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Low-Grade Serous Ovarian Cancer: Current Treatment Paradigms and Future Directions

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Opinion statement

Low-grade serous ovarian cancer (LGSOC) is a rare subtype of ovarian cancer, accounting for approximately 10% of cases of serous ovarian cancer. Patients typically present at a younger age have a protracted clinical course with survival for those with recurrent disease nearing 10 years, and have a high prevalence of somatic (tumor-specific) mutations affecting the mitogen-activated protein kinase (MAPK) pathway. Initial treatment of patients with stage IC–IV disease is similar to that of high-grade serous ovarian cancer with surgery and platinum/taxane-based chemotherapy. Selected patients may benefit from hormonal maintenance therapy following chemotherapy, in particular those with evidence of residual disease at completion of therapy. In the recurrent setting, the highest response rates to chemotherapy have been noted in those patients receiving chemotherapy in combination with bevacizumab. While hormonal therapies may offer disease stabilization with relatively low toxicity, objective response rates remain low. The use of targeted therapies such as MEK inhibitors remains an active area of investigation and those patients with MAPK pathway alterations may derive the greatest benefit from these agents.

Introduction

The most common histologic subtype of epithelial ovarian cancer, serous ovarian cancer, is classified by a two-tiered grading system into high- and low-grade serous ovarian cancer [1••]. Low-grade serous ovarian cancer (LGSOC) is a rare cancer accounting for approximately 10% of serous ovarian cancer cases and is histologically, clinically, and molecularly distinct from high-grade serous ovarian cancer [2]. Women with LGSOC are typically diagnosed at a younger age (55.5 years vs 62.6 years for high-grade serous ovarian cancer), and their tumors are *TP53* wild-type, unlike high-grade serous ovarian cancers, the majority of which are characterized by the presence of *TP53* mutations [3, 4].

LGSOC can develop de novo or from a premalignant precursor lesion referred to as serous borderline disease. Borderline tumors are distinguished from LGSOC by the absence of destructive stromal invasion. Most borderline tumors are confined to the ovary at initial presentation and have an excellent prognosis; however, the risk of death from disease is substantially higher for those patients with extra-ovarian spread (stages II–IV) or invasive implants. In a study of 174 women treated between 1970 and 1982, the 15-year actuarial survival rate was 100% for the 148 stage I tumors, 77% for the 13 stage II tumors, and 64% for the 13 stage III tumors [5]. About 10–15% of patients with treated serous borderline disease will relapse over a 10-year follow-up, the majority with LGSOC [6]. In contrast, LGSOC generally recurs as LGSOC and does not progress to high-grade serous ovarian cancer.

Initial treatment

Surgery remains the mainstay for initial treatment of LGSOC. At time of initial presentation, all patients should be evaluated by a gynecologic oncologist for consideration of primary debulking surgery. For selected patients who are deemed inappropriate for primary debulking surgery, due to the extent of disease or comorbidities, neoadjuvant chemotherapy with a platinum/taxane-based doublet with interval cytoreductive surgery may be considered. However, it is important to note that LGSOC commonly has a calcific radiographic appearance and may take on a more calcified appearance without considerable radiographic shrinkage in response to chemotherapy, making it challenging at times to gauge response to systemic therapy [7]. Similar to high-grade serous ovarian cancer, LGSOC patients with residual disease at completion of initial treatment have an overall worse prognosis, underscoring the importance of appropriate surgical evaluation at time of initial presentation [8].

Following completion of staging surgery, the standard of care for patients with stage II–IV disease remains chemotherapy for six cycles with a platinum/taxane-based doublet. Retrospective studies have shown disappointing response rates to chemotherapy in LGSOC, although due to the calcific nature of this disease, treatment effect is not always measurable by traditional metrics for radiographic response [9, 10]. Chemotherapy is administered with or without bevacizumab, which is now FDA approved in combination with chemotherapy for initial treatment of patients with stage III or IV ovarian cancer following surgery [11, 12]. For those with stage IA or IB disease, observation following complete gross resection of disease is appropriate. Patients with stage IC disease are managed either with observation alone or with adjuvant platinum-based chemotherapy for three to six cycles.

Retrospective data has shown promising responses for the use of hormonal therapy as a maintenance treatment following completion of adjuvant

chemotherapy in patients with advanced LGSOC. Gershenson et al. examined 203 patients with stage II–IV LGSOC who received initial treatment for their disease between 1981 and 2013. All patients received adjuvant chemotherapy with 133 subsequently being followed with observation and 70 receiving post-chemotherapy hormonal maintenance therapy with an aromatase inhibitor, tamoxifen, leuprolide acetate, or depot medroxyprogesterone acetate. Median progression-free survival for patients who underwent observation was 26.4 months vs 64.9 months for those who received hormonal therapy ($p < 0.001$) [13••]. Based on these results, hormonal maintenance therapy may be considered an option for those patients with advanced disease who have completed initial adjuvant chemotherapy. It may also be used in place of chemotherapy in select patients with stage IC–IV disease; although given the lack of prospective data to support this management option, this approach should only be considered in carefully selected patients.

Molecular prognostic indicators

In contrast to high-grade serous ovarian cancer, LGSOC is characterized by activation of the mitogen-activated protein kinase (MAPK) pathway. Different studies have reported a range of prevalence of BRAF mutations in LGSOC, ranging from 0 to 33%, with an average of about 5% of tumors expressing the hotspot BRAF V600E mutation [14]. Presence of BRAF mutation has been shown to be associated with early-stage disease and improved prognosis in patients with LGSOC [15]. In addition to gene sequencing through next-generation sequencing platforms such as Foundation Medicine and MSK IMPACT, VE1 immunohistochemistry has been shown to be a reliable method for detection of BRAF V600E mutations [16].

Treatment of recurrent disease

Chemotherapy

Patients with recurrent LGSOC tend to have a protracted clinical course with median survival of 82–126 months [10, 17, 18]. For those patients with recurrent disease, evaluation by a gynecologic oncologist for consideration of secondary or tertiary debulking is critical; patients with LGSOC will often undergo multiple such debulking surgeries over their lifetime due to the indolent and more chemo-resistant nature of this disease. Chemotherapy with platinum-based regimens in those with platinum-sensitive disease, and non-platinum cytotoxic agents with or without bevacizumab in those with platinum-resistant disease, remains the standard backbone for management of recurrent LGSOC. Prospective data are lacking, but retrospective response rates to chemotherapy have been disappointing. Gershenson et al. reported a study of 59 patients with recurrent LGSOC who were treated with a total of 108 cytotoxic regimens, with a response rate of 3.7% with stable disease observed in 60% of patients [9].

Hormonal therapies

LGSOC is frequently estrogen and progesterone receptor positive, prompting the use of hormonal agents in the recurrent setting. In a study of 64 patients

who received 89 separate hormonal regimens, most commonly anastrozole, letrozole, or tamoxifen, the objective response rate was 9% with > 60% of women exhibiting stable disease and a median time to progression of 7.4 months [19]. In that study, estrogen and progesterone receptor expression data was available for 50 patients with all patients being estrogen receptor positive and 26/50 (52%) also being progesterone receptor positive.

Targeting the MAPK pathway

Somatic alterations affecting the MAPK pathway are found in up to 82% of patients with serous borderline disease or LGSOC [20]. KRAS and BRAF mutations are generally mutually exclusive within this disease with KRAS mutations present in up to 54% of cases and BRAF mutations in up to 48% of cases [16]. While BRAF mutations have been reported in 23–48% of serous borderline tumors, they are associated with a favorable prognosis and a decreased risk of progression to LGSOC, and are therefore found in only 0–6% of cases of LGSOC [21–23, 24••, 25••, 26].

The prevalence of MAPK pathway alterations within this disease has stimulated significant interest in the use of MEK inhibition for treatment of recurrent disease. GOG 0239 was a phase II study of the MEK inhibitor selumetinib in patients with recurrent LGSOC and measurable disease. GOG 0239 showed a promising response rate of 15.4%, prompting the opening of additional phase III studies exploring the use of MEK inhibition for treatment of patients with recurrent disease [27••], including the MILO study that compared the single-agent MEK inhibitor binimetinib to physicians' choice of chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan) (NCT01849874). The study closed in April 2016 after a planned interim analysis showed that the hazard ratio for progression-free survival crossed the predefined futility boundary. A separate phase II/III study of trametinib vs physicians' choice of chemotherapy or hormonal therapy (GOG 0281; NCT02101788) in patients with recurrent LGSOC has completed accrual but results have not yet been reported. Several patients with LGSOC and alterations affecting the MAPK pathway have experienced sustained responses (lasting > 5 years) to treatment with MEK inhibitors [20, 28, 29]. Such extreme responders, while outliers, do indicate that MAPK pathway alterations may drive tumor growth and proliferation in a subset of LGSOC and also confer sensitivity to pathway inhibitors in these patients.

Use of anti-angiogenic agents

Bevacizumab has shown promising response rates in the treatment of recurrent LGSOC. A study of 15 patients with recurrent serous borderline or LGSOC who were treated with bevacizumab at Memorial Sloan Kettering Cancer Center, either as a single agent or in combination with chemotherapy, showed an objective response rate (complete + partial responses by RECIST 1.1 criteria) of 40%. No objective responses were seen in those patients with serous borderline disease. For the 11 patients with LGSOC, the response rate was 55% [30]. Similarly, a study of 40 patients with LGSOC treated at MD Anderson Cancer Center with a total of 45 bevacizumab-containing patient regimens showed an objective response rate of 47.5%, with a median progression-free survival of 10.2 months [31].

Summary

Patients with LGSOC have a younger median age of diagnosis and protracted clinical course versus high-grade serous ovarian cancer. However, patients who develop recurrent disease suffer significant morbidity from their cancer and most eventually die from their disease.

The initial treatment of LGSOC is similar to that of other epithelial ovarian cancer subtypes, with treatment for most patients comprised of surgery and chemotherapy. Selected patients may receive hormonal therapy in place of or following chemotherapy.

In the recurrent setting, objective response rates to chemotherapy have been disappointing, but this in part may be to the calcific nature of LGSOC, namely the tendency for these tumors to calcify instead of shrink in response to therapy. High rates of disease stabilization have been seen with both hormonal therapies and chemotherapy, indicating that these agents may confer clinical benefit. Considerably higher response rates to chemotherapy have been noted when given in conjunction with bevacizumab. MEK inhibitors may be of greatest benefit to those patients with LGSOC who harbor molecular alterations affecting the MAPK pathway. While results of the GOG 0239 were promising, we await the results of GOG 0281 to see if MEK inhibitor displays greater efficacy than physicians' choice of chemotherapy or hormonal therapy.

Compliance With Ethical Standards

Conflict of Interest

Rachel N. Grisham has received compensation from Clovis Oncology for service as a consultant. Gopa Iyer declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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