Rare Epithelial Tumors Arising in or near the Ovary: A Review of the Risk Factors, Presentation, and Future Treatment Direction for Ovarian Clear Cell and Mucinous Carcinoma

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OVERVIEW

Currently all advanced-stage epithelial ovarian cancers are treated with a total abdominal hysterectomy, bilateral oophorectomy, and complete tumor debulking surgery, followed by carboplatin and paclitaxel. This treatment recommendation is based on clinical trials that are mostly populated with women with high-grade serous carcinomas. Patients with mucinous or clear cell carcinomas of the ovary tend to present with earlier-stage disease, and may not require adjuvant chemotherapy; those with advanced-stage disease tend to have carboplatin-resistant disease. Patients with mucinous ovarian carcinoma have presentations and tumor biology that are similar to colorectal carcinomas and may benefit from colorectal regimens containing fluorouracil (FU) and oxaliplatin. Their tumors may also be KRAS wild-type or have HER2 amplification, and could benefit from drugs like cetuximab or trastuzumab. Patients with clear cell carcinoma of the ovary often harbor AIRD1a mutations, an early event in oncogenesis that is not a currently drugable target. Anecdotal cases and our biologic understanding of these malignancies suggest they might be preferentially sensitive to antiangiogenesis inhibitors. Focused international trials will be needed in both of these rare epithelial ovarian cancers to better define optimal treatment regimens.

The typical woman with ovarian cancer presents with advanced-stage serous carcinoma, and indeed the majority of biology, reagents (such as cell lines), and therapeutic recommendations are based on the results of trials heavily dominated by women with serous carcinoma of the ovary. In recent years, the clinical outcomes and more importantly underlying genetics of serous, clear cell, and mucinous cancers arising in or near the ovary has lead to an important shift in our understanding of the biology of what now appear to be completely separate malignancies, much like rectal cancer is different from bladder cancer. Although there is some overlap in clinical presentations and complications, therapeutic recommendations still do not differ despite the improved biologic understanding of these cancers.

Mucinous and clear cell tumors represent two epithelial tumors arising in or near the ovary. Unlike serous cancer of the ovary (sOC), both of these tumors are more commonly found confined to the ovary, and thus surveys of epithelial tumors confined to the ovary typically have a relatively high proportion of mucinous ovarian cancers (mOC) and clear cell tumors of the ovary (cOC).

MUCINOUS CANCER ARISING IN THE OVARY

Epidemiology and Risk Factors for mOC

Three percent of all epithelial ovarian cancers are mucinous, and a significant portion of these tumors present as local tumors within the ovary. Series of stage I epithelial tumors demonstrate that mOC represent approximately 30% of early-stage tumors and are usually cured by surgical resection.1 They have an improved 5-year disease-free survival of 90.8%, compared with sOC, 75.9%.1,2 Patients with mOC tend to have platinum-resistant disease, and when presenting with advanced-stage disease, these patients do not experience responses as positive as those experienced by patients with sOC. In a case-controlled study, 63% of mOC patients with stage III and IV disease had progression of disease while receiving treatment with single-agent carboplatin, single-agent paclitaxel, or platinum combination therapy, and an overall response rate of 26.3%, whereas patients with sOC had response rate of approximately 70%.3 Progression-free survival rates for mOC were lower compared with all epithelial ovarian cancer (eOC), 5.7 months and 14.1 months, respectively, whereas overall survival was 12 months and 36.7 months, respectively.

Risk factors for development of mOC may also differ from those for sOC. In contrast to patients with sOC, patients with mOC tend not have a family history of breast or ovarian cancer. BRCA1 and BRCA2 mutations are not associated with this histology. Risk factors for sOC such as low parity, no breastfeeding, and no use of oral contraceptives are not linked to mOC. A recent meta-analysis of epidemiologic studies has linked smoking history with mucinous cancer.4
Family history, tubal sterilization, hysterectomy, age at menarche, and breastfeeding did not show significant correlation to development of mOC or borderline tumors.

**Origin and Biology of mOC**

mOC is thought to arise from borderline or cystadenomas with alterations in ras/raf pathway as frequent early events in oncogenesis, specifically activating KRAS mutations. KRAS mutations are found in approximately 46% to 55% of cystadenoma precursors, 63% to 73% of borderline tumors, and 75% to 85% of invasive mOC. mOC likely forms in a stepwise fashion, with progression from a cystadenoma to a borderline tumor (usually found surrounding the invasive disease) to invasive tumor. One study has implicated the fimbriated fallopian tube as a possible site of origin of mOC, similar to recent studies in sOC. A subset of tumors harbors HER2 amplification, p53 mutations, and rare APC or CTNNB1 mutations. Some data suggests that these are distinct from the tumors with KRAS mutations and downstream mitogen-activated protein kinase (MAPK) pathway activation. Transcriptional profiling of mOC compared with other types of epithelial tumors arising in the ovary and various normal epithelium demonstrate that the RNA transcriptional pattern of mOC is distinct from other cancers arising in (or near) the ovary and more closely related to normal colonic epithelium compared with ovarian epithelium.

**Presentation of mOC**

The pathologic and clinical presentation of mOC have substantial similarities to colorectal cancers (CRC) making discrimination between these malignancies challenging (Table 1). Most patients with mOC have measurable serum increases of carcinoembryonic antigen (CEA), like CRC, rather than cancer antigen (CA)-125, like sOC. Appendiceal cancer and CRC can mimic mOC with presentation of ascites, adnexal masses, or vaginal bleeding. A colonoscopy should be performed on all patients with suspected mOC to rule out a possible CRC. Seidman9 developed an algorithm to differentiate mOC from CRC. Ovarian tumors greater than 10 cm in size with unilateral ovarian involvement are more likely to be mOC than CRC.9 Immunohistochemical markers for mOC are more likely to be positive for CK 7, CK 20, and CEA, whereas for CRC only CK 20 and CEA are likely to be positive. Histologically, mOC are more likely to show a papillary pattern, expansile pattern of invasion. Metastatic disease from CRC shows a nodular growth pattern with an infiltrative pattern of invasion, and in some cases signet ring cells.

**Treatment of mOC**

When a mOC is expected or known, an appendectomy should be performed along with a careful evaluation of the GI tract to rule out a GI primary tumor with ovarian metastasis. In patients presenting with advanced-stage disease, the specific value of comprehensive surgical cytoreduction in women with mOC has not been specifically studied. However, in light of mOC’s relative resistance to chemotherapy, an argument can be made that such a procedure becomes more valuable.

Patients with localized tumors have a good prognosis and those with stage 1A disease can most likely undergo observation. Of note, these tumors are typically difficult to grade and often are admixed with premalignant tumors. For women with advanced-stage disease, controversy exists as to whether to offer to these women standard paclitaxel and carboplatin (as defined in trials largely predominated by women with sOC) or alternatively to provide offer regimens with efficacy in CRC, such as the current oxaliplatin-based regimens. Both irinotecan- and oxaliplatin-based regimens have been or are being explored in the treatment mOC. Most notably, the Gynecologic Oncology Group (GOG), in cooperation the Gynecologic Cancer Intergroup (GCIG), is currently conducting a clinical trial to compare carboplatin and paclitaxel ± bevaczumab with capectabine and oxaliplatin ± bevaczumab to evaluate for progression-free survival and response rate in women with newly diagnosed mOC. In women with platinum sensitive disease defined as those with recurrence more than 6 months from primary platinum-based therapy, the response rate of mOC to re-treatment with platinum was 36% compared with 63% in women with other types of eOC. Hazard rates of death for women with advanced stage mOC compared with nonmucinous histologies was 2.15.7

Opportunities exist to explore the rational application of molecularly based therapeutic recommendations. Noting the use of EGFR inhibitors in the management of a subset of individuals with CRC, its use can be considered in patients with KRAS wild-type mOC, although this hypothesis has not yet been tested in a clinical trial. Although numerous studies evaluating EGFR inhibitors (both small molecule and antibodies) have been tested in eOC no studies have focused exclusively on this rare subset of patients. Likewise, HER2 is occasionally amplified in mOC. In a case cohort study of 33 cases of mOC, six patients had HER2 amplification and two

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**KEY POINTS**

- The current biologic understanding of clear cell and mucinous malignancies suggests that these tumors are not related to serous tumors of the ovary.
- Early-stage mucinous ovarian cancer may not require adjuvant therapy.
- Future systemic treatment for mucinous ovarian cancer may be similar to treatment used in colorectal cancer, including epidermal growth factor receptor (EGFR) or HER2-based therapy.
- Clear cell ovarian cancer may arise from endometrial tissue, supported by the evidence that similar AIRD1a mutations have been found in endometriosis tissue surrounding clear cell tumors.
- Clear cell ovarian cancer tends to be carboplatin resistant, and future therapies may include antiangiogenesis inhibitors or blockade of the PI3k/AKT/mTOR pathway.
patients had significant responses to trastuzumab.\textsuperscript{11} Dual inhibition with trastuzumab and lapatinib has been reported in a case report of progressive mOC with several months of stable tumor burden.\textsuperscript{12}

Although there a few case reports of bevacizumab treatment of mOC, there are no studies to determine whether the activity of single-agent bevacizumab will be similar to the significant activity it demonstrates in sOC or, alternatively, the very modest single-agent activity seen in CRC.

### CLEAR CELL CARCINOMA OF THE OVARY

#### Epidemiology and Risk Factors for cOC

cOC is the second most common type of epithelial cancer arising in or near the ovary in North America. The collection of epithelial carcinomas arising in or near the ovary account for 90% to 95% of all malignant “ovarian tumors,” and approximately 5% of these are cOC.\textsuperscript{2} Asian patients in the United States have a higher proportion of cOC than seen white, black/African American, or other populations (11.4% vs. 4.8%, 3.1% and 5.5%, respectively).\textsuperscript{13} The prevalence of cOC is higher in Asia—more than 15% in Japan.\textsuperscript{14}

Patients with cOC present at an earlier age than patients with high-grade serous carcinomas, and can present with thrombocytopenic disease more commonly as well.\textsuperscript{14} In a Japanese group of women, 48.5% of patients with cOC presented with stage I disease compared with 16.6% of patients with sOC.

There are several risk factors for cOC. Women with cOC tend to be younger, have a higher body mass index, and have a history of endometriosis. Interestingly a history of smoking, a likely risk factor for mOC, may be slightly protective for cOC. On occasion, these tumors can be found arising in endometriomas, endometriotic cysts, or in extraperitoneal sites. Transcriptional profiling experiments of cOC demonstrates significant similarity to the RNA profile of normal endometrium, suggesting that these “ovarian” malignancies might actually represent malignancies from ectopic endometrium implanted in extraperitoneal sites via retrograde menstruation.\textsuperscript{15}

#### Origin and Biology of cOC

Recently, several groups have described that 50% of cOC and, in certain cases, sites of endometriosis have mutations in adenine-thymine rich interactive domain 1A (ARID1A), a tumor suppressor now thought to serve as an early mutational event in oncogenesis in these malignancies.\textsuperscript{16} ARID1A is responsible for directing the SWI/SNF multiprotein complex to target sites on promoters serving as an epigenetic modulator of transcriptions.\textsuperscript{17} ARID1A is part of the BAF250 protein complex, and cOC with mutations in ARID1A correlated with decreased BAF250a expression by immunohistochemistry. Presumably, ARID1A alterations influence the epigenetic regulation of genes directly associated with cOC oncogenesis. Interestingly, ARID1A is often lost in von Hippel Lindau (VHL)-mutated clear cell cancers of the kidney.

Additional genomic abnormalities have also been described.\textsuperscript{18} For example, 20% of patients may also have a deletion of PTEN, a tumor-suppressing gene from the PIK3CA pathway, or KRAS activation, which has also been shown to induce endometriosis associated with clear cell carcinomas. p53 mutations, ubiquitous in sOC, are not seen in cOC. In addition, the malignancy seems to have more genomic stability as compared with sOC.

### Treatment of cOC

Because of the increased incidence of cOC in Japan, much of the surgical data come from retrospective studies of performed from that region. Although no prospective randomized surgical studies exist, retrospective studies suggest that lymphadenectomy adds little in early-stage cOC and that surgical debulking surgery is important in the management of advanced disease. Specifically, a Japanese retrospective analysis from a multicenter study of 254 patients with complete surgical staging demonstrated that the results of surgical debulking were prognostic for improved progression-free survival (PFS), with median PFS of 39, 7, and 5 months when there was no residual tumor, less than 1 cm of residual tumor, or greater than 1 cm of residual tumor postsurgery, respectively.

Currently, treatment recommendations for patients with cOC are similar to those for patients with sOC: platinum-based therapy, and specifically carboplatin and paclitaxel. Response rates to carboplatin and paclitaxel therapy range from 22% to 56% in trials, compared with 70% in high-grade serous carcinoma.\textsuperscript{19} However, because of its low representation in the trials, the influence of platinum-based therapy on survival is not fully known. In a meta-analysis of 8,000 women from seven international trials of platinum-based front-line therapy, only 2.5% of women had stage III/IV cOC.

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**TABLE 1. Comparison of Mucinous Tumors Arising in the Colon versus the Ovary**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Colon</th>
<th>Ovary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presentation</strong></td>
<td>Ascites, adnexal masses, vaginal bleeding</td>
<td>Ascites, adnexal masses, vaginal bleeding</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>Bilateral, &lt; 10 cm</td>
<td>Unilateral, &gt;10 cm</td>
</tr>
<tr>
<td><strong>Immunohistochemistry</strong></td>
<td>CK 20, CEA</td>
<td>CK 7, CK 20, CEA</td>
</tr>
<tr>
<td><strong>p53 mutation</strong></td>
<td>70%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Nodular growth pattern with an infiltrative pattern</td>
<td>Papillary pattern, expansile pattern of invasion</td>
</tr>
</tbody>
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Abbreviation: CEA, carcinoembryonic antigen.
and their risk of death was increased (hazard ratio = 2.18). Overall survival was 21.3 months compared with 40.8 months for patients with sOC. The Japanese GOG has conducted a trial comparing irinotecan and cisplatin versus carboplatin and paclitaxel in 99 patients with cOC as initial therapy, with no significant difference in PFS.

The future treatment of cOC will likely involve targeted therapies. Unfortunately, the ARID1A tumor-suppressor gene is not druggable or easily replaced with current technologies. However, several pathways have been shown to be overexpressed or activated in cOC. The IL6-STAT3-HIF pathway was found to be activated in cOC. Hypoxia-inducible factor (HIF) is an important transcription factor involved in angiogenesis and controls vascular endothelial growth factor (VEGF)-A expression. Staining of HIF1A and VEGF was higher in cOC than in sOC (p = 0.0001). A variety of VEGF inhibitors have been explored in this setting. Sunitinib, a tyrosine kinase inhibitor of VEGF, platelet-derived growth factor receptor (PDGFR), and KIT was shown to decrease tumor burden in two patients in one study. In addition, a particularly durable partial response was reported in a patient with cOC treated with the antiangiogenic agent methoxyestradiol. Although the PI-3k/AKT/mTOR pathway is known to be activated in cOC, there still is no evidence that targeting this pathway is efficacious with currently available agents. Trials incorporating temsirolimus, a mammalian target of rapamycin (mTOR) inhibitor, was inactive as a single agent and was too toxic in combination with bevacizumab/liposomal doxorubicin and topotecan. Direct inhibitors of phosphoinositide 3-kinase (PI-3k) are in development and worthy of exploration.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

References


