Ovarian Stromal and Germ Cell Tumors

Carolyn R. Koulouris and Richard T. Penson

Cancers arising from the stromal and germ cell layers of the ovary are rare, heterogeneous, difficult to study, and require specialized multidisciplinary management. We present a clinically relevant review of the literature of these malignancies, with particular emphasis on the more typical presentations. These tumors more commonly present in younger patients and have a high cure rate. They are associated with serum markers that are informative for diagnosis and surveillance. Surgery is often part of primary treatment, with staging and preservation of fertility being important priorities. Most patients with germ cell tumors require adjuvant chemotherapy with bleomycin, etoposide, and cisplatin (BEP), as well as careful surveillance. The rarity of these tumors makes basic scientific advances more challenging.

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Within the sex-cord stromal and germ cell cancers, a variety of histopathological subtypes exist, and together they account for approximately 5% of ovarian neoplasms. They generally present unilaterally, at early stages, and have a relatively good prognosis, with the germ cell tumors being very sensitive to chemotherapy.

Patient age can be a predictive factor for diagnosis of non-epithelial ovarian cancers. Germ cell tumors are much more frequent among young women, with a median age of diagnosis of 26 years compared with 60 years for all ovarian cancers. The median age at diagnosis for sex-cord stromal tumor is 50 years.

Normal ovarian stroma is responsible for hormone production, and sex-cord stromal cancers are often hormonally active, or secrete related substances that serve as useful tumor markers.

The introduction of platinum chemotherapy for germ cell tumors has revolutionized outcomes and been one of the truly great success stories of modern oncology. Discovered serendipitously as an anticancer therapy during the investigation of electric flow from platinum electrodes, it is the backbone of all systemic therapy for these classes of tumor.

Sex-cord stromal and germ cell tumors of the ovary are rare, but the histologically parallel tumors of the testicle are more common. Due to difficulty accruing the numbers of cases needed for definitive clinical trials, many of the principles of treatment for these ovarian tumors have been informed by testicular cancer research.

Epidemiology

Almost nothing is known about the etiology of stromal tumors. Germ cell tumors of the testis are associated with cryptorchidism, as well as scrotal trauma. There are no clear ovarian correlates to these trends. Evidence supports a familial or genetic component to testicular germ cell cancers, and there may be significant overlap with ovarian germ cell cancer etiology.

Stettner et al described families with increased rates of both testicular and ovarian germ cell tumors. The age-adjusted incidence rate of malignant germ cell tumors over the past 30 years has been 0.34/100,000. The peak incidence is between the ages of 15 and 19 years, with the vast majority of patients being diagnosed before the age of 40 years. Asian/Pacific Islanders had higher overall rates of germ cell cancers of the ovary than white women, and Hispanic women had a slightly higher overall incidence rate than non-Hispanics. Malignant teratoma rates were significantly higher for non-white women compared to white women.

Individuals with ovarian dysgenesis are at such an elevated risk of developing stromal and germ cell tumors, especially dysgerminoma and gonadoblastoma, that prophylactic surgery is appropriate.

Pathology

Table 1 summarizes the World Health Organization (WHO) classification of histologic subtypes of germ cell

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and sex cord stromal malignancies of the ovary. Review of pathology by an expert in gynecologic pathology is essential to ensure an accurate diagnosis of these unusual histologies.

Sex-cord stromal tumors represent neoplasia arising in the ovarian stroma. This group encompasses several histologies, with the majority being granulosa cell tumors (adult and juvenile types), Sertoli-Leydig cell tumors, and unclassified sex cord-stromal tumors. Granulosa cell tumors account for 90% of ovarian sex-cord stromal malignancies and are usually characterized by indolent growth patterns.9,10

Several histologic types of germ cell tumors are frequently seen. Dysgerminoma is analogous to testicular seminoma and is the most common ovarian malignancy in adolescent girls and young women.11,12 Seventy-five percent are stage I, and they are more commonly bilateral than other non-epithelial ovarian tumors.13 These tumors can contain syncytiotrophoblastic giant cells and express placental alkaline phosphatase (ALP) and lactate dehydrogenase (LDH).14

Endodermal sinus tumors (Yolk sac tumors) represent 25% of malignant germ cell tumors and express alpha-fetoprotein (AFP). Histopathologically they have a characteristic central vessel invagination (Schiller-Duval body).7,15

Teratomas are most commonly divided into immature, mature, and monodermal subtypes. Immature teratomas also are called embryonal teratomas. They are graded according to the content of neural tissue, differentiation, and the presence of embryonal tissues. Mature teratomas, also called dermoids, represent 95% of all teratomas and are almost always benign. Monodermal teratomas have just one cell type and are extraordinarily rare. Disparate histologies from carcinoid and squamous cell carcinomas, to sarcoma and thyroid cancer have been described. Teratomas are treated according to the tissue type without regard to their ovarian origin.7

Ovarian choriocarcinoma are non-gestational and associated with β-human chorionic gonadotropin (βHCG) secretion.16 They are histologically analogous to choriocarcinoma arising in trophoblastic tissue, which occurs more commonly and was one of the first solid tumors to be cured with methotrexate.17 Embryonal carcinoma is rare (4%) and the most malignant. Polyembryomas are rare, often mixed tumors, and are characterized by "embryoid bodies." The most common mixed germ cell tumors are combinations of dysgerminoma and endodermal sinus tumors. Rarer non-epithelial tumors include gonadoblastoma, tumors of rete ovarii, mesothelioma, and lymphoma.

There are a number of incompletely characterized chromosomal and genetic abnormalities observed in germ cell cancers. The hallmark genetic trait of testicular germ cell cancers is an isochrome of the short arm of chromosome 12.18 Chromosome 12p abnormalities also have been found to be highly prevalent in dysgerminoma and mixed germ cell tumors.19,20 In an analysis of pediatric germ cell tumors, endodermal sinus tumors were associated with gains in 1q and chromosome 3, while malignant ovarian teratomas commonly had loss of 1p and gain of 1q and chromosomes 3, 8, 14, and 21.21 The clinical significance of these and other genetic aberrations has not been determined. New tissue makers, such as OCT4 (octamer binding transcription factor 4) and c-kit for dysgerminoma, may be diagnostically helpful and open therapeutic options.22

The role of tumor-suppressor gene p53 in germ cell tumors of the testicle has been linked to their sensitivity to cisplatin-induced apoptotic death. In contrast to most solid malignancies, these tumors express high levels of wild-type p53.23 The cyclin-driven mitosis of tetraploid pachytene spermatocytes, which are in the limited population of spermatogonial cells to express p53, may confer some of this sensitivity to platinum.24

**Table 1. Summary of the WHO Classifications of Ovarian Sex-Cord Stromal and Germ Cell Malignancies**

<table>
<thead>
<tr>
<th>Sex-cord stromal tumors</th>
<th>Germ cell tumors</th>
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<tbody>
<tr>
<td>3. Sex-cord tumor with annular tubules</td>
<td>3. Teratoma: immature, mature monodermal, and mixed</td>
</tr>
<tr>
<td>5. Steroidal or Leydig tumor</td>
<td>5. Embryonal carcinoma</td>
</tr>
<tr>
<td>6. Unclassified</td>
<td>6. Polyembryoma</td>
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**CLINICAL PRESENTATION**

Non-epithelial cancers of the ovary should be on the diagnostic differential when women present with incidental discovery of asymptomatic ovarian mass, hormonal symptoms, or abdominal pain, or symptoms from rapidly progressing metastatic disease. The diagnosis and management of each of these groups will be discussed.

**Tumor Markers**

A variety of tumor markers have an important role diagnostically and in surveillance for tumor recur-
rence (Table 2). It is not cost-effective to survey a panel of makers in all patients with suspected ovarian neoplasm, and their use should be selective.

Granulosa cell tumors may express and secrete (α and β) inhibin, βHCG, Müllerian inhibiting substance (MIS), CA125, estradiol, and occasionally testosterone. Sertoli-Leydig tumors often produce testosterone.

AFP is a 590- amino acid glycoprotein produced by the fetal yolk sac. It is the serum marker identified as significantly elevated in patients with germ cell tumors with a component originating from the endodermal sinus. Talerman et al suggest that this marker is specific enough to be used diagnostically, as well as being an accurate measure of disease in surveillance. It also is produced by pediatric tumors (hepato- and neuroblastoma, and Wilm’s tumor) and hepatocellular carcinoma, and is rarely elevated in hepatitis and colitis. The half-life of AFP as a marker is approximately 5 days. Patients demonstrating an adequate response to therapy will typically have a decline in AFP proportional to its half-life.

βHCG is a 244-amino acid glycoprotein hormone produced by the placenta to maintain corpus luteal production of progesterone, and maintenance of pregnancy. It is a heterodimer with a unique β-subunit, and shares the same α-subunit as luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH). The half-life of βHCG as a marker is approximately 36 hours.

In testicular germ cell tumors, a slow decline in serum levels of βHCG and AFP during the first two cycles of chemotherapy (bleomycin, etoposide, cisplatin [BEP]) had a statistically significantly correlation with poorer progression-free and overall survival.

### ISOLATED ADNEXAL MASS

For patients with discovery of a solid or complex ovarian mass, a non-epithelial neoplasm may be in the differential and must be considered in young women. Approximately one third of ovarian malignancies in women under 25 years of age are germ cell tumors. This situation demands surgical evaluation, by a gynecologic oncologist, for the purposes of diagnosis and staging. Appropriate staging in these tumors provides key prognostic information and guides therapeutic decision-making.

In sex-cord stromal tumors, stage has been the most important predictor of survival in a number of studies, including a recent review by Zhang et al with long-term follow-up on more than 350 patients. Similar results have been found in a retrospective analysis of germ cell cancer outcomes. Furthermore, truly stage I tumors in several histologies may be appropriately managed with surgery alone, but without adequate staging surgeries, it is not possible to completely rule out occult metastatic disease.

The staging system used for sex-cord stromal and germ cell ovarian cancers is the same as the International Federation of Gynecology and Obstetrics (FIGO) staging for epithelial ovarian cancers. This staging involves peritoneal cytology, total abdominal hysterectomy, bilateral salpingo-oophorectomy, biopsy of malignant peritoneal lesions or staging biopsies including left and right pelvic cul-de-sac, bladder, para- colic gutter, and diaphragm biopsies, and resection of positive lymph nodes or pelvic and para-aortic lymph node dissection. Staging procedures in these patients should occur at the time of initial surgical evaluation to avoid additional procedures and delays. There is an increasing acceptance that similar prognostic criteria as

<table>
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<th>Table 2. Ovarian Germ Cell and Stromal Tumor Markers</th>
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<tr>
<td><strong>E2</strong></td>
</tr>
<tr>
<td>Granulosa cell</td>
</tr>
<tr>
<td>Theca-fibroma</td>
</tr>
<tr>
<td>Sertoli-Leydig</td>
</tr>
<tr>
<td>Dysgerminoma</td>
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<tr>
<td>Yolk sac</td>
</tr>
<tr>
<td>Embryonal</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
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<tr>
<td>Immature teratoma</td>
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<tr>
<td>Gonadoblastoma</td>
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Isochrome p12 ([1(12)p] can be helpful diagnostically in tissue for diagnosis of germ cell tumors. Others: monodermal struma ovarii (T4), carcinoid (5-hydroxyindoleacetic acid-positive). CA125 can be elevated in advanced disease.

Abbreviations: E2, estradiol; Inhib, inhibin; MIS, Müllerian inhibiting substance; T, testosterone; A, androstenedione; DHEA, dihydroepiandrosterone; AFP, alpha-fetoprotein; hCG, human chorionic gonadotrophin; pALP, placental alkaline phosphatase; LDH, lactate dehydrogenase; VEGF, vascular endothelial growth factor.
used in germ cell tumors of the testicle may be applicable to ovarian germ cell tumors. Table 3 provides staging outlines.

Young women with gynecological malignancies may wish to preserve fertility. For patients with germ cell ovarian cancers presenting as an isolated adnexal mass, fertility-sparing surgery, in which hysterectomy and contralateral salpingo-oophorectomy are omitted from standard staging procedures, is acceptable practice. No difference in outcome has been attributed to fertility-preserving surgery for clinically stage I germ cell tumors in several large retrospective series. Although fewer studies have explored fertility-preserving surgery in advanced disease, they do point to equivalent oncologic outcomes with little impact made by resection of a grossly normal ovary.

As a large proportion of ovarian germ cell cancer patients will potentially desire fertility-sparing procedures, it is important that these be offered at the center where they receive care. Although treatment-induced menopause has been observed in a small percentage of patients, studies of fertility outcomes among these patients indicate that most (87%) in one Gynecologic Oncology Group (GOG) protocol report normal post-treatment menstrual function and a number have reported healthy live births. Gravidity can confound surveillance for recurrence, and avoiding pregnancy for the first year of surveillance has been recommended.

Fertility-sparing surgery is not well studied in sex-cord stromal tumors of the ovary, although Gershenson suggests that due to the generally indolent nature of this disease, especially when treated at an early stage, young patients can be offered fertility-sparing measures. In a retrospective review, Chan et al reported three recurrences in 12 patients with stage I sex-cord stromal tumors who underwent fertility-sparing surgeries. Zhang et al found equivalent survival for patients with stage I disease who underwent uterine-sparing procedures in a population of 131 patients.

**HORMONAL SYMPTOMS**

When women or girls present with abnormal hormonal symptoms and an adnexal mass, sex-cord stromal or germ cell cancers should be on the list of differential diagnoses. Aberrant vaginal bleeding stratifies by menstrual status to include premenarche bleeding, dysmenorrhea, amenorrhea, or postmenopausal bleeding. While other diagnoses are far more common, assessment of the adnexae should be part of the diagnostic procedures. A substantial minority (10%) of germ cell ovarian tumors present with abnormal vaginal bleeding and a small percentage are responsible for isosexual precocity in children.

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Tumor confined to ovaries</td>
</tr>
<tr>
<td>IA</td>
<td>Tumor limited to one ovary, capsule intact</td>
</tr>
<tr>
<td>IB</td>
<td>Tumor in both ovaries</td>
</tr>
<tr>
<td>IC</td>
<td>Tumor in one or both ovaries, with a capsule ruptured, surface involvement, cytologically positive ascites or peritoneal washings</td>
</tr>
<tr>
<td>II</td>
<td>Tumor involves one or both ovaries with pelvic extension to the uterus (A), other structures (B), or with positive peritoneal washings (C)</td>
</tr>
<tr>
<td>III</td>
<td>Tumor involves one or both ovaries with microscopically (A) or macroscopically [(B), or &gt;2 cm (C)] confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastases</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastasis beyond the peritoneal cavity</td>
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Note: Liver capsule metastasis is stage III, liver parenchymal metastasis is stage IV. Pleural effusion must have positive cytology.

Modified staging for testicular germ cell tumors

| IM | Rising markers post gonadectomy |
| II | Abdominal lymph nodes (A) <2 cm, (B) 2–5 cm, (C) >5 cm |
| III | Supradiaphragmatic lymph nodes |
| IV | Extranodal disease |

Prognostic Groups

<table>
<thead>
<tr>
<th>Prognostic Groups</th>
<th>AFP</th>
<th>βHCG</th>
<th>LDH</th>
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<tbody>
<tr>
<td>Good</td>
<td>&lt;1,000</td>
<td>&lt;5,000</td>
<td>&lt;1.5 × ULN</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1000-10K</td>
<td>5,000-50K</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>&gt;10K</td>
<td>&gt;50K</td>
<td>Mediastinal liver or CNS metastases</td>
</tr>
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</table>

Note: This is not accepted staging for ovarian germ cell tumors, but can be clinically helpful to stratify patients by potential risk. While multivariate analysis does support the prognostic importance of tumor markers in ovarian germ cell tumors, this is not as formalized as testicular germ cell tumors. Units: AFP ng/mL, βHCG IU/L.

Abbreviations: ULN, upper limit of normal; AFP, alpha fetoprotein; βHCG, beta-human chorionic gonadotropin; LDH, lactate dehydrogenase; CNS, central nervous system.
Granulosa cell tumors often produce excess estrogen, and abnormal vaginal bleeding is present in two thirds of patients at diagnosis. In a retrospective review of 200 granulosa and thecoma cell tumors, endometrial abnormalities were noted in about two thirds of the cases. These included endometrial hyperplasia and well-differentiated adenocarcinoma, and were not limited to postmenopausal women. With Sertoli-Leydig tumors, 70% to 85% of patients show signs of virilization (hirsutism; male pattern balding, strength, and voice; clitoromegally; and anovulation) due to elevated androgen production.

If an adnexal mass is discovered in the setting of abnormal hormonal symptoms, then surgical evaluation, with potential staging, becomes appropriate. With this presentation, attention should be given to the potential for concurrent endometrial pathology.

**ABDOMINAL PAIN**

Acute pain is a common presenting symptom in germ cell or sex-cord stromal tumors. There are several potential etiologies of this pain, including torsion, rupture, and hemoperitoneum. In a case review of 83 patients with sex-cord stromal tumors, Chan et al reported 22% presenting with abdominal pain, although no distinction was made between acute and chronic pain. Hemoperitoneum, from tumor rupture into the abdominal cavity, has long been described as a presenting feature of granulosa cell tumors. This is a potentially fatal condition, and requires emergent surgical evaluation. Granulosa cell tumor rupture may be the cause of atraumatic hemoperitoneum in women, which is helpful information to surgeons attempting to control this bleeding. Torsion, or twisting of the ovary on its pedicle, causes acute pain. In one series of 66 pediatric patients with ovarian germ cell tumors, 16 (24%) patients went to emergent surgery for torsion.

In cases where acute abdominal pain is the operative indication, comprehensive staging may not be feasible. A further definitive staging procedure may be indicated, but clinical practice varies widely. Some centers only pursue staging if computed tomography (CT) scans and pelvic magnetic resonance imaging are normal, to define whether the patient has a low enough risk for surveillance alone to be safe, and others restage only if the postoperative CT scan is abnormal.

**ADVANCED DISEASE**

Although the majority of girls and women are diagnosed with early-stage sex-cord and germ cell tumors, approximately 20% with sex-cord stromal tumors and 25% to 50% with germ cell tumors are advanced stage (III or IV) malignancies at the time of diagnosis. Patients with bulky advanced disease may have symptoms from peritoneal metastases, ascites, or visceral metastases.

**SURGERY**

Although controversial, debulking (removing the maximum amount of gross disease surgically) has been advocated to improve treatment outcomes. Most studies of germ cell and stromal ovarian cancers have reported a negative prognostic value of residual disease after primary surgery, similar to epithelial ovarian cancer. In retrospective multivariate analysis, complete surgical resection of disease was found to be independently predictive of survival in sex-cord stromal tumors. Analysis of prospective chemotherapy trials in germ cell tumors has similarly found residual disease to be a predictor of negative outcome.

For stromal tumors that may be markedly less chemosensitive, such as granulosa cell tumors, cytoreduction plays an important role, and many patients live for years with indolent disease, benefiting from repeated surgical procedures.

Dysgerminoma is thought to be the one histology where debulking may be inappropriate, delaying definitive treatment in this exquisitely chemosensitive tumor. An Indian report serves as a graphic example with all 11 patients with dysgerminoma, irrespective of the residual bulk, reaching complete sustained remission with BEP chemotherapy. Only three of six patients with non-dysgerminomatous tumors and bulky residual disease achieved a sustained remission.

**POSTOPERATIVE TREATMENT**

Postoperative treatment recommendations for patients diagnosed with germ cell or sex-cord stromal tumors of the ovary are based on tumor stage and final pathologic assessment of histology.

**STROMAL TUMORS**

Recommended first-line therapy for high-risk stage I and more advanced staged sex-cord stromal malignancies is typically combination platinum-based chemotherapy, such as BEP or paclitaxel and carboplatin, and possibly radiotherapy. However, these recommendations are not well supported by evidence. Stage IA granulosa cell tumors resected with comprehensive surgical staging have a very low recurrence rate with surgery alone. More advanced sex-cord stromal tumors have a poorer prognosis, leading to recommendations for adjuvant chemotherapy, although retrospective review has been unable to definitively demonstrate the value of postsurgical chemotherapy. However, these reviews always span a wide time frame and a variety of treatment regimens, making them difficult to interpret.
While increasing rates of complete responses have been observed in single-arm trials, sustained remissions in women with measurable disease have been more elusive. There have been no randomized controlled trials in this rare tumor type, and guidance has been drawn from other ovarian tumors.

Platinum-based therapy has been pursued in various combination regimens beginning with cisplatin, doxorubicin, and cyclophosphamide, where Gershenson et al reported a 63% response rate in metastatic sex-cord stromal tumors.46 Cisplatin, vinblastine, and bleomycin (PVB) were used in several studies with response rates ranging between 54% and 84%.59 The GOG then pursued the most active germ cell regimen, BEP, in metastatic and recurrent sex-cord stromal malignancies. Sixteen patients were enrolled after primary cytoreduction, and 12 of these patients had a complete response (75%). The overall negative second-look rate was 37%.47 All of these trials lacked durability of remissions, and oncologists are still working to improve adjuvant chemotherapy in these cancers. Brown et al have reported the activity of taxanes in sex-cord stromal tumors, especially in combination with platinum.48 Combined carboplatin and paclitaxel is likely to be the next regimen pursued in this disease. The National Comprehensive Cancer Network (NCCN) guidelines reflect the lack of strong evidence supporting a particular regimen in this setting, where the additional toxicities of BEP chemotherapy may not provide benefit over carboplatin/paclitaxel.45

**GERM CELL TUMORS**

According to current NCCN guidelines, stage I dysgerminoma and stage IA, grade 1 immature teratoma need only surgery. All other ovarian germ cell tumors carry the recommendation of three to four cycles of BEP combination therapy (bleomycin 30 U administered intravenously weekly, etoposide 100 mg/m²/d on days 1-5, and cisplatin 20 mg/m²/d on days 1-5 repeated on a 21-day cycle).45,49,50 Compressing the treatment to 3 days is likely equally effective.51 Cisplatin-based chemotherapy is highly effective, but it is still associated with risks, including pulmonary insufficiency (15% reduction in transfer factor for carbon monoxide) and a small incidence of infertility, secondary malignancy, and nerve damage.

Careful surveillance instead of adjuvant therapy in other early-stage tumors is controversial and an area of interest in germ cell research.7,22 Reserving chemotherapy for rarely needed salvage has the advantage of avoiding unnecessary treatment with potentially harmful agents. Dark et al reported a series of 24 patients with stage IA tumors and normal postoperative serum markers who were managed without adjuvant chemotherapy; this included patients with high-grade immature teratomas, endodermal sinus tumors, and dysgerminomas. Five-year survival was 95%. Six patients had recurred during follow-up, with evidence of chemotherapy-sensitive disease in all women with recurrent disease. One patient died of a pulmonary embolus while receiving salvage chemotherapy.35

American clinicians are typically more conservative and view all ovarian germ cell tumors as potentially of poorer prognosis than testicular tumors, and often consider four cycles of BEP to be the standard.

**NON-DYSGERMINOMA GERM CELL TUMOR CHEMOTHERAPY**

Postoperative treatment with chemotherapy has dramatically improved outcomes in germ cell tumors of the ovary. As recently reviewed by Gershenson, surgery alone is associated with a survival for patients with germ cell tumors of between 5% and 20%, while chemotherapy-induced cure rates are greater than 95% in patients with early-stage disease and over 75% in those with advanced-stage disease.7 Ovarian germ cell tumors are closely related histologically to testicular germ cell cancers, and parallels have often been drawn from randomized results in these more common tumors. Classically, dysgerminoma has been separated from other histologies because it was effectively treated with radiation and is extremely sensitive to platinum-based chemotherapy.

The GOG first reported on a study of vincristine, dactinomycin, and cyclophosphamide in non-dysgerminomatous germ cell tumors with approximately 70% long-term survival with initially completely resected disease of any stage. Results were less impressive in unresectable disease, with a failure rate of 68% within the studied follow-up period.43 Success of cisplatin-based chemotherapy in testicular germ cell cancer prompted study of cisplatin, vinblastine, and bleomycin in recurrent and advanced germ cell tumors of all histologies. Responses were much improved over previous regimens, with a 2-year survival rate of 71%.52 This study solidified the effectiveness of platinum chemotherapy in this disease group.

GOG-93 was the largest study of adjuvant BEP in optimally cytoreduced stage I, II, or III non-dysgerminomatous ovarian germ cell tumors.50 The study results have been updated and the cure rate remains impressive, with 89 patients continuously free and 91 of the 93 patients “currently” free of germ cell cancer. Two patients developed secondary malignancies, a known late consequence of etoposide.50 Bleomycin toxicity includes fatal pulmonary fibrosis, and patients should be advised to wear an alert bracelet and told to avoid supplemental oxygen for the rest of their lives. Many clinicians modify the bleomycin schedule (infusion, every 21 days, or intramuscular) to minimize the peak dose, and the drug may be contraindicated in the presence of significant renal impairment.53
The impressive cure rates in single-arm BEP chemotherapy trials have led to its adoption as the standard of care in non-dysgerminoma germ cell tumors. There have been no randomized trials to determine the number of cycles to treat, and this remains a point of debate. Significant toxicities were observed on the BEP trial, including more than a 10% rate of febrile neutropenia, although 90 of 93 patients were able to complete all three cycles of therapy. POMB/ACE (cisdplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide, and etoposide) also has shown high response rates (87% at 3 years) in a trial of 59 patients newly diagnosed with metastatic ovarian germ cell tumors.

On the basis that cure is most likely with two cycles of treatment beyond complete remission, there has been strong advocacy for two cycles of adjuvant cisplatin-based chemotherapy with the largest experience coming from the Medical Research Council report in testicular cancer. This study of 114 patients, with an expected relapse rate of about 50%, suggests that the relapse rate after adjuvant chemotherapy with just two cycles of treatment falls below 5% in small, low-risk postoperative marker-negative disease, with an extremely good prognosis. With the continuing aim of reducing dangerous toxicity while maintaining positive outcomes, oncologists have explored alterations to the BEP regimen. In good-risk patients with metastatic germ cell testicular cancers, high complete response rates (98%) to cisplatin and etoposide in a large single-arm trial have led to the suggestion that this regimen could replace BEP in this population.

With the transition from adjuvant cisplatin to carboplatin in epithelial ovarian cancer, oncologists have asked whether carboplatin could be substituted for cisplatin in the treatment of germ cell tumors. The use of carboplatin is attractive because of reduced gastrointestinal and neurotoxicity. However, the standard treatment of ovarian germ cell tumors is the informed experience in testicular germ cell cancers, where carboplatin has been shown to be inferior to cisplatin in randomized trials. In a few single-arm studies, carboplatin has been used with good reported outcomes, but uncontrolled data are insufficient to defend the use of carboplatin when the goal is cure.

DYSGERMINOMA CHEMOTHERAPY

Dysgerminomas have even higher response rates to platinum-based chemotherapy, with sustained remission rates of greater than 95% even in advanced disease. The testicular pathology equivalent to ovarian dysgerminoma is seminoma. Both of these tumors have a history of successful treatment with radiotherapy. The morbidity of radiation, including reproductive loss and late iatrogenic cancers, has prompted investigation into the use of chemotherapy in these treatment-sensitive tumors. A German group has, for some time, advocated single-agent carboplatin in seminoma. Randomized data in stage I testicular seminoma have demonstrated the non-inferiority of single-agent carboplatin compared with radiotherapy.

The high response rate to platinum, and experience in the analogous seminoma of the testicle, led to the pursuit of a less toxic regimen: carboplatin and etoposide. In 39 patients with stage IB–III completely resected dysgerminoma, the GOG reported 100% sustained remission after three courses of carboplatin and etoposide. The median follow-up was 7.8 years, and neurotoxicity was less than observed with BEP chemotherapy. There may be a small, but clinically significant, increased risk of relapse with this regimen, given that carboplatin has been shown inferior in favorable prognosis metastatic testicular cancer.

POST-CHEMOTHERAPY SURGERY

Although response rates are high, some patients will have residual disease at the end of adjuvant chemotherapy. For patients with teratomatous germ cell tumors, there is a role for surgery in this context.

Based on data from several platinum-based GOG studies of ovarian germ cell tumors that included post-treatment laparotomy, Williams et al concluded that these procedures were only beneficial in patients who had elements of teratoma in their original pathology. Sixteen of 24 patients with teratomatous elements had mature teratomas at second-look laparotomy, with resection of bulky disease in six patients. Discovery of other histologies at second-look laparotomy led to very poor prognosis, not clearly ameliorated by the surgical procedure. These mature teratomas, thought to be chemotherapy-converted from immature teratomas, can be treated with surgical resection. Hariprasad et al argue that surgical evaluation of patients with teratomatous germ cell tumors with residual disease after chemotherapy avoids unnecessary and ineffective additional chemotherapy. Gershenson et al reviewed 53 non-dysgerminoma ovarian germ cell cancer patients who underwent second-look laparotomy. Only one patient had a positive second-look procedure, and was successfully salvaged with chemotherapy. The only patient with disease-related mortality within the follow-up period had a negative second-look laparotomy. These data support post-treatment surgical evaluation of patients with teratomatous germ cell tumors and suspected residual disease. However, second-look laparoscopy or laparotomy is not necessary as a general practice.

For patients with sex-cord stromal tumors persisting through primary chemotherapy, heroic surgery may have little merit for refractory disease and should be carefully considered in the clinical context.
POST-TREATMENT PROGNOSIS AND FOLLOW-UP

Although the initial treatment of sex-cord stromal and germ cell ovarian malignancies has some similarities, recurrent disease presents dramatic differences. Only 10% to perhaps a third of patients with recurrent germ cell tumors that previously have been treated can be cured, and the refractory disease course can be rapid. While recurrences of stromal tumors are never cured, they can be extraordinarily indolent, with our latest recorded relapse occurring at 42 years.

Patients with germ cell tumors treated appropriately with surgery and postoperative BEP chemotherapy have an excellent chance for remission without recurrence. For patients with early-stage disease, the likelihood of cure after adjuvant chemotherapy is near 100%. In patients with advanced disease, cure rates are about 75%. Patients who recur usually do so within 24 months of diagnosis. Appropriate surveillance includes pelvic examination and serum markers, and continued assessment of fertility, lung function, and audiometry.

Our clinical practice is to monitor markers with serum AFP, 𝛽HCG, CA125, and LDH regardless of their initial value. This is done every 2 weeks for the first 6 months, then monthly, every 2 months in the second year, every 3 months in the third year, every 4 months in the fourth year, and every 2 years out to 10 years.

Granulosa cell tumors have a propensity for late recurrence that necessarily changes appropriate posttreatment surveillance. Patients initially presenting with metastatic disease have a much higher rate of recurrence, even with postoperative chemotherapy. Appropriate surveillance for recurrence in these patients includes pelvic examination and serum makers, and must be extended many years after the diagnosis due to the risk of late recurrence and the benefit of further surgery. The average time to recurrence for granulosa cell tumors is 4 to 6 years.

RECURRENT AND REFRACTORY DISEASE

In these rare tumors, which recur or persist even less frequently, there is no standardized approach to the treatment of recurrent disease. Resection of recurrent disease after long periods of remission is largely accepted to have a similar effect to primary cytoreductive surgery. For indolent cancers, this is an especially appropriate treatment.

Single case reports make up the bulk of the recurrent ovarian germ cell cancer literature. Li et al recently reported their experience with secondary surgery and chemotherapy against 34 cases of ovary germ cell tumors after primary treatment failure. They reported a 5-year survival of 61% in patients who had less than 1 cm of residual disease after a second surgical procedure, compared to 14% for patients who had suboptimal cytoreductions. They also found that salvage was more successful in patients who had previously not received optimal chemotherapy regimens (identified as BEP and PVB [cisplatin, vinblastine, and bleomycin]) and in dysgerminoma and immature teratoma histologies. Chemotherapy regimens used in this context vary widely and include the same regimens used in primary therapy and agents active against recurrent testicular germ cell cancers.

Further platinum-based combination therapy is the best chance for salvage. When the disease is platinum-refractory, the prognosis is typically dismal. However, for germ cell tumors, high-dose chemotherapy with autologous stem cell support may be considered. Other testicular germ cell salvage regimens include POMB/ACE, ICE (ifosfamide, platinum, and etoposide), TIP (paclitaxel, ifosfamide, cisplatin), modified Wetlauffer (methotrexate, bleomycin, vincristine, cisplatin [M-BOP]), and GAMEC (an intensive cisplatin-based regimen that incorporates high-dose methotrexate, actinomycin D, and etoposide every 14 days).

There also is no standard approach to recurrent disease in sex-cord ovarian tumors. For the often indolent, late recurrence associated with granulosa cell tumors, surgery is the primary modality, often with adjuvant chemotherapy. Treatment of these recurrences is a challenge for oncologists, because few well-established regimens exist and patients may require treatment for serial recurrences. BEP chemotherapy was studied in metastatic and recurrent sex-cord stromal tumors, with responses in both groups, although there was a lack of durable remissions. This regimen remains a top choice for treating recurrent disease. There also are reported responses to taxane chemotherapy in recurrent granulosa cell tumors, and this is an emerging option for second-line chemotherapy after platinum resistance or toxicity. Hormonal activity is a defining characteristic of granulosa cell tumors, and activity has been reported with the use of hormonal agents, including aromatase inhibitors and gonadotropin-releasing hormone (GnRH) agonists, against recurrent disease.

In non–granulosa cell sex-cord stromal tumors, there are even fewer data for treatment of recurrences, based predominantly on case reports. One such report demonstrates successful salvage of a recurrent ovarian Sertoli-Leydig cell tumor with secondary surgical procedure followed by cisplatin, vinblastine, and bleomycin chemotherapy.

In non-epithelial ovarian cancers, platinum-based chemotherapy appears to be the most active regimen in recurrent disease, although no prospective randomized evidence exists to prove this, given the rarity of the disease. Secondary cytoreductive procedures have been demonstrated as therapeutic, but this benefit may be limited to cases where optimal debulking is feasible.
CONCLUSION

Stromal and germ cell tumors of the ovary are rare, heterogeneous, and poorly understood. They challenge our understanding of biology, as much as they hold out the hope that rational therapy will unlock the quantum leap from treatment to cure.

REFERENCES

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