day 1	
Paclitaxel + carboplatin (dose-dense)	Paclitaxel 80 mg/m^2 IV (1-hour infusion) on days 1, 8, 15	Every 21 days
	Carboplatin AUC 5-6 IV day 1 or AUC 2 on days 1, 8, and 15	
Paclitaxel + cisplatin (IP)	Paclitaxel 135 mg/m^2 IV infused over 24 hours on day 1	Every 21 days
	Cisplatin 100 mg/m^2 IP infused over 1 hour on day 2	
	Paclitaxel 60 mg/m^2 IP infused over 1 hour on day 8	
Carboplatin + pegylated liposomal doxorubicin	Carboplatin AUC 5 IV day 1	Every 28 days
	Pegylated liposomal doxorubicin 30 mg/m^2 IV day 1	
Docetaxel + carboplatin	Docetaxel 75 mg/m^2 IV day 1	Every 21 days
	Carboplatin AUC 5-6 IV day 1	

Single-agent alkylating agents such as melphalan, and later cyclophosphamide, were used for the treatment of advanced ovarian cancer until cisplatin was introduced in the 1970s. Combination chemotherapy regimens containing cisplatin and cyclophosphamide achieved higher response and overall survival rates than regimens without cisplatin in patients with advanced ovarian cancer.[31] Based on the results of these trials, the combination of cisplatin plus cyclophosphamide remained the standard of care for the treatment of ovarian cancer until the early 1990s.

The combination of paclitaxel (135 mg/m^2 over 24 hours) and cisplatin (75 mg/m^2) has been an accepted standard of care for the treatment of ovarian cancer because of its effectiveness since the early 1990s. It is associated with a median progression-free survival of 18 months and overall survival of 38 months from the Gynecologic Oncology Group (GOG)-11 and OV10 studies.[32,33] Neutropenia, alopecia, and peripheral neuropathy are common adverse drug reactions.

Carboplatin can be substituted for cisplatin, which spares patients from the significant nephrotoxicity and peripheral neuropathy associated with cisplatin. Several prospective randomized comparisons of carboplatin plus paclitaxel versus cisplatin plus paclitaxel in patients with advanced ovarian cancer have shown carboplatin plus paclitaxel is equally efficacious and better tolerated than cisplatin and paclitaxel.[34-37] As expected, the incidence of nausea and vomiting, nephrotoxicity, and peripheral neuropathy is higher in patients in the cisplatin arm, while patients in the carboplatin arm experienced more thrombocytopenia. Based on these results, paclitaxel plus carboplatin is the preferred standard-of-care regimen.

While most chemotherapy drugs used to treat ovarian cancer are dosed according to body surface area, or BSA, carboplatin dosing is personalized based on each individual's renal function with the Calvert formula: carboplatin dose = area under the curve (AUC) × (glomerular filtration rate [GFR] + 25).[38] When it was originally developed and validated, measured GFR was used in the Calvert equation. However, estimated creatinine clearance (CrCl) is now used in clinical practice in place of measured GFR. Despite more than 30 years of clinical use, it is still not clear which equation to use to estimate CrCl and the best method to estimate CrCl in certain patient subgroups. The use of personalized carboplatin dose has reduced potential toxicity such as thrombocytopenia, neuropathy, and nephrotoxicity.[38] Personalized dosing of carboplatin is one of the reasons why it is the preferred platinum agent over cisplatin for primary treatment for ovarian cancer.[36]

Similarly the use of docetaxel as a substitute for paclitaxel has been evaluated as paclitaxel can cause significant peripheral neuropathy over time. The results of the Scottish Randomized Trial in Ovarian Cancer, or SCOTROC, study showed that the substitution of docetaxel for paclitaxel does not compromise efficacy and improves tolerability, particularly neurotoxicity, but patients receiving docetaxel experienced more grade 3 to 4 neutropenia and neutropenic complications.[39] These findings were not confirmed in another randomized controlled trial. However, based on the results of this study, the combination of docetaxel plus carboplatin is considered a reasonable treatment option for patients with advanced ovarian cancer. Docetaxel and paclitaxel both cause alopecia and have a risk of infusion-related reactions or true hypersensitivity reactions, though reactions are more common with paclitaxel. Paclitaxel infusions require premedication with a corticosteroid, diphenhydramine, and an H_2-blocker like famotidine to help prevent severe reactions. Due to the risk of fluid retention with docetaxel, premedication with dexamethasone is recommended to reduce the incidence and severity. Six cycles of paclitaxel plus carboplatin following tumor-debulking surgery remain the current standard of care for treatment of advanced ovarian cancer. Although the choice of taxane or platinum agent does not appear to have a major effect on antitumor activity, the impact of paclitaxel dose and frequency of administration has been controversial.[40-42] Due to less favorable treatment-related toxicities and questionable benefit on progression-free survival, dose-dense weekly paclitaxel regimens are not widely used.

Intraperitoneal (IP) chemotherapy was initially employed as palliative care in the management of ascites and uncontrolled intra-abdominal tumors based on the rationale that exposure of the tumor to high drug concentrations would increase tumor drug uptake by passive diffusion and ultimately cancer cell death.[43] The increase in AUC exposure in the peritoneal cavity was demonstrated, but the correlative increase in drug uptake in tumor tissue has yet to be validated in any preclinical or clinical study.

IP chemotherapy has demonstrated benefit in the first-line treatment of patients with optimally debulked advanced-stage ovarian cancer.[44,45] In a landmark GOG-172 study, which evaluated the intravenous combination regimen of paclitaxel (135 mg/m^2 over 24 hours) and cisplatin (75 mg/m^2) or a new combination regimen that included intravenous paclitaxel (135 mg/m^2 over 24 hours) followed by cisplatin 100 mg/m^2 IP infused over 1 hour on day 2, and then paclitaxel 60 mg/m^2 IP infused over 1 hour on day 8.[46] Both treatment regimens were given once every 21 days for a total of six cycles. Patients receiving IP chemotherapy experienced a 5.5-month increase in median progression-free survival and a 15.9-month increase in overall survival.[46] A secondary analysis by Tewari and colleagues[47] of patients from GOG-172 and GOG-114 IP therapy studies reported a 10.4 month improvement in the median overall survival and 23% decreased risk of death in those patients that had received IP chemotherapy compared to IV chemotherapy. Contributing factors that negatively impacted survival included gross residual disease, clear cell or mucinous histology, and not completing all six cycles of IP chemotherapy.

A limitation of IP therapy is significantly more toxicity, including pain, fatigue, myelosuppression, gastrointestinal, metabolic, and neurotoxicity.[18,46,48,49] The significant increase in systemic toxicity, primarily neurotoxicity, has led to the question of whether IP carboplatin could be substituted for IP cisplatin. Although these platinum agents have demonstrated equal efficacy when administered intravenously (IV) to ovarian cancer patients, it is difficult to extrapolate the IP activity of cisplatin to carboplatin because of the difference in molecular size of cisplatin versus carboplatin and the importance of passive diffusion of drug into the tumor. Most clinical trials used platinum agents given IP until the GOG-172 trial that incorporated IP paclitaxel. Many clinicians are concerned about how to manage hypersensitivity reactions to either platinum or taxane agents when administered IP.

In the National Comprehensive Cancer Network (NCCN) guidelines, IP chemotherapy is an option for first-line treatment of stage II to III, optimally debulked, <1 cm residual disease, ovarian cancer but is not without clinical controversy.[18] Because of the significant toxicities associated with IP therapy, only carefully selected patients should receive IP therapy. Ideal candidates for IP therapy are younger patients with good performance status, minimal comorbidities, adequate renal and liver function, and optimally debulked disease without significant bowel resection.[18,49] The IP regimens

have recently fallen out of favor due to the results of GOG-252. Bevacizumab was administered in combination with IV/IP paclitaxel and carboplatin compared to IV/IP paclitaxel and cisplatin, or IV paclitaxel and carboplatin.[50] With the addition of bevacizumab to first-line chemotherapy, no progression-free or overall survival benefit with IP administration was observed and the IV regimen was as effective and better tolerated.[50]

Neoadjuvant Chemotherapy

7 Neoadjuvant chemotherapy is first-line treatment for patients who are poor surgical candidates or patients with bulky or significant tumor burden.[51] The neoadjuvant chemotherapy regimen typically includes a combination of taxane with platinum agent and is administered every 21 to 28 days as tolerated with intent to reduce tumor burden to where it potentially could be surgically resected and ideally optimally debulked during surgery.[51] After surgery, patients usually receive another three to six cycles (IV or IP/IV), depending on their response to chemotherapy.[18,52] In patients who are poor candidates for surgery because of comorbidities, the primary intent of neoadjuvant chemotherapy is to relieve symptoms and slow disease progression. In this setting, palliative chemotherapy alone has not been curative for patients with advanced ovarian cancer.[51] If tolerated, these patients will receive the standard taxane plus platinum chemotherapy regimen once every 3 to 4 weeks. Another option for palliative neoadjuvant chemotherapy, especially in older adult patients, is single-agent carboplatin once every 4 weeks.

Consolidation Therapy and Maintenance Therapy

Consolidation therapy is given to patients without “measurable disease” after the completion of primary chemotherapy, with the goal of eliminating any microscopic residual disease that may be present to extend progression-free and overall survival. It will have a set duration to therapy and typically is less toxicity than primary chemotherapy regimens. Patients undergoing consolidation therapy are monitored for signs of recurrent disease. Maintenance therapy, however, is given to patients with measurable disease, with the goal of prevent progression/growth of disease. It is given for an undetermined duration and may alternate or “switch maintenance” between aggressive cytotoxic regimens and less toxic regimens. Patients undergoing maintenance therapy are monitored for clinical response or progression of disease. Both bevacizumab and PARP inhibitors are the only agents approved by the US Food and Drug Administration for use as consolidation in the first-line setting however mislabeled as “first-line maintenance”. For the purpose of this chapter, this therapy will be referred to consolidation because there is no measurable disease and it is administered for a defined two-year duration.

Consolidation with bevacizumab and/or PARP inhibitor therapy is recommended by the NCCN guidelines following first-line treatment depending on the agents used as first-line therapy and the patient’s mutation status (category 2A recommendation).[18] Single-agent bevacizumab is recommended as consolidation therapy only if it was used with first-line chemotherapy based on GOG-0218 and ICON7.[18] No data exists to support bevacizumab consolidation if it was not used with first-line chemotherapy.

Olaparib, an oral PARP inhibitor, should be considered as consolidation therapy in individuals with a germline mutation in *BRCA1* or *BRCA2* and a response to first-line platinum-based therapy. Continuous twice-daily oral dosing of olaparib provides substantial clinical benefit in progression-free survival when compared to placebo.[53] The use of consolidation therapy with olaparib results in a 70% lower risk of disease progression or death. Niraparib, another PARP inhibitor, should also be considered as consolidation because it improves progression-free survival by 5.6 months (13.8 months compared to 8.2 months with placebo).[54] This effect is more pronounced in patients with *BRCA* or other homologous recombination repair gene mutations. The NCCN guidelines recommend niraparib as an option for those who are *BRCA1/2* wild-type or unknown who did not receive bevacizumab with primary treatment and as an option for patients with a *BRCA1/2* mutation.[18]

Bevacizumab in combination with olaparib was studied as consolidation following frontline chemotherapy with bevacizumab in patients with homologous recombination repair gene mutations, including those without *BRCA* mutations, in the PAOLA-1 study.[55] The addition of olaparib to bevacizumab resulted in a 51% risk reduction in disease progression or death compared to bevacizumab alone.[55] One major limitation of this study is that it did not include an arm with olaparib alone, so the addition of bevacizumab to olaparib compared to single-agent olaparib is unknown.

The clinical challenge with consolidation therapy after first-line treatment is selection of which agent based on molecular profile and cost of therapy. Patients need to be evaluated for tumor molecular status, residual toxicity, renal function, and comorbidities to determine if bevacizumab or PARP inhibitor or perhaps combination of bevacizumab plus PARP inhibitor would be the best option for consolidation. However, from the cost perspective neither bevacizumab nor PARP inhibitors are cost effective for consolidation therapy after completion of primary treatment of ovarian cancer.[56]

Treatment of Recurrent Disease

Although most patients will achieve a complete response to initial treatment, most patients will eventually have recurrence of their disease within the first 2 years. When a patient relapses, the prognostic factors are similar to the factors after initial surgery except that the disease-free interval—defined as the length of time that has lapsed since the completion of chemotherapy—should be considered to determine if the tumor is likely to be drug resistant to agents used in first-line treatment (ie, platinum and taxanes). If recurrence occurs less than 6 months after completion of chemotherapy or if the patient progresses during platinum-based chemotherapy, the tumor is defined as platinum-resistant. Patients with platinum-sensitive disease generally have a better prognosis than platinum-resistant patients.

[8,9] If the patient had a clinical complete response to first-line chemotherapy and the recurrence occurred more than 6 months after chemotherapy is completed, the tumor is considered platinum-sensitive. In patients with platinum-sensitive ovarian cancer, the standard of care is to treat the first recurrence with a doublet, platinum-containing chemotherapy regimen (Table 156-2). Because the chemotherapy agents used for second-line treatment of recurrent or refractory platinum-resistant disease have similar response rates that average less than 30%, the selection of the agent depends on the toxicity profile of the agent, physician preference, patient performance status, residual toxicities, and patient convenience (see Fig. 156-3). In this setting, the intent of treatment is to prolong survival and alleviate symptoms, not necessarily and unlikely to achieve another “complete response” to chemotherapy. Because of poor response rates of the available agents, participation in a clinical trial of an investigational agent is recommended if available for patients with recurrent platinum-resistant ovarian cancer.

TABLE 156-2

Chemotherapy Regimens for Platinum-Sensitive Recurrent Ovarian Cancer

Regimen	Initial Dose(s)/Usual Range	Cycle Frequency
Carboplatin + gemcitabine	Carboplatin AUC 5 IV day 1	Every 21 days
	Gemcitabine 800 mg/m^2 IV days 1 and 8	
Carboplatin + gemcitabine + bevacizumab	Carboplatin AUC 5 IV day 1	Every 21 days
	Gemcitabine 800 mg/m^2 IV days 1 and 8	
	Bevacizumab 15 mg/kg IV day 1	
Carboplatin + pegylated liposomal doxorubicin	Carboplatin AUC 5 IV day 1	Every 28 days
	Pegylated liposomal doxorubicin 30 mg/m^2 IV day	
Carboplatin + pegylated liposomal doxorubicin + bevacizumab	Carboplatin AUC 5 IV day 1	Every 28 days
	Pegylated liposomal doxorubicin 30 mg/m^2 IV day	
	Bevacizumab 15 mg/kg IV days 1 and 15	
Carboplatin + paclitaxel	Carboplatin AUC 5-6 IV day 1	Every 21 days
	Paclitaxel 175 mg/m^2 IV day 1	
Carboplatin + paclitaxel + bevacizumab	Carboplatin AUC 5-6 IV day 1	Every 21 days
	Paclitaxel 175 mg/m^2 IV day 1	
	Bevacizumab 15 mg/kg IV day 1	
Cisplatin + gemcitabine	Cisplatin 30 mg/m^2 IV days 1 and 8	Every 28 days
	Gemcitabine 600-750 mg/m^2 IV days 1 and 8	
Bevacizumab	Bevacizumab 10 mg/kg on days 1 and 15 or	Every 28 days
	Bevacizumab 15 mg/kg IV on day 1	Every 21 days
Olaparib	300 mg PO twice daily	
Niraparib	300 mg PO daily	
Rucaparib	600 mg PO twice daily	

PO, by mouth.

Platinum-Sensitive Disease

Retreatment with a platinum-containing regimen should be considered in patients with platinum-sensitive disease. The 2021 NCCN guidelines recommend the combination of platinum agent with gemcitabine, pegylated liposomal doxorubicin, or paclitaxel for treatment of platinum-sensitive recurrent ovarian cancer (Table 156-3).[18] In addition, the combination of gemcitabine plus cisplatin, gemcitabine plus carboplatin and bevacizumab and carboplatin plus paclitaxel and bevacizumab has demonstrated improvement in progression-free survival.[57-59] Carboplatin alone or any of the second-line agents is recommended for patients with platinum-sensitive disease who are unable to tolerate additional combination chemotherapy regimens because of residual toxicity or poor performance status.

TABLE 156-3

Chemotherapy Regimens for Platinum-Resistant Recurrent Ovarian Cancer

Drug(s)	Initial Dose(s)/Usual Range	Cycle Frequency
Paclitaxel + bevacizumab	Paclitaxel 60-80 mg/m^2 IV days 1, 8, 15, and 22	Every 28 days
	Bevacizumab 10 mg/m^2 IV days 1 and 15	
Paclitaxel	60-80 mg/m^2 IV days 1, 8, 15, and 22	Every 28 days
Pegylated liposomal doxorubicin + bevacizumab	Pegylated liposomal doxorubicin 40 mg/m^2 IV day 1	Every 28 days
	Bevacizumab 10 mg/m^2 IV days 1 and 15	
Pegylated liposomal doxorubicin	40 mg/m^2 IV day 1	Every 28 days
Topotecan + bevacizumab	Topotecan 3-4 mg/m^2 IV days 1, 8, and 15	Every 28 days
	Bevacizumab 10 mg/m^2 IV days 1 and 15	
Topotecan	3-4 mg/m^2 IV days 1, 8, and 15	Every 28 days
Gemcitabine	800 mg/m^2 IV days 1 and 8	Every 21 days
Docetaxel	100 mg/m^2 IV day 1	Every 21 days
Etoposide (oral)	50 mg/m^2 PO daily on days 1-21	Every 28 days
Cyclophosphamide (oral) + bevacizumab	Cyclophosphamide 50 mg PO once daily	Every 28 days
	Bevacizumab 10 mg/kg on days 1 and 15	
Bevacizumab	10 mg/kg on days 1 and 15 OR	Every 28 days
	15 mg/kg IV on day 1	Every 21 days
Olaparib	300 mg PO twice daily	
Niraparib	300 mg PO daily	
Rucaparib	600 mg PO twice daily	

Biologic and targeted agents play an important role in the treatment of recurrent disease. Bevacizumab is a recombinant humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), a key mediator of angiogenesis. In patients with platinum-sensitive recurrent disease, the addition of bevacizumab to chemotherapy (eg, carboplatin/gemcitabine, carboplatin/paclitaxel) improves disease outcomes.[58,59] Due to the toxicity profile of bevacizumab, patients considered for bevacizumab therapy must be carefully selected. Further details regarding the role of bevacizumab and other targeted and biologic agents in the treatment of ovarian cancer will be discussed in the following section.

The preferred regimen for platinum-sensitive recurrent disease varies by clinician. Some clinicians will recommend retreatment with a chemotherapy regimen including a platinum agent. Other clinicians suggest that the platinum-free interval for these patients should be extended and recommend that recurrent disease first be treated with a nonplatinum regimen (ie, liposomal doxorubicin) and reserve the platinum agent until the next relapse.

Platinum-Resistant Disease

Patients frequently present with recurrent drug-resistant disease after initial platinum-based therapy and cytoreductive surgery.[2] Patients who progress on a platinum agent or have no response are considered "platinum-refractory," while those patients who have recurrence within 6 months of completing a platinum-containing regimen are considered "platinum-resistant."[18] The NCCN guidelines list many possible treatment options for recurrent platinum-resistant or refractory ovarian carcinoma.[18] The optimal chemotherapeutic agent or regimen in the treatment of platinum-resistant disease is unclear. Ideally, the agent should be active in ovarian cancer and non–cross-resistant with taxanes or platinum agents. Unfortunately, the response rate is low for all agents in platinum-refractory or resistant ovarian cancer.[2] Patients should typically be evaluated for response after treatment with at least three cycles of the chemotherapy agent or regimen. Because partial responses are rare, stable disease with relief of symptoms is considered a treatment success. If no response is observed, then an alternative chemotherapy regimen may be selected. Because all the potential agents have similar efficacy, the selection of agents and sequence used for treatment as the patient progresses will vary based on residual toxicity **and the adverse effect profile of the regimen** (**Table 156-4**), dosing schedule, patient convenience, and physician preference.

TABLE 156-4

Adverse Drug Reactions of Treatments for Ovarian Cancer

Class	Drug	Common Adverse Drug Reactions
Taxane agents	Paclitaxel	Peripheral neuropathy (DLT), nausea/vomiting, alopecia, hypersensitivity reactions
	Docetaxel	Neutropenia (DLT), fluid retention, nail disorders, myelosuppression, alopecia
Platinum analogues	Carboplatin	Myelosuppression (DLT), nephrotoxicity, nausea/vomiting, electrolyte wasting, hypersensitivity reactions
	Cisplatin	Nephrotoxicity (DLT), nausea/vomiting, ototoxicity, peripheral neuropathy, myelosuppression, electrolyte wasting, diarrhea
Anthracycline	Liposomal doxorubicin	Hand-foot syndrome, mucositis, myelosuppression, discoloration of body fluids, cardiotoxicity
Pyrimidine Antimetabolite	Gemcitabine	Myelosuppression, flu-like symptoms (fever, headache, arthralgias, myalgias), transient skin rash, transient hepatic dysfunction, pneumonitis
Topoisomerase Inhibitor	Topotecan	Myelosuppression (DLT), fatigue
Anti-angiogenesis agent	Bevacizumab	Hypertension, proteinuria, headache, increased risk of thrombosis, surgery and wound healing complications
PARP inhibitors	Olaparib	Fatigue, anemia, nausea
	Niraparib	Fatigue, nausea, thrombocytopenia, neutropenia, elevated liver function tests
	Rucaparib	Nausea, fatigue, anemia, elevations in liver function tests, rash

DLT, dose limiting toxicity; PARP, poly-ADP-ribose polymerase.

Topotecan, an analog of the plant alkaloid 20(S)-camptothecin, is active in patients with metastatic ovarian cancer and is non–cross-resistant with platinum-based chemotherapy.[60] It produces an overall response rate of 21%, with a median time-to-progression of 32 weeks.[61] Topotecan is well-tolerated with minimal nonhematologic toxicities.[61,62] The dose-limiting toxicity is myelosuppression with neutropenia as the most common adverse drug reaction but patients may experience fatigue as well. Patients receiving topotecan have often received multiple other lines of chemotherapy, so they may require dose adjustments or treatment delays for their counts to recover between cycles. For patients unable to tolerate conventional topotecan over 5 days, weekly topotecan on days 1, 8, and 15 of a 28-day cycle may be considered as it has been found to be better tolerated.[63]

Pegylated liposomal doxorubicin is one of the primary agents used for second-line therapy of recurrent ovarian cancer.[64-66] The drug tends to be better tolerated than topotecan, which is important for heavily pretreated patients with advanced disease. The overall response rate with pegylated liposomal doxorubicin is 20%.[65] Median overall survival is longer with pegylated liposomal doxorubicin than topotecan, with a median of 108 weeks versus 71 weeks. Palmar–plantar erythrodysesthesia (PPE) occurs with pegylated liposomal doxorubicin. However, the incidence of PPE in current clinical practice has decreased because the standard dose of pegylated liposomal doxorubicin used currently (40 mg/m^2) is less than the dose that was used in the initial clinical trials and approved by the FDA.[67] Other adverse drug reactions include cardiotoxicity, mucositis, skin rash or hyperpigmentation, and discoloration of urine or body fluids for a day or two following the infusion due to the red color of the drug.

Gemcitabine, a pyrimidine antimetabolite, is also widely used in the treatment of recurrent platinum-resistant ovarian cancer. Although the overall response rate is only about 13% to 22% with single-agent gemcitabine in patients with platinum-refractory recurrent ovarian cancer, an additional 16% to 50% of patients have stable disease for a median of 7 months.[68] The main toxicities include myelosuppression, fatigue, myalgia, and skin rash.

Other agents that have shown an overall response rate of 10% to 25% in patients with recurrent ovarian cancer include etoposide, capecitabine, tamoxifen, letrozole, vinorelbine, and oxaliplatin.[18] Response rates tend to be higher in the platinum-sensitive subgroups. Most of these agents are available in oral formulations, which allows for outpatient administration in the palliative care setting.

The three most commonly used agents in clinical practice are pegylated liposomal doxorubicin, gemcitabine, and topotecan. These agents have demonstrated efficacy when used as a single agent and in combination with other agents. Selection of chemotherapy for treatment of recurrent disease is based on the patient's residual toxicities, scheduling and convenience, and physician preference.

Biologic and Targeted Agents

Although biologic agents as single agents have not demonstrated significant activity for the treatment of ovarian cancer, the results of several clinical trials show that the addition of bevacizumab into first-line and consolidation regimens improves progression-free survival. However, the impact on overall survival is controversial. PARP inhibitors have become a mainstay for ovarian cancer, especially for patients with BRCA mutations, while other targeted therapies, like tyrosine kinase inhibitors, have a limited scope within this malignancy. Though immunotherapy has been found to be effective in many other disease types, ovarian cancer is far more resistant to its effects except in very specific situations like high microsatellite instability.

Anti-Angiogenesis Agents

Bevacizumab is a recombinant humanized monoclonal antibody that targets VEGF, a key mediator of angiogenesis. In the setting of recurrent disease, single-agent bevacizumab produces a response rate similar to other therapies of 16% to 21%.[69,70] Response rates with combinations of bevacizumab range from 15% to 80%.[69-74] However, these phase II trials have also reported a higher risk of bowel perforation in patients treated with bevacizumab-containing regimens.[69,70] Bevacizumab should therefore not be given to patients who have had recent bowel surgery or a history of significant bowel resections. Common adverse drug reactions with bevacizumab include hypertension, proteinuria, and headache, while rare but serious adverse drug reactions include thrombotic events, surgery and wound healing complications, and posterior reversible encephalopathy syndrome. Overall, bevacizumab is typically well-tolerated. In an open-label phase III study (AURELIA Study) that evaluated the combination of bevacizumab in combination with chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan), the addition of bevacizumab to chemotherapy had no significant impact on overall survival but did improve median progression-free survival (6.4 vs 3.7 months).[75] Based on this study, bevacizumab was approved for use in combination with pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan for treatment of recurrent ovarian cancer.

Recent efforts have focused on the use of bevacizumab in first-line treatment regimens. Although bevacizumab has demonstrated some progression-free survival advantages when used in combination, its effect on overall survival is not clear.[76,77] Furthermore, the benefits do not appear to justify the high cost of bevacizumab (based on pharmacoeconomic studies).[78] As a result, health insurance companies do not consistently reimburse for bevacizumab when used for the primary treatment of ovarian cancer.

Pazopanib, an oral anti-angiogenesis agent, is an alternative treatment regimen for platinum-refractory recurrence.[79] A phase 2 trial assessed oral pazopanib in patients with low-volume recurrent disease who had achieved complete response to initial therapy, with an overall response rate 18%. Single-agent pazopanib is listed as an alternative option for the treatment of platinum-resistant disease in the NCCN guidelines (category 2B recommendation).[18] Adverse drug reactions of pazopanib include diarrhea, hypertension, hair discoloration, hand-foot skin reaction, and a boxed warning for hepatoxicity.

PARP Inhibitors

10 PARP plays a critical role in the repair of single-strand DNA breaks via the base-excision repair pathway. Specifically, PARP keeps the low-fidelity nonhomologous-end-joining DNA repair machinery functioning. PARP inhibition results in double-stranded DNA breaks that cannot be repaired in cancer cells with homologous recombinant deficiency, such as those with *BRCA1/2* mutations. Three oral PARP inhibitors are commercially approved for treatment of ovarian cancer—olaparib, rucaparib, and niraparib—with similar FDA-labeled approvals for treatment and maintenance therapy for

recurrent ovarian cancer. Both olaparib and niraparib also have FDA-approved indications for "first-line maintenance treatment" after achieving a clinical complete response to platinum-based regimen for ovarian cancers.

In the treatment setting, patients with platinum-sensitive disease have a higher response rate to PARP inhibitors compared to those with platinum-resistant disease (66% vs 20%-30%).[80] However, PARP inhibitors are considered a preferred option in this setting because of the lack of active agents in platinum-resistant disease.[18]

While not commonly discussed, creatinine is a substrate of the MATE 1/2 renal transporter and drug interactions that inhibit or induce the MATE 1/2 pathway will alter serum creatinine levels and ultimately cause a change in CrCl. The class of PARP inhibitors are substrates of and inhibit the MATE 1/2 renal transporter that influences CrCl, so caution is needed in patients with renal insufficiency to monitor for cumulative toxicity.[81] Rucaparib is the only PARP inhibitor with known cytochrome P450 drug interactions involving the 1A2 and 2D6 pathways, so drug interactions must be closely evaluated.[82] The common adverse drug reactions associated with PARP inhibitors include nausea and vomiting and significant anemia with associated fatigue. Patients often require antiemetics and some require transfusion support due to drug-induced anemia. Additional serious but infrequent toxicities include thrombocytopenia, neutropenia, and rarely secondary myelodysplastic syndrome or acute myeloid leukemia. The challenge of combining PARP inhibitors with chemotherapy has been the fatigue, nausea, and significant hematological toxicity, primarily anemia, thrombocytopenia, and neutropenia. The three PARP inhibitors have comparable efficacy and toxicity profiles. Selection of PARP inhibitors will dependent upon patient factors, renal function, and potential drug interactions with concomitant medication.

Other Targeted Agents

Tyrosine kinase inhibitors such as sorafenib and pazopanib inhibit angiogenesis by specifically targeting the VEGF receptor, or VEGFR. When given as single agents, tyrosine kinase inhibitors have demonstrated some antitumor activity in ovarian cancer, but these agents are rarely used due to the toxicity profile. Estrogen receptor antagonists and aromatase inhibitors have also been studied in early phase clinical trials with modest responses.[83] Hormone therapy may be considered in patients who cannot tolerate other regimens or who have not responded to chemotherapy.[18,84]

Immunotherapy

Based on changes in chromosomal instability and epigenetic silencing in ovarian cancer, in theory immunotherapy would be a useful treatment option; however, studies to date have not demonstrated benefit in ovarian cancer. Improved survival has been correlated with the increased presence of CD3+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T-cell ratio in ovarian cancer patients provides evidence for the immunogenicity of this tumor.[85,86] Increased tumor-infiltrating lymphocytes are linked to tumors with high chromosomal instability such as those with *BRCA* mutation or epigenetic loss. Immunotherapy with pembrolizumab is currently indicated for those with high microsatellite instability, or MSI-H, tumors, which are only seen in 2% of ovarian cancers, or in patients with high tumor mutational burden with at least 10 mutations/megabase and no satisfactory alternative treatment options.[18] Dostarlimab-gxly was also recently approved in patients with solid tumors and no alternative treatment options who have deficient mismatch repair, or dMMR, or high microsatellite instability.[18]

EVALUATION OF THERAPEUTIC OUTCOMES

11 During chemotherapy, patients may experience numerous adverse drug reactions such as nausea and vomiting, myelosuppression, neuropathy, and changes in organ function. Patients receiving a taxane or platinum chemotherapy regimen should be monitored for signs of hypersensitivity or infusion-related reactions. Patients treated with paclitaxel often experience infusion-related reactions, which have been attributed to the polyethoxylated castor oil (Cremophor) diluent. Premedications including an H_1-blocker, H_2-blocker, and steroid should be administered prior to each chemotherapy administration to prevent hypersensitivity reactions. If a patient has a reaction, increasing the duration of the infusion from 3 to 6 hours may help with infusion-related reactions. For patients with a true taxane allergy, paclitaxel desensitization can be attempted with 24 hours of premedications (H_1-blocker, H_2-blocker, and steroids) followed by paclitaxel given as a titrated infusion (1:1000 → 1:100 → 1:10 → full dose) over 8 hours. With repeated exposure (ie, seven cycles or more) to carboplatin, patients can develop a delayed hypersensitivity reaction. A similar protocol can be used for carboplatin desensitization.

Ovarian cancer patients receive multiple courses of chemotherapy that can have varying effects on kidney and liver function, often with a delayed

onset. Appropriate laboratory tests should be ordered to assess organ function so that chemotherapy doses can be adjusted as indicated. Patients on platinum-containing regimens can often experience electrolyte wasting, so patients should be monitored for electrolyte replacement, IV or oral, as indicated. The use of myeloid growth factors should be considered to prevent treatment delays or dose reductions. Prevention of nausea and vomiting, both acute and delayed, is critical for patients receiving emetogenic chemotherapy regimens.

During initial taxane plus platinum chemotherapy, a CA-125 level should be obtained with each cycle and monitored for at least a 50% reduction in CA-125 after completion of four cycles, which is related to an improved prognosis. Patients who achieve a complete response after completion of first-line treatment should have follow-up once every 3 months, including CA-125, physical examination, pelvic examination, and appropriate diagnostic scans (eg, computed tomography, magnetic resonance imaging, or positron emission tomography), which should be evaluated for presence of disease. In addition to routine follow-up examinations, clinicians should monitor for resolution of any residual chemotherapy-related adverse drug reactions, including neuropathies, nephrotoxicity, ototoxicity, myelosuppression, and nausea and vomiting.

In the progressive disease or recurrent setting, CA-125 levels can be used to monitor for response and should be checked with each cycle, although no change in therapy is recommended until after completion of at least three cycles of the second-line chemotherapy. In addition to laboratory monitoring, appropriate diagnostic scans (eg, computed tomography, magnetic resonance imaging, or positron emission tomography) should be done once every three cycles. Patients need to be monitored with each cycle of chemotherapy to evaluate for new or persistent toxicities such as neuropathies, fluid retention, PPE, myelosuppression, and nausea and vomiting. Another precaution to keep in mind for patients with significant ascites, the “dry weight” or an adjusted body weight should be used for dosing chemotherapy.

Most patients with ovarian cancer will eventually progress through all chemotherapy regimens and investigational treatment options, after which the best supportive care measures should be provided to maintain patient comfort and quality of life. A plan to treat common complications of progressive ovarian cancer, including thrombosis, ascites, uncontrollable pain, and small bowel obstruction, should be developed. This plan should include an opioid-based pain regimen with both long-acting agents and short-acting opioids for breakthrough or progressive pain; it should also include a bowel regimen to prevent opioid-induced constipation. Nausea can be a problem in individuals with advanced ovarian cancer when disease progression causes ascites or partial/complete bowel obstruction. Both antiemetic medications and nonpharmacologic interventions with nutrition and hydration can be helpful. Management of partial or complete small bowel obstruction focuses on controlling symptoms of pain and nausea. Bowel rest with best supportive care may lead to spontaneous resolution of the small bowel obstruction but most often it is a complication associated with rapidly progressive disease. Palliative surgery may be considered for selected patients to relieve symptoms.

ABBREVIATIONS

AUC	area under the curve
BRCA1	breast cancer activator gene 1
BRCA2	breast cancer activator gene 2
CA-125	cancer antigen 125
CrCl	creatinine clearance
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
GFR	glomerular filtration rate
GOG	Gynecologic Oncology Group
H_1-blocker	histamine receptor 1 blocker
H_2-blocker	histamine receptor 2 blocker
IP	intraperitoneal
IV	intravenous
NCCN	National Comprehensive Cancer Network
PARP	poly-ADP-ribose polymerase
PPE	palmar–plantar erythrodysesthesia
TAH/BSO	total abdominal hysterectomy/bilateral salpingo-oophorectomy
TVUS	transvaginal ultrasound
VEGF	vascular endothelial growth factor

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SELF-ASSESSMENT QUESTIONS

1. SC is a 34-year-old individual that has no children and has a CA-125 of 18 U/mL (kU/L) that presents to the Ovarian Cancer Prevention clinic to be

screened and counseled on risk for developing ovarian cancer. SC's mother died from ovarian cancer at the age of 56 years and older sister has just been diagnosed with ovarian cancer at the age of 42 years. Does SC need to be concerned about developing ovarian cancer too?

A. No, there is hereditary relationship for the risk of developing ovarian cancer.

B. No, SC's CA-125 is within normal range.

C. Yes, individuals with two or more immediate family members with ovarian cancers have an increased risk of developing ovarian cancer.

D. Yes, SC has an elevated CA-125 and could already have cancer.

2. What are the screening recommendations for individual at average risk for the development of ovarian cancer?

A. Annual Papanicolao smear

B. CA-125 level and TVU once every 6 months

C. Annual pelvic exam

D. No screening recommended

3. Which patients should be considered for the addition of neoadjuvant chemotherapy for management of advanced ovarian cancer?

A. All patients

B. *BRCA1/2*+ patients

C. Patients with localized disease

D. Patients presenting with significant tumor burden

4. A patient with *BRCA*-mutated ovarian cancer received adjuvant carboplatin and paclitaxel with a complete response and went on to receive consolidation with olaparib. Unfortunately, 5 months after initial chemotherapy, the patient presents with worsening symptoms and progression shown on CT scans. Which of the following regimens would be appropriate for this patient to receive at this time?

A. Paclitaxel plus cisplatin

B. Paclitaxel plus carboplatin plus bevacizumab

C. Treatment on an investigational study

D. Carboplatin plus gemcitabine plus bevacizumab

5. In a patient with diabetic neuropathy, what chemotherapy regimen would you recommend for primary chemotherapy treatment of ovarian cancer?

A. Paclitaxel 175 mg/m^2 over 3 hours plus carboplatin AUC = 5 over 1 hour

B. Paclitaxel 135 mg/m^2 over 24 hours plus cisplatin 75 mg/m^2 over 4 hours

C. Docetaxel 75 mg/m^2 over 1 hour plus carboplatin AUC = 5 over 1 hour

D. Docetaxel 75 mg/m^2 over 1 hour plus cisplatin 75 mg/m^2 over 4 hours

6. A patient is receiving paclitaxel 175 mg/m^2 IV over 3 hours with carboplatin AUC 5 for primary treatment of ovarian cancer experiences a rare true allergic reaction during the first paclitaxel infusion. Which of the following would be reasonable options to allow completion of the primary chemotherapy treatment?

A. Increase the duration of the paclitaxel infusion time to 6 hours

B. Administer premedications including steroid H_1-blocker and H_2-blocker 24 hours prior to paclitaxel desensitization

C. Discontinue paclitaxel and continue with carboplatin alone for the remaining five cycles

D. Discontinue paclitaxel and replace with topotecan for the remaining five cycles

7. RT is a 27-year-old female that presented with a solid mass on the right ovary. RT underwent TAH/BSO tumor-debulking surgery and was diagnosed with Stage IIA, low-grade ovarian cancer. What adjuvant treatment should RT receive after surgery?

A. Pelvic radiation one-shot

B. Observation with routine 3-month follow-up exams

C. Paclitaxel 175 mg/m^2 over 3 hours plus carboplatin AUC = 5 over 1 hour for six cycles

D. Bevacizumab 15 mg/kg once every 3 weeks for 12 months

8. MP is a 63-year-old female with platinum-sensitive, BRCA1 positive recurrent ovarian cancer that is interested in PARP inhibitor. Which is the most common adverse drug reaction associated with olaparib that would need to be monitored for during therapy?

A. Anemia

B. Thrombocytopenia

C. Constipation

D. Liver dysfunction

9. Which of the following is a common complication of progressive ovarian cancer that may require a surgical intervention for patient comfort?

A. New peritoneal implants

B. Small bowel obstruction

C. Lung nodule

D. Ascites

10. Which of the following would be the most appropriate chemotherapy treatment for patient with recurrent platinum-sensitive cancer?

A. Six cycles of carboplatin plus gemcitabine

B. Six cycles of topotecan plus bevacizumab

C. Six cycles of pegylated liposomal doxorubicin plus bevacizumab

D. Six cycles of paclitaxel plus gemcitabine

11. What supportive medications should be included in the management of ovarian cancer patient with a small bowel obstruction?

A. Ondansetron and oxycodone

B. Loperamide and oxycodone

C. Ondansetron and ibuprofen

D. Loperamide and ibuprofen

12. Which of the following regimens would be most appropriate for the treatment of platinum-resistant recurrent ovarian cancer with a low tumor mutational burden and no identified tumor mutations?

    A. Weekly paclitaxel plus carboplatin

    B. Gemcitabine plus cisplatin

    C. Pembrolizumab

    D. Pegylated liposomal doxorubicin plus bevacizumab

13. Which of the following would improve the activity of olaparib?

    A. Microsatellite instability

    B. HER2 positive disease

    C. BRCA mutation

    D. Lynch syndrome

14. Which of the following is TRUE about ovarian cancer?

    A. It is typically diagnosed at an early stage

    B. Patients often present with nonspecific, vague gastrointestinal symptoms

    C. Patients with advanced disease are often asymptomatic

    D. A common symptom of early disease is bowel obstruction

15. Which of the following is TRUE regarding CA-125 in ovarian cancer?

    A. It is a routine screening test for the detection of ovarian cancer in asymptomatic patients

    B. If within the normal range at diagnosis, changes in levels correlate with tumor burden

    C. Rising levels are often associated with disease progression

    D. In the recurrent setting, levels should be checked every 3 months

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** The risk for ovarian cancer is greater than 50% if there are two or more first-degree relatives with a diagnosis of ovarian cancer or multiple cases of ovarian and breast cancer within the same family. See "Etiology" section in the chapter for more information.

2. **D.** There is no known effective screening method for individuals of average risk of developing ovarian cancer. See "Screening and Prevention" section in the chapter for more information.

3. **D.** In patients with bulky disease, the goal of neoadjuvant chemotherapy is to reduce tumor burden to make surgery more feasible and optimal tumor debulking more likely. See "Neoadjuvant Chemotherapy" section in the chapter for more information.

4. **C.** This patient had recurrence within 6 months of the last platinum therapy, so has platinum-resistant disease. Enrollment in an investigational study is an appropriate regimen for platinum-resistant disease. See "Platinum-Resistant Disease" section in the chapter for more information.

5. **C.** The substitution of docetaxel for paclitaxel does not compromise efficacy and improves tolerability, particularly neurotoxicity in first-line ovarian cancer. Cisplatin also has a higher incidence of peripheral neuropathy than carboplatin, so carboplatin would be preferred as it has similar efficacy and is better tolerated. See "First-Line Chemotherapy" section in the chapter for more information.

6. **B.** Patients with true allergic reactions to paclitaxel can undergo desensitization with 24 hours of premedications prior to administration that is titrated dilutions until at the full rate. See "Evaluation of Therapeutic Outcomes" section in the chapter for more information.

7. **C.** Systemic chemotherapy with a taxane and platinum regimen following optimal surgical debulking is the standard of care for treatment of epithelial ovarian cancer. See the "Treatment" section (First-line Chemotherapy) in the chapter for more information.

8. **A.** The most common adverse drug reactions associated with olaparib include nausea and vomiting and significant anemia with associated fatigue. Thrombocytopenia is most common with niraparib and transient liver toxicity is more often seen with rucaparib. Neutropenia may occur with any PARP inhibitor but is less common. See "Treatment" section (PARP inhibitors) in the chapter for more information.

9. **B.** Common complications of progressive ovarian cancer include thrombosis, ascites, uncontrollable pain, and small bowel obstruction. See "Evaluation of Therapeutic Outcomes" section in the chapter for more information.

10. **D.** See "Table 156-2" for acceptable regimens for recurrent platinum-sensitive ovarian cancer. If the patient is platinum-sensitive, the treatment regimen should contain a platinum agent if patient performance status and comorbidities allow.

11. **A.** Patients with small bowel obstructions should be offered an opioid-based pain regimen with both long-acting agents and short-acting opioids for breakthrough or progressive pain; it should also include a bowel regimen to prevent opioid-induced constipation. Antiemetics are appropriate supportive care as nausea is common with bowel obstructions. See "Evaluation of Therapeutic Outcomes" section in the chapter for more information.

12. **D.** Pegylated liposomal doxorubicin plus bevacizumab would be an appropriate treatment option for platinum-resistant recurrent disease since it is non-cross resistant with platinum agents. Since the patient is platinum-resistant, they should not receive another platinum agent (ie, cisplatin or carboplatin). Immunotherapy with pembrolizumab would be inappropriate since the patient has low tumor mutational burden. See the "Platinum-Resistant Disease" and "Immunotherapy" sections in the chapter for more information.

13. **C.** Olaparib is a PARP inhibitor. PARP inhibition results in double-stranded DNA breaks that cannot be repaired in cancer cells with homologous recombinant deficiency such as those with BRCA1/2 mutations. See "PARP Inhibitors" section in the chapter for more information.

14. **B.** Patients with ovarian cancer often present with nonspecific, vague symptoms such as abdominal bloating, pressure or pain, indigestion, or change in bowel movements. By the time they are diagnosed, the disease is usually advanced leading it to be called "silent killer." Patients with early stage disease are often asymptomatic. See "Clinical Presentation" section in the chapter for more information.

15. 15. C. CA-125 should not be used for routine screening for ovarian cancer for asymptomatic individuals who do not have a high-risk hereditary cancer syndrome. CA-125 is a nonspecific antigen used as a tumor marker for diagnosis and monitoring of epithelial ovarian cancer. Rising levels in those with high baseline levels are associated with disease burden and progression. See "Screening," "Clinical Presentation," and "Evaluation of Therapeutic Outcomes" sections in the chapter for more information.