The Life and Times of Low-Grade Serous Carcinoma of the Ovary

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OVERVIEW

For the past several years, all women with epithelial ovarian cancer have been treated identically, whether in a clinical trial or off protocol. Over the past decade, we have come to appreciate the magnitude of the heterogeneity of ovarian cancer. The development of the binary grading system for serous carcinoma was a major advance, leading to separate clinical trials for patients with this subtype, originating from the Gynecologic Oncology Group’s Rare Tumor Committee. The mitogen-activated protein kinase (MAPK) pathway appears to play a prominent role in the pathogenesis of this subtype. Approximately 20% to 40% of low-grade serous carcinomas have a KRAS mutation, while BRAF mutations are rare—approximately 5%. In genomic profiling studies, these tumors appear to cluster with serous tumors of low malignant potential. Compared with high-grade serous carcinomas, low-grade serous carcinomas are also characterized by a low frequency of p53 mutations, greater expression of ER and PR, and greater expression of PAX2 and IGF-1. Primary treatment of low-grade serous carcinoma includes surgery plus platinum-based chemotherapy (either adjuvant or neoadjuvant). Clinical behavior is characterized by young age at diagnosis, relative chemoresistance, and prolonged overall survival. Current options for treatment of relapsed disease include secondary cytoreduction in selected patients, salvage chemotherapy, or hormone therapy. A recently completed trial of a MEK inhibitor for women with recurrent disease demonstrated promising activity. Future directions will include further investigations of the molecular biology and biomarker-driven clinical trials with targeted agent monotherapy and combinations.

O ver the past decade, it has become increasingly clear that ovarian cancer is not one but several distinct entities. Even today, the vast majority of ovarian cancer clinical trials include women with all histologic subtypes. Such is true in both the front-line and the recurrent settings. However, advances in our understanding of the heterogeneity of ovarian cancer have emerged on the basis of refinement of pathologic diagnostic criteria, molecular biology and genetic investigations, and reports of hypothesis-generating clinical studies.

Specifically, for low-grade serous carcinoma of the ovary, the confluence of two major factors—reports of the binary grading system for serous carcinoma1,2 and the establishment of the Gynecologic Oncology Group’s Rare Tumor Committee in 2005—has led to a widespread recognition of this histologic subtype and to the dawn of separate clinical trials for women diagnosed with this rare entity. The principle of separate clinical trials for major rare histologic subtypes of ovarian cancer—clear cell carcinoma, mucinous carcinoma, and low-grade serous carcinoma—was subsequently validated in two consensus conferences.3,4

Based on initial studies, it is estimated that approximately 10% of serous carcinomas are low-grade. Most are metastatic at diagnosis. Low-grade serous carcinoma may arise de novo or as a recurrence after a diagnosis of a serous tumor of low malignant potential with peritoneal implants.5–8 Of the serous tumors of low-malignant potential that recur, approximately 75% to 80% do so as a low-grade serous carcinoma.5,8 In addition, serous tumor of low malignant potential is found coexisting in approximately 60% of newly diagnosed low-grade serous carcinomas.1 Furthermore, comparison of newly diagnosed low-grade serous carcinoma and serous tumors of low malignant potential has indicated that the age at diagnosis, the overall survival time, and the progression-free survival (PFS) time of stages II–IV low-grade serous carcinoma of the ovary are similar to those of serous ovarian tumors of low malignant potential that recur as low-grade serous carcinoma (measured from the diagnosis of relapse).9 Thus, these two tumor types—serous tumor of low malignant potential and low-grade serous carcinoma—appear to exist on a continuum.

This article will discuss the unique features of low-grade serous carcinoma of the ovary in terms of its histologic characteristics, molecular biology, and clinical behavior.

PATHOLOGY OF LOW-GRADE SEROUS CARCINOMA OF THE OVARY

Although several studies have shown that histologic grade is an important prognostic factor in serous carcinoma of the
Although the authors observed a KRAS mutation frequency of 19% in the low-grade serous carcinomas, only one specimen (2%) harbored a BRAF mutation. In addition, they concluded that the low frequency of BRAF mutations in advanced stage low-grade serous carcinomas, which contrasted with previous reports, suggested that low-grade serous carcinomas are more likely derived from serous tumors of low malignant potential without BRAF mutation and that
advanced stage low-grade serous carcinoma patients with BRAF mutation have a better clinical outcome. A recent article, in which 56 serous tumors of low malignant potential and 19 low-grade serous carcinomas were analyzed, confirmed the MD Anderson findings. Although the BRAF mutation frequency was 45% in the serous tumors of low malignant potential, only a single case (5.3%) of low-grade serous carcinoma had a BRAF mutation. Furthermore, the findings suggested that the presence of BRAFV600E mutation is associated with early-stage disease and improved prognosis in serous tumors of low malignant potential and low-grade serous carcinomas. Interestingly, none of the 22 patients who received chemotherapy had BRAF mutant tumors.

Genomic profiling studies have also indicated that low-grade serous carcinomas segregate from high-grade serous carcinomas but are similar to serous tumors of low malignant potential. Bonome and colleagues found that the majority of low-grade serous carcinomas clustered with serous tumors of low malignant potential. They also noted that pathways present in high-grade tumors—cell-cycle progression, cellular proliferation, and chromosomal instability—were absent in both low-grade serous types.

Several other studies have characterized the molecular biology and genetics of low-grade serous carcinoma. Compared with high-grade serous carcinomas, low-grade tumors have a much lower frequency of p53 mutations or p53 expression, greater expression ER and PR, greater expression of PAX2, overexpression of anterior gradient homolog 3 (AGR3), and overexpression of IGF-1.

CLINICAL BEHAVIOR AND TREATMENT OF LOW-GRADE SEROUS CARCINOMA OF THE OVARY

Newly Diagnosed Low-Grade Serous Carcinoma

Primary surgery. There is no evidence to date that indicates that the primary surgical management of low-grade serous carcinoma is different from that of ovarian cancer in general. Options include primary surgery—comprehensive surgical staging for apparent early-stage disease or maximum cytoreductive surgery for advanced-stage disease—or interval debulking surgery following neoadjuvant chemotherapy for select patients with apparent unresectable disease or significant comorbidities.

Postoperative therapy. Evidence to date suggests that low-grade serous carcinoma is relatively resistant to first-line chemotherapy on the basis of the metrics that we have available. In a review of 112 patients with newly diagnosed stage II-IV low-grade serous carcinoma of the ovary treated with primary surgery and platinum-based chemotherapy, it appeared that treatment was not as successful as expected on the basis of the high frequency of persistent disease at completion of therapy and low negative second-look rate. Of note as well, the median age of patients was only 43 years, and the median overall survival was 82 months. This relative chemoinsensitivity was also observed in a review of women who received neoadjuvant chemotherapy for advanced stage low-grade serous carcinoma. In this report, despite the fact that half of evaluable patients had a greater than 50% reduction in serum CA 125 levels after neoadjuvant chemotherapy, only one patient had an objective response by imaging assessment. One of the questions raised by these observations is whether our standard parameters for evaluation of response—serial imaging and CA 125—are adequate to determine outcome. Currently, although there are legitimate concerns about the efficacy of chemotherapy as standard first-line therapy, a potentially better alternative is not immediately evident.

Recurrence Low-Grade Serous Carcinoma

Secondary surgery. Secondary cytoreductive surgery may be indicated for selective patients with recurrent low-grade serous carcinoma—either following an original diagnosis of serous tumor of low malignant potential or advanced-stage low-grade serous carcinoma. Of course, as with all subtypes of ovarian cancer, supporting evidence for this subtype is retrospective. Based on current information, optimal candidates include those with platinum-sensitive disease and a limited number of recurrent sites (in contradistinction to patients with carcinomatosis).

Crispens and colleagues reported 35 patients with recurrent low-grade serous carcinoma after a diagnosis of serous tumor of low malignant potential who underwent 48 procedures. Patients who had suboptimal residual tumor were more likely to die of disease than those with optimal residual tumor. Likewise, Bristow and colleagues observed significantly better survival in patients who had optimal secondary surgical resection compared with those who did not.

Chemotherapy. Similar to observations in the first-line setting, recurrent low-grade serous carcinoma appears to be relatively chemoresistant. Of 58 patients who received a total of 108 separate salvage chemotherapy regimens, the overall response rate was 3.7%. However, stable disease was observed in 60% of patient-regimens. In addition, the median progression-free survival was about 7 months. Whether the high stable disease rate is more related to tumor biology or therapy remains unclear.

Hormone therapy. Gershenson and colleagues reported their experience with 64 women with recurrent low-grade serous carcinoma who received 89 separate hormone therapy regimens. The overall response rate was 9%, and the stable disease rate was 61%. The median progression-free survival was 7.4 months. Moreover, patients whose tumors were ER+/PR+ had a longer median time to progression (8.9 months) than those with ER+/PR- tumors (6.2 months). However, this difference approached but did not reach statistical significance. Hormonal agents that have demonstrated some degree of activity include the aromatase inhibitors, tamoxifen, and leuprolide acetate.
TABLE 1. Studies of Systemic Treatment for Recurrent Low-Grade Serous Carcinoma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chemotherapy</th>
<th>Hormonal Therapy</th>
<th>Selumetinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>58</td>
<td>64</td>
<td>52</td>
</tr>
<tr>
<td>No. Regimens</td>
<td>108</td>
<td>89</td>
<td>52</td>
</tr>
<tr>
<td>CR (%)</td>
<td>1</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>PR (%)</td>
<td>2.8</td>
<td>2</td>
<td>13.5</td>
</tr>
<tr>
<td>SD (%)</td>
<td>60.2</td>
<td>62</td>
<td>65</td>
</tr>
<tr>
<td>% Median PFS</td>
<td>64</td>
<td>71</td>
<td>80.5</td>
</tr>
<tr>
<td>% PFS &gt;6 mos.</td>
<td>58</td>
<td>61</td>
<td>63</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; PFS, progression-free survival; PR, partial remission; SD, stable disease.

Targeted therapy. Based on the observations that low-grade serous carcinomas may be related to driver mutations in the MAPK pathway, agents that target this pathway are of great interest. In the initial study of this type, Farley and colleagues recently reported the results of a GOG phase II trial of selumetinib, a MEK 1/2 inhibitor, in 52 women with recurrent low-grade serous carcinoma. The response rate was 15%, and 65% of patients had stable disease. Median PFS was 11 months. Good quality formalin-fixed paraffin-embedded tissue was available in 34 patients and underwent mutational analysis. Two (6%) tumors had BRAF mutations, and 14 (41%) had KRAS mutations. However, there was no correlation between tumor response and mutational status. Table 1 compares the results of this GOG trial with historic information regarding treatment with chemotherapy or hormone therapy. Currently, an international randomized phase II/III study of another MEK inhibitor, trametinib, compared with standard therapy is under development for women with recurrent low-grade serous carcinoma. Embedded in this trial is a much more robust translational research component that will hopefully link outcome to mutational status. In addition, preclinical studies suggest that dual blockade of the MAPK and PI3K/AKT pathways may result in greater efficacy.

CONCLUSION

The study of low-grade serous carcinoma of the ovary has been greatly facilitated by development of a binary grading system. Consequently, a major advance over the past few years has been the initiation of separate clinical trials for this subtype. Chemotherapy has limited benefit against this tumor type but remains the standard for treatment of primary disease. In the recurrent setting, options include chemotherapy, hormone therapy, or targeted agents. Over the next several years, biomarker-driven clinical trials should increase our ability to achieve our goal of personalized cancer medicine.


