

GYNECOLOGIC CANCERS



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LEARNING OBJECTIVES

1. Apply knowledge of the pathophysiology, etiology, presenting symptoms, and diagnostic evaluation of each of the gynecologic cancers to care of patients.
2. Evaluate the role and limitations of screening for early detection of endometrial and ovarian cancers.
3. Develop a treatment plan for a patient with a newly diagnosed gynecologic cancer.
4. Assess the role of consolidation treatment and the impact on overall survival of patients with gynecologic malignancies.
5. Develop an algorithm for the selection of a chemotherapy regimen for the treatment of recurrent gynecologic malignancies.

INTRODUCTION

The gynecologic cancers remain a pharmacotherapeutic challenge. In general, the primary and most effective treatment is surgery if the cancer is diagnosed in the early stages. Both endometrial and cervical cancers are more likely to be diagnosed in the early stages because of their symptoms and the availability of effective screening tools. Regrettably, ovarian cancer is denoted the “silent killer” among the gynecologic cancers because it

is often not diagnosed until an advanced stage when a cure is difficult. This chapter describes the treatment of endometrial, ovarian, and cervical cancers. Vaginal and vulvar cancers are not discussed in this chapter; however, the treatment approaches used in the management of cervical cancer can generally be applied to vaginal or vulvar cancers.

Overall, the etiology of gynecologic cancers is not well understood. Two exceptions are the distinct associations between human papillomavirus (HPV) infection and development of cervical cancer; and hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome, which increases the risk of both ovarian and endometrial cancers. Box 1-1 lists risk factors for the three gynecologic malignancies.

With all three gynecologic malignancies, patients are generally asymptomatic in the early stage of disease, with symptoms appearing as the cancer progresses. Although the symptoms of ovarian cancer are nonspecific and have an insidious onset often leading to delay in diagnosis, postmenopausal bleeding associated with endometrial cancer and postcoital bleeding and pain associated with cervical cancer result in women seeking gynecologic care and obtaining an earlier diagnosis. Box 1-2 lists common presenting symptoms.

BASELINE REVIEW RESOURCES

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Smith JA, Wolf JK. Ovarian cancer. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*, 7th ed. Boston: McGraw-Hill, 2008: 2245–58.
- Mach CM, Cloutier L. Endometrial cancer. In: Borgelt LM, O’Connell MB, Smith JA, Calis KA, eds. *Women’s Health Across the Lifespan: A Pharmacotherapeutic Approach*. Bethesda: American Society of Health-System Pharmacists, 2010:721–34.
- Smith JA. Cervical cancer. In: Borgelt LM, O’Connell MB, Smith JA, Calis KA, eds. *Women’s Health Across the Lifespan: A Pharmacotherapeutic Approach*. Bethesda: American Society of Health-System Pharmacists, 2010:749–60.

ABBREVIATIONS IN THIS CHAPTER

CA	Cancer antigen
FIGO	International Federation of Gynecology and Obstetrics
GOG	Gynecologic Oncology Group
HNPCC	Hereditary nonpolyposis colorectal cancer
HPV	Human papillomavirus
IDMS	Isotope dilution mass spectrometry
TVUS	Transvaginal ultrasonography

For ovarian cancer, the diagnosis and stage are confirmed during the initial surgery because the tumors are often difficult to access, and peritoneal seeding can occur if a needle biopsy is performed before surgery. Although both cervical and endometrial cancer diagnoses can be confirmed from biopsy, staging for endometrial cancer is a combination of diagnostic tests and surgical examination, whereas advanced cervical cancer is most often staged by diagnostic tests alone. Because most women undergo surgery as part of their primary treatment, the staging work-up is completed during surgery. All gynecologic cancer staging is classified by the International Federation of Gynecology and Obstetrics (FIGO) staging system, which is described in depth in the baseline review references. This staging system requires extensive surgery and expert pathological review. It is recommended that a trained gynecologic oncology surgeon complete the tumor-debulking surgery and staging when cancer is suspected in order to prevent understaging and to improve the overall outcome.

All three gynecologic cancers may spread by direct extension to surrounding organs (e.g., vagina, ovaries, uterus, fallopian tubes, bladder, rectum, pelvic peritoneum). Another primary mechanism of metastasis is through the lymphatic system, typically involving the pelvic and para-aortic lymph nodes, which may be enlarged upon palpation. Ovarian cancer may also disseminate throughout the peritoneum through the peritoneal fluid. Tumor cells then are able to adhere to and invade abdominal and/or pelvic organs, resulting in disseminated disease at distant sites such as the surface of the diaphragm or liver, as well as pulmonary and pleural involvement. Finally, distant metastasis may occur from spread of cancer cells through the hematogenous route.

When diagnosed in early stages, interventions are often curative with a minimal impact on quality of life. Similar to most cancers, a delay in diagnosis until a more advanced stage of disease is associated with a much poorer prognosis. In general, progressive and recurrent

Box 1-1. Risk Factors for Gynecologic Cancers

Endometrial Cancer

- African American race
- Hereditary nonpolyposis colorectal cancer
- Insulinemia
- Non–insulin-dependent diabetes
- Nulliparity
- Obesity
- Tamoxifen
- Unopposed estrogen therapy

Cervical Cancer

- Human papillomavirus infection
- Immunosuppression
- Multiple sexual partners
- Other sexually transmitted diseases
- Smoking
- Unprotected sexual activity
- Use of oral contraceptives

Ovarian Cancer

- Early menarche (before age 12 years)
- Fertility drugs
- Hereditary breast/ovarian cancer – *BRCA1*, *BRCA2*
- Hereditary nonpolyposis colorectal cancer
- Infertility
- Late menopause (after age 60 years)
- Nulliparity
- Obesity
- Western/developed countries

gynecologic cancers are associated with inherent or acquired drug resistance and have a poor prognosis (5-year survival of less than 20%).

Other considerations that influence prognosis include tumor grade, histology, age, race, endocrine status, depth of tumor invasion, extension of disease within the pelvic cavity, presence of positive lymph nodes, and presence of distant metastases. In addition, the success of the primary surgery to achieve optimal tumor reduction (less than 1 cm of detectable disease) is a significant prognostic factor, especially for ovarian cancer. Furthermore, treatment of advanced and recurrent disease is often associated with complications that affect the overall quality of life (e.g., fistulas, neuropathies, permanent damage to the bowel).

ENDOMETRIAL CANCER

Endometrial or uterine cancer is the most common gynecologic cancer in the United States, with more than 43,470 estimated new cases annually. Among the gynecologic cancers, it has the best prognosis with only about 7950 (18.2%) deaths annually.

Box 1-2. Clinical Presentation of Gynecologic Cancers

Endometrial Cancer

Abdominal fullness/pressure

Abnormal vaginal bleeding

- Pre- or perimenopausal woman: heavy or prolonged vaginal bleeding
- Postmenopausal woman: resumption of vaginal bleeding

Cervical Cancer

Abnormal Papanicolaou smear

Abnormal vaginal bleeding

Abnormal vaginal discharge

Difficult bowel movements

Flank pain

Hematuria

Postcoital vaginal bleeding

Pain during/after intercourse

Unilateral hip, buttock, leg pain

Urinary frequency

Ovarian Cancer

Weight change

Abdominal discomfort/distention

Abdominal fullness/bloating

Early satiety

Indigestion/reflux

Nausea

Change in bowel habits (flatulence, diarrhea, or constipation)

Ascites

Abdominal pain

Urinary urgency/frequency

Irregular vaginal bleeding

Elevated cancer antigen (CA)-125 (normal concentration less than 35 units/mL)

Etiology

The etiology of endometrial cancer has not been fully determined. The risk of endometrial cancer is associated with either family history or factors that contribute to increased exposure to estrogen and its metabolites. Obesity is considered a major risk factor for endometrial cancer. Women with an excess 13–23 kg of body weight have an associated 3- to 5-fold greater risk of developing endometrial cancer compared with the general population. Obesity is associated with a higher percentage of adipose tissue, which is where the conversion of androgens to estrogens occurs through several pathways including the aromatization of androstenedione to estrone. The net result is increased estrogen exposure that results in an increased risk of endometrial

hyperplasia and ultimately the potential for progression to invasive endometrial cancer.

Other conditions associated with an increased risk are polycystic ovarian syndrome, a hyperestrogenic state; and HNPCC, which is associated with a 40% to 60% increased risk of developing endometrial cancer. Although primarily an antiestrogen, tamoxifen use has also been associated with an increased risk of endometrial cancer because of its mixed estrogenic effects on the endometrial lining.

Women with a known hereditary risk should have annual screening after age 35, but there is no standardized algorithm, so screening should be based on clinical judgment. Women receiving tamoxifen who still have a uterus are also at an increased risk of developing endometrial cancer and should have annual screening while on therapy and for at least 1 year after completion of therapy. Annual screening may include pelvic examination, transvaginal ultrasonography (TVUS), pelvic ultrasonography, and endometrial biopsies as indicated (e.g., for irregular bleeding). For women without risk factors, routine screening is not recommended.

Diagnosis

Although the diagnosis of endometrial cancer can be confirmed from biopsy, staging for endometrial cancer is based on a combination of diagnostic tests and surgical examination. When women present with irregular vaginal bleeding and there is a suspicion of endometrial cancer, an endometrial biopsy is usually performed during an office visit. If the biopsy is negative, then a dilation and curettage is completed to gather better sampling and confirm clinical findings. A positive biopsy is often followed up by a TVUS to determine endometrial thickness; if it is more than 4–5 mm, it requires further evaluation. A cervical biopsy should be performed if cervical invasion is a concern. Hysteroscopy may also be included in the initial work-up to inspect the uterine cavity for polyps and visualization of the endometrium, and is often done in conjunction with dilation and curettage. Once a diagnosis is reached, the extent of disease in other pelvic organs and beyond the pelvic cavity is determined by diagnostic modalities such as cystoscopy, proctoscopy, computed tomography (CT), and magnetic resonance imaging (MRI) as appropriate.

Treatment

Therapeutic Goals

Early stage endometrial cancer can be cured with timely and aggressive treatment involving surgery, chemotherapy, and/or radiation. Therapeutic goals in recurrent and metastatic cancer are to alleviate symptoms and decrease disease progression. The achievement of stable disease is often considered a reasonable therapeutic goal for recurrent gynecologic cancers.

Surgery and Radiation

Surgery is the primary treatment for early stage endometrial cancer. This should include a thorough pathologic assessment of the depth of myometrial invasion in relation to the overall myometrial thickness, tumor size and location within the uterus, histology and grade, and extent of any lymphatic invasion. After complete resection of all disease (including a vaginal or total hysterectomy and bilateral salpingo-oophorectomy), pelvic washings are necessary to complete surgical staging. Although associated with some controversy, pelvic and/or para-aortic lymphadenectomy is a precise method for identifying nodal metastases and has been associated with improved survival rates in endometrial cancer.

Radiation alone is a treatment option to consider in patients who are medically inoperable because operative risk is high. Morbid obesity and severe cardiopulmonary disease are the most common reasons a patient with endometrial carcinoma is deemed medically inoperable. More often, radiation is an adjuvant to either surgery or chemotherapy. After surgery, patients may receive internal radiation therapy (brachytherapy) in combination with external beam radiotherapy when there is lymph node involvement or other features that place the patient at high risk of recurrence. In recent clinical trials, the use of adjuvant radiation in patients with stage I/II low- and intermediate-risk disease resulted in reduced local and regional recurrence but had no impact on overall survival.

Adjuvant radiation therapy is also warranted in patients with high-grade tumor and increased depth of tumor invasion in the myometrium, lymphovascular space invasion, large tumor volume, and involvement of the lower uterine segment or cervix. Although the addition of radiation does not improve overall survival, it reduces the risk of recurrence by 50%. The decision to treat depends on whether patients have any of the risk factors associated with disease discussed above and patient factors such as age, body weight (obesity), and comorbidities. Finally, most recurrences of endometrial cancer are within the vaginal vault and may be treated with salvage external beam radiation with or without vaginal brachytherapy.

Drug Therapy

Until recently, chemotherapy has not played a role in the primary treatment of endometrial cancer. Although clinical trials have demonstrated improved rates of complete response and progression-free survival and new regimens are beginning to emerge, most of the current regimens have been established through clinical practice experience. Historically, doxorubicin with or without cisplatin has demonstrated an increased overall response rate and progression-free survival for patients with early stage disease. Unfortunately, chemotherapy has had no impact on overall survival in patients with

advanced stages of endometrial cancer. The combination of paclitaxel, doxorubicin, and cisplatin for first-line treatment of advanced endometrial cancer did improve progression-free and overall survival, but the toxicity associated with this regimen has limited its clinical use. Although a standard for first-line chemotherapy has yet to be identified for metastatic or recurrent endometrial cancer, multiple phase II studies have suggested that paclitaxel plus carboplatin is a well-tolerated regimen, and it is commonly used in the treatment of endometrial cancer.

Chemotherapy for recurrent endometrial cancer consists of either a single agent or a combination of agents with or without radiation therapy. Single-agent regimens include gemcitabine, doxorubicin, cisplatin, carboplatin, topotecan, and paclitaxel (Table 1-1). Paclitaxel/carboplatin, gemcitabine/cisplatin, and gemcitabine/carboplatin have demonstrated an improvement in progression-free survival. Ifosfamide and vincristine have moderate activity but also significant toxicities, so these agents are used primarily for sarcomatous and endometrioid histologies.

Hormonal agents are commonly used for the treatment of endometrial cancer and are typically selected based upon the hormone receptor expression of the tumor (i.e., progesterone or estrogen receptor). Hormonal agents are attractive for the management of recurrent disease in patients with estrogen- or progesterone-positive tumors because they are administered orally and are generally well tolerated. Megestrol acetate or medroxyprogesterone can be used for recurrent endometrial cancer. Patients should receive the lowest effective dosage of hormonal agent to limit toxicity. The use of tamoxifen and aromatase inhibitors has been limited because of low response rates (9% to 14%) and an estimated progression-free interval of 1–6 months. Luteinizing hormone-releasing hormone and gonadotropin-releasing hormone receptors are present in endometrial cancer tissue and have the ability to indirectly inhibit estrogen pathway (negative feedback), but the overall response rates have not been impressive (see Table 1-1).

Prevention

Some lifestyle choices offer a protective mechanism and lower the risk of developing endometrial cancer. First, timely and proper medical treatment should be sought for precursor disorders of the endometrium to decrease the opportunity for progression to endometrial cancer. Women should avoid the use of unopposed estrogens in the presence of an intact uterus, and all women should avoid long-term hormone therapy. Caution is also recommended with the use of phytoestrogens because their long-term safety is unknown. Finally, appropriate diet and exercise interventions are important to decrease the risk of obesity.

Table 1-1. Chemotherapy for Treatment of Gynecologic Cancers

Drug(s)	Dosage	Cycle Frequency
Combination Regimens		
Paclitaxel and carboplatin	175 mg/m ² IV (3-hr infusion) AUC 5–7.5 IV	Every 21 days
Paclitaxel and cisplatin	135 mg/m ² IV (24-hr infusion) 75 mg/m ² IV	Every 21 days
Paclitaxel and cisplatin	135 mg/m ² IV over 24 hours on day 1 and 100 mg/m ² IP over 1 hour on day 2 60 mg/m ² IP over 1 hour on day 8	Every 21 days
Cisplatin and cyclophosphamide	50–100 mg/m ² IV 500–1000 mg/m ² IV	Every 21–28 days
Cisplatin with radiation	40 mg/m ² IV (cap at 70 mg) weekly	5 weeks total
Cisplatin and fluorouracil with radiation	40 mg/m ² /day IV daily for 4 days 250 mg/m ² /day daily for 4 days	Every 21 days
Docetaxel and carboplatin	75 mg/m ² IV AUC 5 IV	Every 21 days
Gemcitabine and carboplatin	800 mg/m ² IV days 1 & 8 AUC 5 IV day 1	Every 21 days
Gemcitabine and cisplatin	800 mg/m ² IV days 1 and 8 40 mg/m ² IV days 1 and 8	Every 21 days
Liposomal doxorubicin and carboplatin	30 mg/m ² IV over 1–3 hr AUC 5 IV	Every 28 days
Cyclophosphamide and bevacizumab	50 mg PO once daily 10 mg/kg IV days 1 and 5	Every 28 days (continuous)
Topotecan and cisplatin	0.75 mg IV days 1, 2, and 3 50 mg/m ² IV day 1 only	Every 21 days
Ifosfamide and doxorubicin	1500 mg/m ² /day continuous IV infusion for 3 days 30 mg/m ² /day continuous IV infusion for 2 days	Every 21 days
Single Agents		
Docetaxel	75 mg/m ² IV	Every 21 days
Liposomal doxorubicin	40 mg/m ² IV	Every 28 days
Gemcitabine	800–1000 mg/m ² IV days 1, 8, and 15	Every 28 days
Paclitaxel	60–80 mg/m ² IV (1-hr infusion)	Every week
Paclitaxel	135–175 mg/m ² IV (3-hr infusion)	Every 21 days
Carboplatin	AUC 5–7.5 IV	Every 21–28 days
Cisplatin	50–75 mg/m ² IV	Every 21–28 days
Ifosfamide	1500 mg/m ² /day for 3–5 days	Every 21 days
Topotecan	1.3–1.5 mg/m ² IV days 1–5	Every 21 days
Topotecan	4 mg/m ² IV days 1, 8, and 15	Every 28 days
Etoposide	50 mg/m ² PO once daily days 1–10	Every 21–28 days
Capecitabine	1800–2000 mg/m ² PO in divided doses two times/day for 2 weeks	Every 21 days
Altretamine	260 mg/m ² PO divided into four doses/day for 14–21 days	Every 28 days
Hormonal Agents		
Tamoxifen	20 mg PO two times/day	Continuous
Letrozole	2.5 mg PO once daily	Continuous
Medroxyprogesterone	200–400 mg PO in divided doses two times/day	Continuous
Megestrol acetate	40 mg PO four times/day	Continuous
Leuprolide	3.75 mg IM	Monthly

AUC = area under the curve (mg/L*h); carboplatin dose then calculated based on Calvert formula (carboplatin dose = [GFR+25] AUC); IM = intramuscularly; IP = intraperitoneal; IV = intravenous; PO = orally.

CERVICAL CANCER

Although cervical cancer is the second most common cancer in women worldwide, it is the least common among gynecologic malignancies in the United States with only 12,200 estimated new cases in 2010. It is associated with moderately high mortality (34.5%). Most cases of cervical cancers occur in developing countries (more than 85%) because of the limited availability of advanced screening techniques.

Etiology

Cervical cancer is the most preventable of gynecologic cancers and is considered a cancer caused by unfavorable behaviors including smoking, multiple sexual partners, and unprotected sexual activity. Human papillomavirus infection causes virtually all cervical cancer. Oncogenic HPV gains access to the basal layer of epithelium through microtraumas that occur commonly during intercourse. Because HPV replicates in a non-lytic (not associated with cell death) manner in the infected basal cells, it does not cause release of pro-inflammatory cytokines and exists in the cervical basal cell layer in the absence of an innate immune response. This allows for persistent infections, which can lead to the development of precancerous and cancerous lesions in susceptible patients.

In addition to HPV infection, the most common contributing risk factor for cervical cancer is the use of tobacco products. Nicotine and its active metabolite, cotinine, may affect multiple pathways leading to cancer and have been associated with metaplasia, angiogenesis, and proliferation in epithelial cells. Both nicotine and cotinine have been detected in cervical mucus, confirming that these and other carcinogens present in tobacco smoke are carried by the blood to the cervix. These carcinogens are associated with induction of cellular and DNA damage and the formation of chemically stable DNA adducts that promote genetic instability within the cervical epithelium.

Screening

The introduction of the Papanicolaou test (Pap smear) into clinical practice and the improvement in access to and adherence with cervical cancer screening guidelines have been associated with a 74% reduction in the incidence of cervical cancer. Screening for cervical cancer should begin about 3 years after the onset of vaginal intercourse but no later than 21 years of age. Screening consists of an annual Pap smear and pelvic examination. Recent updates to the American Congress of Obstetrics and Gynecology screening guidelines recommend that when a woman between 21 and 30 years old without known risk factors for cervical cancer has had three or more consecutive annual examinations with normal findings, the Pap smear may be performed less often, once every 2 years, at the discretion of her gynecologist.

However, women with one or more high-risk factors should continue cervical cancer screening with an annual Pap smear and pelvic examination. After age 30, HPV testing should be completed once and repeated whenever an abnormal Pap smear occurs or periodically in a woman who has multiple sexual partners.

Serological HPV tests cannot distinguish between past and current infections; therefore, current infections can only be detected through identification of viral DNA in clinical samples. This requires sensitive-type specific HPV DNA tests. Two tests are used in clinical practice with the ability to detect 13 high-risk HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). The HPV tests cannot distinguish the subtype(s) of HPV but are quantitative for the viral load present. Testing is completed on the Pap smear sample. No effective treatment is available to eradicate HPV infections. A woman with a diagnosis of a high-risk HPV infection should be closely monitored with Pap smears every 6 months, with the addition of a colposcopy examination if a Pap smear is abnormal, to prevent progression to cervical cancer.

Diagnosis

Because the Pap smear is an effective screening tool for cervical cancer, most cases of cervical cancer are detected as precancerous lesions. Once an abnormal Pap smear is reported, follow-up is recommended. For early signs such as atypical cells or mild dysplasia, the recommended follow-up is a repeat Pap smear within 6 months. However, for higher-grade lesions, the recommended follow-up includes colposcopy examination with endocervical curettage and biopsies. When cervical cancer is confirmed in biopsy samples, additional diagnostic tests are required (e.g., blood tests; imaging by CT, MRI, or positron emission tomography) to evaluate the extent of disease. Histology is also determined from the biopsy samples; most are squamous cell carcinomas, followed by adenocarcinomas, and rarely neuroendocrine or small cell carcinomas.

Treatment

Therapeutic Goals

Early stage cervical cancer can be cured with timely surgery. Recurrent and metastatic cervical cancer does not respond well to chemotherapy; the primary goal of treatment is palliation of symptoms and controlling tumor growth and progression. Stable disease is often considered a reasonable therapeutic goal for any recurrent gynecologic cancer.

Surgery and Radiation Therapy

Surgery is reserved for early stage cervical cancer (i.e., either FIGO stage IA or IB1 disease), when it is possible to completely excise the tumor with negative margins. Surgery includes a hysterectomy (simple or radical) with pelvic and/or para-aortic lymph node dissection.

Although this is a definitive treatment of the cervical cancer, it eliminates the possibility for reproduction. Hence, patients with stage IA disease may seek fertility-sparing surgical interventions such as a radical trachelectomy (removal of the cervix and parametrium) and laparoscopic lymphadenectomy. A radical trachelectomy is a more complicated procedure than a hysterectomy and requires a skilled surgeon for a successful outcome.

When there is an isolated recurrence within a previously radiated field, a procedure called an exenteration may be considered. This surgery involves multiple procedures to remove the tumor and any adjacent organs at potential risk of microscopic invasion. Total pelvic exenteration involves the removal of the bladder, descending colon, rectum, uterus, ovaries, fallopian tubes, and vagina; two stomas are placed for urine and fecal elimination. In an anterior exenteration, the colon and rectum are not removed and only one stoma is placed for urinary elimination. Finally, in a posterior pelvic exenteration, the bladder is not removed, and only a colostomy is placed. When feasible and clinically appropriate, the vagina is rebuilt to enable sexual intercourse. Exenteration has a significant impact on quality of life. An extensive diagnostic imaging and workup is completed to verify no metastases before embarking on exenteration.

Radiation therapy is most often used in combination with chemotherapy. Specifically, radiation plus weekly cisplatin is considered the standard of care for locally advanced and metastatic cervical cancer stages IIB, IIIA, IIIB, and IVA. The chemoradiation regimen includes cisplatin 40 mg/m²/week (maximum of six doses) concurrently while receiving 45 Gray (Gy) of external beam pelvic radiation. This is followed by internal radiation (brachytherapy), most often administered through after-loading tandem and ovoid insertion for 72 hours or high-dose intracavitary brachytherapy.

Chemotherapy

Cisplatin is more effective in cervical cancer than carboplatin. As a result, unlike other gynecologic cancers, the substitution of carboplatin for cisplatin to decrease toxicity is not well accepted or recommended. Use of chemotherapy alone is reserved for recurrences within the radiation field or where the desired outcome is the relief of symptoms. First-line treatment with chemotherapy alone is appropriate in patients with stage IV disease because chemoradiation is not curative. Similar to other gynecologic cancers, single-agent platinum-based therapy has been the standard of care; however, new clinical trial data support the use of combination platinum-based regimens. Topotecan plus cisplatin is one of the few combinations with approved U.S. Food and Drug Administration (FDA) labeling for recurrent cervical cancer. Once the disease progresses and becomes platinum resistant, there is no standard of care for chemotherapy. Depending on physician preference, residual toxicities, and patient

preference, any one of the non-platinum chemotherapy agents listed in Table 1-1 may be considered.

Prevention

Cervical cancer is almost completely preventable. The most successful approach for prevention is abstinence from any sexual activity; however, this is unrealistic to continue throughout life. Mutual monogamy and condoms are less effective for preventing cervical cancer. Although a couple may achieve mutual monogamy, one or more previous partners may have provided exposure to HPV. Each additional partner adds another 25% to the risk of HPV exposure. A meta-analysis evaluating the use of condoms to prevent HPV infection demonstrated a lack of published studies regarding condom use and HPV infection. Limited evidence supports a protective effect of condom use on HPV DNA detection, and some studies actually show an increased incidence of HPV lesions with condom use.

The HPV quadrivalent vaccine (against types 6, 11, 16, and 18) and the bivalent HPV vaccine (against types 16 and 18) are both indicated for preventing HPV infection and reducing the risk of developing cervical cancer. To be effective, the HPV vaccine should be administered before any potential exposure to the virus (i.e., before any sexual activity). However, it is also effective in individuals who have been sexually active and test negative for HPV. Neither of the vaccines is effective for treatment of HPV infections or cervical cancer.

The quadrivalent HPV vaccine has limited cross-neutralization ability against other HPV genotypes. Preliminary data from follow-up clinical studies suggest that the immunity achieved from the HPV vaccine is not likely to be lifelong. Additional studies are needed to determine the timing for boosters or whether repeating the series is necessary. The HPV vaccine is effective for at least 5 years for HPV-16, but additional evaluation to determine the effective geometric titer is needed. In one study, the HPV-18 titers in patients treated with the vaccine increased initially but were at concentrations similar to the geometric titers in the placebo group by 36 months after vaccination. The three-shot series must be completed within the 6-month time frame for an adequate geometric titer to be achieved. The reduced efficacy in those not completing the full three-shot series is still a concern. The true impact of the use of the HPV vaccines on the prevention of cervical cancer will not be apparent for decades.

OVARIAN CANCER

Ovarian cancer is the most deadly of the gynecologic malignancies in the United States. It is the fifth leading cause of cancer-related deaths in women and has a mortality rate of more than 60%. An estimated 21,880 new cases in United States are diagnosed annually. This high

mortality rate can be attributed to the late stage of diagnosis and to inherent drug resistance.

Etiology

The etiology of most cases of ovarian cancer remains unclear and unpredictable. The two primary theories are the incessant ovulation hypothesis and the gonadotropin hypothesis. Both hypotheses are based on the premise that an increasing number of ovulations or proliferations of the ovary epithelium leads to an increased potential for aberrant cell repair and mutations, which is thought to eventually lead to the formation of cancer. Another theory suggests that chronic inflammation from use of talc products or asbestos exposure is a contributing factor; however, this association has not been confirmed in longitudinal epidemiology studies.

Ovarian cancer is considered a sporadic cancer, with less than 10% of all cases being attributed to hereditary risk. However, if more than one first-degree relative (e.g., a mother and sister) is afflicted with ovarian cancer, the risk increases to more than 50%.

The tumor suppressor genes *BRCA1* and *BRCA2* are thought to be involved in one or more pathways of DNA damage, including both the recognition and repair of genes associated with development of ovarian cancer. Of the two genes, *BRCA1* is more prevalent, being associated with 90% of inherited and 10% of sporadic cases of ovarian cancer. Patients with *BRCA1*-associated ovarian cancer are usually younger and the tumors are more aggressive with moderate to high grade, serous histology. The two most common genetic abnormalities of familial ovarian cancer are hereditary breast/ovarian cancer syndrome and hereditary HNPCC. Hereditary breast/ovarian cancer syndrome is associated with germ-line mutations in *BRCA1* and *BRCA2* and with earlier onset of cancer and often multiple cancers in the same patient. The *BRCA* mutations have also been associated with Ashkenazi Jewish ancestry. The HNPCC syndrome has also been associated with up to 12% of hereditary ovarian cancer cases. In patients testing positive for HNPCC genetic mutations, ovarian cancer occurs at an earlier age than in the general population, and these patients are more likely to have a synchronous endometrial cancer. In addition, the cancer is more likely to be well or moderately differentiated.

Supporting the two primary hypotheses of the development of ovarian cancer, conditions that increase the total number of ovulations in women's reproductive history also have been identified as risk factors for ovarian cancer (see Box 1-1).

Unlike cervical cancer, ovarian cancer does not have a known pre-invasive component or premalignant process. Hence it is difficult to screen patients to detect early disease. Large-scale clinical studies have failed to demonstrate a benefit for routine screening using cancer antigen (CA)-125 concentrations or TVUS in the

general population. However, in women with a positive family history who are at high risk of ovarian cancer, the National Institutes of Health recommends monitoring with an annual pelvic examination, CA-125 concentration, and TVUS every 6 months.

Diagnosis

Early disease is typically asymptomatic. As the disease advances, patients experience nonspecific symptoms often confused with symptoms of common benign gastrointestinal disorders (see Box 1-2). This often results in delays in seeking a gynecologic examination and in diagnosis. A key element for improving patient outcomes in women with ovarian cancer is the education of the public and other health care providers. Women must seek medical attention earlier when experiencing any of the nonspecific symptoms described above for more than 6 weeks.

During a gynecologic examination, signs that indicate the need for further testing include presence of an adnexal mass or any irregularity, solid features, and nodularity of the ovary. Patients with advanced disease may exhibit signs of abdominal distension because of ascites and increased tumor burden, or dyspnea or cough because of pleural effusions.

In addition to a physical examination, a complete blood count, chemistry profile including liver and kidney function tests, and tests for tumors markers including CA-125 and CA-19 concentrations should be performed to support diagnosis. The CA-125 marker is a nonspecific antigen but is currently the best tumor marker for epithelial ovarian carcinoma. A normal CA-125 concentration is less than 35 units/mL; when elevated at the time of diagnosis, changes in CA-125 concentrations correlate with response and progression. The CA-125 concentrations may also be elevated in benign conditions such as during ovulation and/or menses, diverticulitis, and endometriosis. Other nongynecologic cancers may also produce elevations in the marker. To further evaluate the extent of disease and confirm the diagnosis, other diagnostic tests may include TVUS or abdominal ultrasonography, gastrointestinal evaluations, chest radiography, CT, MRI, or positron emission tomography.

Treatment

Therapeutic Goals

Early stage ovarian cancer can be cured with timely and aggressive treatment involving surgery, chemotherapy, and/or radiation. In many cases, women with advanced ovarian cancer may achieve a complete response to initial surgery and chemotherapy although more than 75% of these cancers will recur within the first 2 years. In recurrent or metastatic ovarian cancer, the primary goal of treatment is palliation of symptoms and controlling tumor growth and progression. Stable disease is often

considered a reasonable therapeutic goal for recurrent ovarian cancer.

Surgery and Radiation Therapy

Surgery is the primary treatment intervention for ovarian cancer; it also confirms the diagnosis and staging. Surgery is often curative for patients with stage IA disease, with long-term survival exceeding 90%. The surgical treatment for ovarian cancer includes a total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and lymph node dissection. The primary objective of surgery is to optimally debulk the tumor to less than 1 cm of detectable residual disease. Optimal cytoreduction is associated with higher complete response rates to chemotherapy and longer overall survival.

Additional surgery after completion of chemotherapy is referred to as secondary cytoreduction or interval debulking if followed by additional cycles of chemotherapy. Cytoreduction is thought to facilitate the response to chemotherapy and improve overall survival. However, randomized trials of secondary surgical cytoreduction have reported conflicting results. Current clinical practice is not standardized and remains contentious.

Also controversial is second-look surgery, which is performed in patients with a clinical complete response after primary chemotherapy. The purpose is to examine the peritoneal cavity for any visible or microscopic disease to determine whether additional chemotherapy is warranted. However, this procedure has not been shown to improve overall survival, and about 50% of patients with a negative second-look surgery still relapse. Finally, surgical interventions are considered in patients with recurrent disease to improve quality of life by relieving symptoms associated with complications (e.g., small bowel obstruction).

Radiation has no impact on overall survival when used in early stage disease. Its primary role is for palliation of symptoms in patients with recurrent pelvic disease, which is often associated with small bowel obstruction. Either external beam whole-abdominal irradiation with 35–45 Gy or intraperitoneal isotopes such as ³²P can be used in the management of ovarian cancer to alleviate symptoms; these are associated with an improvement in the woman's quality of life.

Chemotherapy

Primary Treatment

Controversy exists regarding the standard treatment for FIGO stage IA and IB ovarian cancer. Many clinicians treat with three to six cycles of paclitaxel and carboplatin because of the high risk of recurrence. The standard treatment for patients with FIGO stage IC–IV disease or incomplete staging is six to eight cycles of a taxane plus platinum agent, most often carboplatin and paclitaxel (see Table 1-1).

Despite being included in guidelines from the National Comprehensive Cancer Network and National Cancer Institute, the route of administration remains controversial in clinical practice. Administration of chemotherapy through intraperitoneal delivery is not a new concept; however, phase III trials investigating intraperitoneal therapy conducted in the past decade have brought the intraperitoneal/intravenous issue back to the clinical arena. Three randomized phase III studies evaluating the role of intraperitoneal chemotherapy in ovarian cancer demonstrated an improvement in progression-free survival. In two trials, the improvement in overall survival was small and was associated with more toxicity. Thus, these regimens did not translate into clinical practice. The Gynecologic Oncology Group (GOG) trial 172, published in 2006, was the first to demonstrate an improvement in overall survival as well. This study compared intravenous paclitaxel and intravenous cisplatin (intravenous group) with intravenous paclitaxel over 24 hours on day 1 followed by intraperitoneal cisplatin on day 2 and intraperitoneal paclitaxel on day 8 (intraperitoneal group) in patients with optimally debulked stage III ovarian cancer. The median duration of overall survival was higher in the intraperitoneal group than in the intravenous group (65.6 months vs. 49.7 months). The quality of life was significantly worse for patients in the intraperitoneal group during therapy because of increased nausea, vomiting, dehydration, electrolyte abnormalities, infection, and neuropathy. However, by 6 weeks after completion of chemotherapy, no differences in quality of life were observed.

Appropriate patient selection is critical for intraperitoneal administration. Patients should have a diagnosis of stage III disease; optimal cytoreduction; adequate organ function; limited or no intra-abdominal lesions; and be willing to tolerate adverse event such as infection, abdominal pain, discomfort, and catheter complications.

Neoadjuvant chemotherapy is defined as chemotherapy that is given before primary surgical intervention. When a patient presents with metastatic ovarian cancer and/or is not a surgical candidate, neoadjuvant chemotherapy is an alternative to primary debulking surgery with the goal of decreasing tumor size/volume and ultimately increasing the chance of maximal tumor resection when surgery becomes feasible. In addition, advantages of neoadjuvant chemotherapy include less preoperative morbidity, less need for aggressive surgery, and a survival rate similar to that of patients who underwent primary debulking surgery.

Consolidation Therapy

At the end of the primary six cycles of chemotherapy, all patients are assessed for evidence of disease. Based on the GOG 178 study that evaluated 3 versus 12 cycles

of paclitaxel 135 mg/m² over 3 hours once a month after patients achieved a complete response to primary treatment (surgery plus 6 cycles of paclitaxel and carboplatin), the standard consolidation chemotherapy regimen is single-agent paclitaxel for 12 cycles. Single-agent carboplatin is also a reasonable option for patients with platinum-sensitive disease who may have significant residual neurotoxicity. However, its efficacy for consolidation has not been confirmed in randomized clinical trials. A partial response to primary chemotherapy is defined as a greater than 50% decline in CA-125 (from the presurgery concentration) or tumor regression. It is also a reasonable option to continue with single-agent paclitaxel or carboplatin in patients who have achieved a partial response to primary treatment in an attempt to achieve a complete response.

When the tumor has not achieved a partial response to primary treatment with a taxane/platinum regimen, alternative chemotherapy agents should be considered (see Table 1-1). Treatment is continued until a complete response is achieved. If the patient has no or minimal disease after completion of primary chemotherapy, an acceptable management approach is to observe the patient every 3–4 months. Surveillance includes physical examination, CA-125 concentration (if a marker), and radiologic imaging as indicated. During the observation period, supportive care should be provided as indicated until the disease progresses and chemotherapy is reinitiated.

Chemotherapy for Recurrent Disease

Surgery and radiation provide limited or no benefit for recurrent ovarian cancer. Chemotherapy is considered the primary treatment option for recurrent ovarian cancer. Platinum sensitivity is a major prognostic factor for any chemotherapy in recurrent ovarian cancer.

Several mechanisms can contribute to drug resistance in ovarian cancer, including increasing DNA repair, increasing drug inactivation, the expression of oncogenes, and the level of p53 function. Multidrug resistance continues to be a hurdle to overcome in the management of cancer chemotherapy. When cancer recurs more than 6 months after the last platinum therapy, tumors are considered to have platinum-sensitive disease and may respond to a second course of platinum-based treatment with response rates of 20% to 70%. Conversely, in patients with platinum-resistant disease (relapse less than 6 months after platinum therapy), treatment options include agents with an alternative mechanism of action (e.g., taxanes, topoisomerase I inhibitors, anthracyclines, cytidine analogs, aromatase inhibitors, antiestrogens, luteinizing hormone–releasing hormone agonists) or targeted agents discussed in the following section (see Table 1-1). These agents are usually given as single-agent, sequential therapies.

Response rates are comparable for all the chemotherapy agents currently used in the treatment of recurrent ovarian cancer. There are no guidelines that specify a defined sequence or number of cycles. Because response rates are generally poor, a more viable option is for patients with platinum-resistant ovarian cancer to consider investigational trials. Treatment decisions are based on physician preference; on patient factors such as age, comorbidities, residual toxicities, and hypersensitivities; and on past treatments.

Biological and Targeted Agents

During the past 5 years, clinical research has centered on the evaluation and incorporation of targeted agents such as the monoclonal antibodies (e.g., bevacizumab, cetuximab) and the small-molecule tyrosine inhibitors (e.g., sunitinib, gefitinib, sorafenib) for treatment of all gynecologic malignancies. The most progress has been demonstrated with bevacizumab as both a single agent and in combination regimens for the treatment of recurrent ovarian cancer. Preliminary results of two multicenter phase III trials provide clinical data to support the incorporation of bevacizumab into first-line and maintenance regimens to improve progression-free survival in ovarian cancer. The impact on overall survival is unknown. In addition, multiple phase II studies have been conducted to evaluate the combination of bevacizumab with oral cyclophosphamide, paclitaxel, and other second-line agents (see Table 1-1). Although initial data suggest an improvement in progression-free survival based on recent clinical experience in other malignancies, it is too early to determine the impact of bevacizumab on overall survival of patients with ovarian cancer.

Prevention

The use of oral contraceptives reduces the risk of ovarian cancer by about 30%. The risk continues to decrease by about 5% each year, totaling up to 50% with 10 or more years of use. Protection continues for 20 years after discontinuation of the oral contraceptive agent. In the general population, oral contraceptives are reasonable to recommend for the prevention of sporadic (nonhereditary) ovarian cancer. However, risk versus benefit should be considered for patients with a family history of ovarian and breast cancer because use of oral contraceptives has been associated with an increased risk of breast cancer. Although findings have not been confirmed in controlled trials, use of aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs has been associated with an estimated 47% risk reduction of ovarian cancer. Several *in vitro* preclinical studies suggest that retinoids also prevent ovarian cancer.

In women with known familial or genetic risk of developing ovarian cancer, prophylactic surgery is an option and is often considered after completion of childbearing. Prophylactic procedures include a bilateral salpingo-

oophorectomy and tubal ligation with or without hysterectomy. Before surgery, patients should understand that prophylactic surgery is not absolute with regard to risk reduction. For example, bilateral salpingo-oophorectomy in patients with *BRCA* mutations reduced the cancer risk by 80%; however, a residual risk of peritoneal cancer remained in these patients with an estimated cumulative incidence of 4.3% at 20 years after surgery. Although the mechanism of the prevention/reduction of risk is not well understood, it may be caused by impaired ovarian function or decreased passage of inflammatory substances and interruption of retrograde transport of carcinogens through the fallopian tube. The reported reduction in risk is as great as 30% for tubal ligation and/or hysterectomy and persists for 20–25 years after the procedure.

QUALITY PHARMACEUTICAL CARE

Chemotherapy

In recurrent cancer, patients often receive some form of chemotherapy for an extended period or even for the duration of their lives. Preserving organ function and bone marrow as well as minimizing cumulative toxicities are important considerations in administering chemotherapy both during primary treatment and in the management of patients with recurrent disease. Many chemotherapy agents do not have specific dose modification guidelines for organ dysfunction; rather, the recommendation is to use clinical judgment, taking into consideration patient and treatment factors (Table 1-2). In patients with recurrent gynecologic cancer, especially with platinum-resistant disease, a conservative approach should be employed for dosing chemotherapy. Typically, dosage adjustments are made for a creatinine clearance below 50 mL/minute and/or liver enzymes or bilirubin above the normal limits.

Caveats specific to gynecologic oncology include assessment of kidney function and use of the appropriate method of estimating creatinine clearance. In 2008, the National Kidney Foundation made recommendations to use the new isotope dilution mass spectrometry (IDMS) assay as the more accurate quantification of serum creatinine to help with earlier detection of chronic kidney disease. However, the current equations for estimating creatinine clearance (e.g., Cockcroft-Gault, Jelliffe) have not been adjusted, standardized, or validated with the IDMS serum creatinine values. Use of the IDMS serum creatinine in these equations tends to overestimate kidney function. Therefore, the assay manufacturer should provide legacy standards to the IDMS laboratory to develop a specific equation for conversion of the reported IDMS value to the non-IDMS serum creatinine for dosing all drugs with significant renal clearance, especially carboplatin. One such equation is: non-IDMS serum creatinine value = (IDMS reported serum creatinine value x 1.065) + 0.067. When the reported serum creatinine value is less than 0.60 mg/dL (IDMS) or 0.8 mg/dL (non-IDMS), some cancer treatment centers use an assigned serum creatinine value of 0.7–1 mg/dL in equations for estimating creatinine clearance.

The other variable for assessment of kidney function for carboplatin dosing is body weight, which is relevant when using the Cockcroft-Gault equation. In clinical practice, the adjustment made for obesity is highly variable. Often, when a patient's actual body weight is 20% to 30% above the ideal body weight (or more recently for body mass index greater than 30 kg/m²), an adjusted body weight is used to estimate kidney function. The appropriate use of the Cockcroft-Gault equation for the estimation of kidney function for drug dosing remains controversial.

Table 1-2. Drugs Requiring Dosage Adjustment in Presence of Organ Dysfunction^a

Kidney dysfunction (in general, consider when CrCl is less than 50 mL/min)	Liver dysfunction (in general, based on elevations in bilirubin, ALT, and/or AST)
Bleomycin	Capecitabine
Capecitabine	Docetaxel
Cisplatin	Doxorubicin
Cyclophosphamide	Etoposide
Etoposide	Gemcitabine
Fluorouracil	Liposomal doxorubicin
Gemcitabine	Paclitaxel
Ifosfamide	Vincristine
Liposomal doxorubicin	Vinorelbine
Topotecan	

^aWhen evaluating the need for a dosage adjustment for chemotherapy agents based on organ function other factors needed to be considered including: intention of treatment; patient comorbidities; performance status; other organ function; complexity of regimen (single agent versus multiple agents); and risks associated with toxicity (i.e., options for management and impact on quality of life).

ALT = alanine aminotransferase ; AST = aspartate aminotransferase ; CrCl = creatinine clearance.

Supportive Care

To prevent hematologic toxicity, use of filgrastim is an alternative to dose reductions or increasing the treatment interval. Because of disease-related factors, female sex, and cumulative treatment, patients with gynecologic malignancies are susceptible to chemotherapy-induced nausea/vomiting. Consequently, antiemetics might be needed with regimens not typically associated with emesis. Finally, as disease progresses, patients with gynecologic malignancies, especially ovarian cancer, may have significant ascites. For agents dosed by body surface area or total body weight, the dry weight or an estimated adjusted body weight should be used for dosage calculations.

Hypersensitivity reactions are common in the treatment of gynecologic cancers and have an incidence greater than 12% to 15% because of the use of taxanes and platinum analogs. Paclitaxel is associated with infusion-related reactions that can be attributed to the polyethoxylated castor oil diluent. Premedications including a histamine-1 or histamine-2 blocker and corticosteroids should be administered before each dose to prevent hypersensitivity reactions. If a patient still has an infusion-related reaction, increasing the duration of the infusion or premedicating with corticosteroids the night before treatment will often prevent symptoms. If a patient develops a true allergy, she should be desensitized as described in the following.

Platinum hypersensitivity reactions are often delayed type IV hypersensitivity reactions; they can occur at any time but are more common after seven or eight lifetime cycles of carboplatin or cisplatin. All patients receiving a platinum agent should be instructed to report any signs of a rash (one of the initial signs of platinum hypersensitivity) between cycles. Platinum hypersensitivity reactions can be severe and are sometimes fatal. Cross-sensitivity exists between carboplatin and cisplatin. If a patient has a reaction to one platinum agent, desensitization is required to receive any future platinum agents. Platinum desensitization can be attempted with 24 hours of premedication including a histamine-1 or histamine-2 blocker and corticosteroids, followed by the platinum agent given as a titrated infusion (1:1000, then 1:100, then 1:10, then full dose) over 4 hours. If the patient experiences signs of hypersensitivity at any time during the titrated infusions or during the cycle between doses, it is considered a desensitization failure and alternative chemotherapy or treatment options should be considered.

Patient Education

Until better screening tools are available, patient education remains the most important intervention for prevention of gynecologic cancers. Women and health care providers need to be educated on the early signs and symptoms of ovarian cancer. These signs include a

change in bowel or bladder habits, gastrointestinal disturbances, weight gain, abdominal bloating, and early satiety. Women should seek medical attention if they experience these symptoms for more than 6 weeks.

Ovarian cancer is often denoted the silent killer; women often ignore early signs and symptoms because they are so vague and typically present with advanced disease and a poor overall prognosis. Women should also know their family medical history, specifically in regards to cancer, to determine if additional genetic screening and prophylactic surgical interventions are appropriate. Finally, with the recent introduction of the HPV vaccines, women (and mothers) should be reminded that they only protect against 2 of the 15 HPV subtypes associated with development of cervical cancer. In addition, routine Pap smear screening is still recommended in sexually active young women despite vaccination. Cervical cancer is preventable by maintaining healthy sexual lifestyle choices as well as HPV vaccination as appropriate. Young adults should be educated on prevention of all sexually transmitted diseases, including HPV.

ROLE OF THE PHARMACIST

The pharmacist can assist the health care team in the medical management of women with gynecologic cancer. First, all pharmacists can provide patient education on options for prevention of gynecologic cancers, including use of the HPV vaccine, limiting the use of postmenopausal hormone therapy, and possible risk/benefits of long-term oral contraceptives use. Patient education can be provided to patients by pharmacists to promote early detection of the gynecologic malignancies. Pharmacists also have a key role in the prevention and management of chemotherapy-induced toxicities. Toxicity can be prevented with the proactive assessment of organ function and recommending dosage adjustments, appropriate use of granulocyte-stimulating growth factors, and antiemetic regimens. Pharmacists can also contribute to development of supportive care plans needed to provide comfort throughout treatment. This is especially critical when women are preparing for the end of life.

CONCLUSION

There have been significant advancements during the past 60 years in the management of gynecologic malignancies. These include the addition of bevacizumab to treatment regimens for recurrent disease, adoption of intraperitoneal chemotherapy as first-line treatment of ovarian cancer, and introduction of the HPV vaccine for the prevention of cervical cancer. Nonetheless, major challenges remain in the management of gynecologic cancers. Patient education is essential to assist with early diagnosis and to improve the potential for

achieving cure. Women must be aware of the signs and symptoms of all the gynecologic cancers, especially the vague signs and symptoms associated with ovarian cancer. Until better treatment options are made available that result in higher cure rates, a gentler, more conservative approach to patient care will help maintain quality of life for patients living with gynecologic cancers.

ANNOTATED BIBLIOGRAPHY

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The authors of this report screened a large series of women with HNPCC. The results were first presented for prevention of endometrial cancer, then were later developed and validated as predictive for prevention of colon cancer. Authors screened five HNPCC registries to obtain information on age at cancer diagnosis and type of cancer that had developed (e.g., colon, endometrial/ovarian). Data were analyzed for associations between genetic factors and development of cancer. The report demonstrates the value and role of genetic screening in prevention of second cancers. This study has been foundational in identifying women at high risk of endometrial cancer and offering genetic counseling and/or genetic screening as appropriate to them and extended family members. The study identifies the continued obstacles of genetic screening including insurance issues, confidentiality, and the need for better screening/monitoring tools for patients identified to be at high risk based on genetic testing.

2. Sorbe B, Andersson H, Boman K, Rosenberg P, Kalling M. Treatment of primary advanced and recurrent endometrial carcinoma with a combination of carboplatin and paclitaxel-long-term follow-up. *Int J Gynecol Cancer* 2008;18:803–8.

Although paclitaxel and carboplatin are the standard of care for ovarian cancer, it has taken some time for this regimen to be used in the primary adjuvant treatment of endometrial cancer. This is one of the initial reports that demonstrated a long-term benefit for addition of taxanes to a platinum-based regimen for the treatment of primary as well as recurrent endometrial cancer. A total of 66 patients with endometrial cancer (18 primary and 48 recurrent) were treated with six cycles of paclitaxel 175 mg/m² over 3 hours plus carboplatin (AUC = 5). The overall response rate was 67%, with 29% achieving a complete response and 38% achieving a partial response. The study demonstrated an improvement in progression-free and overall survival, with the 1-year survival exceeding 80% and 3-year survival exceeding 33%. Six cycles of paclitaxel and carboplatin are now commonly administered after completion of primary surgery and/or chemotherapy (cisplatin) plus radiation. The addition of chemotherapy to primary treatment of endometrial cancer has had significant improvement in achieving and sustaining complete response. Even

in recurrent disease, treatment with the combination of paclitaxel plus carboplatin achieves better responses compared with either agent alone.

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Radiation is an active treatment modality for endometrial cancer; however, the long-term benefit of radiation in combination with surgery has been unclear. This phase III study randomized patients with newly diagnosed endometrial cancer to receive whole pelvis radiation (5040 cGy) to be initiated 8 weeks after surgery compared with no additional treatment. This study differentiated patients based on risk of recurrence – either high intermediate risk or low intermediate risk based on tumor histology, lymphovascular involvement, age older than 50 years versus older than 70; this was considered imperative to determine the benefit of the addition of adjuvant external radiation after surgery. A total of 392 women were enrolled and had 69 months of follow-up. Radiation reduced pelvic and vaginal recurrences by 83% compared with the no additional treatment group. Overall survival improved from 86% for patients with no additional treatment to 92% in patients who received radiation, but this was not statistically significant. Adjuvant radiation is a common recommendation in clinical practice today after primary surgery for early stage endometrial cancer, especially for women at high intermediate risk; less benefit is observed in women with a low risk. Considering the morbidity and the impact of potential complications of whole abdominal radiation on quality of life, appropriate patient selection for the addition of radiation to primary treatment is important.

4. Obel JC, Friberg G, Fleming GF. Chemotherapy in endometrial cancer. *Clin Adv Hematol Oncol* 2006;4:459–68.

In the past 5 years, the role of chemotherapy for the treatment of endometrial cancer has significantly increased. This clinical review describes the current chemotherapy treatment options for endometrial cancer. The number of patients with recurrent endometrial cancer is small, so only limited comparative randomized clinical trials are available for each chemotherapy regimen. Hence, literature reviews such as this one of common regimens in clinical practice are useful resources for treatment planning in patients with recurrent endometrial cancer. This review is a good overview of the chemotherapy agents and combination regimens commonly used in clinical practice. Although randomized clinical trials cannot be used to predict response rates, this information is still useful for current clinical practice and has potential for development of newer regimens to be evaluated in the future. The limitations and toxicity of each agent and combination regimen are described in depth.

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This phase II study evaluated the combination of gemcitabine 1000 mg/m² plus cisplatin 35 mg/m² administered on days 1 and 8 for treatment of platinum-sensitive and platinum-resistant endometrial cancer. A total of 20 patients were treated in this single-institution, phase II study. A median of five cycles were received, with progression-free survival of 7.5 months. The objective response rate was 50%, including two complete responses in patients with platinum-resistant endometrial cancer, eight partial responses, and six patients with stable disease, and only four patients with progressive disease. This study reports one of the more promising clinical trial outcomes for endometrial cancer. Overall, gemcitabine plus cisplatin was well tolerated, but the use of filgrastim was recommended by the investigators to maintain dose intensity and prevent treatment delays that were observed during the study secondary to neutropenia. This regimen is also commonly used in the treatment of recurrent ovarian cancer.

6. Marnitz S, Kohler C, Muller M, Behrens K, Hasenbein K, Schneider A. Indications for primary and secondary exenterations in patients with cervical cancer. *Gynecol Oncol* 2006;103:1023–30.

The extensive diagnostic and clinical evaluation required to confirm patient eligibility for a complicated surgical exenteration is described in this excellent review. Exenterations have considerable impact on a patient's quality life, but with appropriate patient selection it can be a curative surgery for recurrent cervical and/or endometrial cancers. This review also differentiates the indications for total, anterior, and posterior exenterations. Because pharmacists have limited appreciation of this complicated surgical procedure, this paper is a helpful resource to provide foundation knowledge when working with women who have a gynecologic cancer.

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This is the 5-year follow-up report of the clinical efficacy of the quadrivalent HPV vaccine phase II randomized, double blind, placebo controlled licensing trial to prevent HPV infections and pre-invasive cervical cancer lesions. A total of 277 women aged 16–23 years were randomized to the HPV 6/11/16/18 vaccine given at 1, 2, and 6 months; they were then compared with 275 women aged 16–23 years who received placebo at the same time intervals. The primary end point was incidence of infection and/or cervical or external genital disease. Sexual activity and HPV exposure were not documented during the study. Data were analyzed on

the basis of the intent to treat regardless if the woman completed study or not. This study should be reviewed because it was one of the first reports of a decline in HPV geometric titers due to the use of a vaccine. This study has since led to research to determine if/when a booster of quadrivalent HPV vaccine is needed or if repeating the vaccine series might be indicated. Despite the decline in geometric titers for HPV 18, the HPV vaccine in the intent to treat group still had statistically significant reductions in incidence of HPV infection and pre-invasive cancer lesions.

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This landmark study by the Radiation Therapy Oncology Group demonstrated that adding chemotherapy to radiation therapy improved the progression-free and overall survival of patients with cervical cancer. This trial was the first randomized clinical study to demonstrate that addition of cisplatin plus fluorouracil chemotherapy to the standard radiation regimen had a statistically significant improvement in the progression-free and overall survival for women with advanced stage IIB and III cervical cancer. The chemotherapy regimen included the combination of cisplatin 75 mg/m² with fluorouracil 1000 mg/m²/day times 4 days given during daily concurrent radiation treatments once every 3 weeks for total of three cycles. This study created a paradigm shift in the treatment of cervical cancer: chemoradiation rather than radiation alone is given to patients with advanced cervical cancer. However, because of unacceptable toxicity, fluorouracil has been dropped.

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Historically, single-agent cisplatin was the mainstay of treatment for recurrent cervical cancer. Recently, the use of cisplatin-containing doublets has evolved in phase II and phase III trials in an effort to enhance efficacy and overcome inherent drug resistance. Cisplatin plus either paclitaxel, gemcitabine, topotecan, or vinorelbine were compared in 513 women with primary stage IV or persistent/recurrent cervical cancer in this phase III study (GOG 204). The progression-free and overall survival were equivalent. The ultimate conclusion from this study was that no superiority was observed for vinorelbine, topotecan, or gemcitabine in combination with cisplatin compared with the standard regimen of paclitaxel plus cisplatin. In addition, with the exception of myelosuppression and alopecia, there was no significant difference in toxicity between the four regimens. The cisplatin plus gemcitabine arm was the least myelotoxic, and the cisplatin plus paclitaxel

arm was predictably associated with the highest incidence of alopecia.

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This phase III study evaluated the efficacy of consolidation chemotherapy with 12 cycles of paclitaxel in patients with advanced ovarian cancer who achieved a complete response after completion of primary treatment. The study was stopped early after the interim analysis found a statistically significant improvement in progression-free survival compared with the control arm of consolidation with only three cycles of paclitaxel. After this interim report, many women enrolled in the control arm chose to cross over to the 12 cycles of paclitaxel arm, making it difficult to determine what impact, if any, extending treatment had on overall survival. This final report on the 26 patients, 13 in each arm of the study, suggested an improvement in both progression-free survival (12 months vs. 24 months) and overall survival (38 vs. 80 months). Although the study did achieve statistical significance, larger confirmatory studies are needed and are ongoing.

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The use of targeted agents has become a predominant focus of drug development in oncology, and ovarian cancer is no exception. This phase II study in patients with recurrent ovarian cancer was one of the first to demonstrate the benefit of the combination of bevacizumab 10 mg/kg once every 2 weeks and oral cyclophosphamide 50 mg once daily on progression-free survival in recurrent ovarian cancer. The combination of metronomic, low-dose oral cyclophosphamide, defined as frequent administration of low-dose cytotoxic chemotherapy given at frequent intervals (daily in this study), and bevacizumab intravenously once every 2 weeks on a continuous (28-day) regimen is commonly used in clinical practice today. The 70 patients enrolled in this the study had a 6-month progression-free survival of 56% and a 24% partial response rate. Estimated overall survival was 16.9 months. The combination is well tolerated with only limited toxicity (e.g., hypertension, fatigue, pain). The potential for intestinal perforation has been the biggest concern in patients with ovarian cancer. Appropriate patient selection is important. The cost and reimbursement for bevacizumab can be a problem for many patients, even those with insurance, but pharmacy assistance programs are available to allow access to this beneficial regimen.

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This phase III study conducted in Japan generated significant international controversy because the findings suggested a role for dose-dense chemotherapy. Historically, dose intensity has not demonstrated any improvement in progression-free or overall survival in women with ovarian cancer; rather, this approach has significantly increased toxicity. Hence, there is hesitancy to adapt dose density. The results of this study are provocative because the reported improvement in median survival is 16 months in the study arm when compared with standard therapy. An improvement of this significance has not been noted since the 2006 intraperitoneal chemotherapy trial (see annotated bibliography 13) or the introduction of paclitaxel use in the early 1990s. Additional follow-up is needed to determine whether these robust results will be maintained. Some variations in the control chemotherapy arm occurred in this clinical trial from the standard taxane/platinum regimen used in Western countries. An ongoing study is evaluating this dose-dense taxane/platinum regimen (paclitaxel 175 mg/m² weekly plus carboplatin AUC 5 every 3 weeks) compared with the standard taxane/platinum regimen (every 3 weeks) in women with advanced ovarian cancer. Dose-dense regimens are still considered investigational in the United States.

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Although intraperitoneal chemotherapy has been evaluated in gynecologic oncology for more than 30 years, this publication changed national guidelines and many clinical practices. This was the first study of intraperitoneal chemotherapy to demonstrate a statistically significant improvement in both progression-free and overall survival. This regimen includes paclitaxel 135 mg/m² intravenously over 24 hours on day 1 followed by cisplatin 100 mg/m² intraperitoneally on day 2, and paclitaxel 60 mg/m² intraperitoneally on day 8. The rationale and importance of the day 8 paclitaxel has generated significant discussion because many patients cannot tolerate intraperitoneal chemotherapy on day 8. This report, as well as many follow-up reports from this trial emphasizes that patient selection is critical to achieve benefit and limit toxicity of intraperitoneal therapy.

