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GYNECOLOGIC CANCERS (NS REED, SECTION EDITOR)

Low-grade Serous Tumors: Are We Making Progress?

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Abstract

Purpose of Review This review provides an overview of the current clinical standard in low-grade serous ovarian cancer (LGSOC). The available evidence for surgery and standard treatments is elaborated. In addition, we discuss recent findings and novel treatments for LGSOC.

Recent Findings Two large multicenter trials studying MEK inhibitors in LGSOC have been presented in the last year. Binimetinib demonstrated an activity in LGSOC, especially in *KRAS*-mutated disease. Trametinib was associated with an improved progression-free survival in relapsed LGSOC. Based on the current results, MEK inhibitors could be an alternative treatment for LGSOC.

Summary Surgery is an important step in the treatment of LGSOC. Hormonal therapy and bevacizumab can be beneficial, next to chemotherapy. Targeted treatments, such as the MEK-inhibitor trametinib, seem to be efficient and should be introduced into clinical practice.

Keywords Ovarian cancer · Low-grade serous - rare tumor · MEK inhibitor

Introduction

Ovarian cancer is the fifth most frequent malignant tumor in women, affecting 1 in 52 women [1, 2]. Up to 90% of ovarian cancers are from epithelial origin [3]. Epithelial ovarian cancers are classified into different subtypes based on histological markers and immunohistochemistry. The most common subtypes are as follows: high-grade serous (70%), low-grade serous (< 5%), high-grade endometrioid, low-grade endometrioid, clear cell, and mucinous carcinomas of the ovary [4]. In 2004, Malpica et al. introduced a two-tier classification system to differentiate between high-grade and low-grade serous ovarian carcinomas (LGSOC) [5]. Based on differences in nuclear atypia and the mitotic rate, LGSOC was identified as a separate entity with specific genetic mutations and clinical behavior [5]. This two-tier classification system was validated retrospectively by the GOG [6]. Between 5 and 8% of ovarian carcinomas are classified as LGSOC [4, 7]. Patients diagnosed with LGSOC are typically younger with a median age at diagnosis of 46.9 years, compared with 63 years for epithelial ovarian cancer in general [8]. In addition, prognosis of LGSOC is favorable, with an estimated 10-year overall survival of 37.3% (95% CI 29.0–45.7) in advanced LGSOC compared with only 15.0% (95% CI 13.9–16.1) for high-grade serous ovarian carcinoma [9].

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Diagnosis and Characteristics of LGSOC

Similar to other types of epithelial ovarian cancer, LGSOC can develop de novo and present with vague symptoms such as abdominal discomfort, bloating, dyspnea, dyspepsia, and changes in bowel movement pattern. Alternatively, LGSOC can arise as a malignant transformation of a borderline ovarian tumor [10]. Approximately one-third of patients with a presumed relapse of a borderline tumor turned out to have a

malignant transformation [11]. Since 2014, borderline tumors with invasive implants are considered peritoneal LGSOC [12, 13]. In a retrospective cohort, malignant transformation of a borderline tumor accounted for approximately 60% of LGSOC cases [14]. Adequate sampling is crucial in this respect to reduce the number of patients with occult LGSOC classified as a borderline tumor with non-invasive implants [15]. Computer tomography (CT) is commonly used in the staging of LGSOC. Calcified implants are easily recognizable CT features, which are present in 90% of LGSOC [16].

LGSOC is characterized using immunohistochemistry as WT1 positive (95%), p53 wild-type (90%), ER positive (57%), and PR positive (78%) [17]. LGSOC typically present activating mutations in the *RAS-RAF-MEK-ERK* pathway. *KRAS* mutations have been described in 24% of LGSOC patients, ranging from 15.8 to 54.4%, *BRAF* mutations were less frequent with 7.8% (0–32%) of cases, and *NRAS* mutations were present in 8.3% of LGSOC (3.6–22%) [18•]. Additionally, mutations in *PIK3CA*, *USP9X*, *EGFR*, *ESR1*, and *EIF1AX* and low-level copy number alterations have been described [19–21]. Van Nieuwenhuysen et al. described loss of 1p36.33 as the most frequent genomic alteration in LGSOC, reflecting a reduction in tumor suppressor activity [18•]. These mutations could identify a specific focus for targeted therapy.

Surgical Management

Surgery is an essential step in the treatment of LGSOC [22]. In presumed early-stage LGSOC surgical staging, including peritoneal biopsies, omentectomy and systematic lymphadenectomy should be performed [23]. Systematic lymphadenectomy should not be omitted in these patients as approximately 20% of T1–2 LGSOC present occult lymph node metastasis [24]. In young patients with FIGO IA or IC1 LGSOC, fertility-preserving surgery can be offered [25, 26]. Assisted reproductive techniques with controlled ovarian stimulation are contraindicated in LGSOC, due to frequent estrogen and progesterone sensitivity [26].

In advanced ovarian cancer, patients should be offered primary debulking surgery. Complete cytoreduction at primary surgery was feasible in 51–65% of patients with LGSOC in retrospective series [27, 28]. The aim of surgery should be no residual disease [29], as a macroscopic complete resection at primary debulking surgery led to a better median overall survival (97 vs 35 months, $p < 0.001$). However, cytoreduction to residual disease 1–10 mm led to a risk reduction as well (HR 0.514, 95% CI 0.258–1.022) [27]. Patients with a malignant transformation of a borderline tumor should be offered surgery. In a retrospective analysis, complete resection after malignant transformation of a serous borderline tumor was also linked to improved survival [30]. Similar to other histological subtypes of epithelial ovarian cancer, neoadjuvant chemotherapy can be an option in patients with contraindications for primary surgery. If preoperative poor performance status or evidence of unresectable disease is available, the diagnosis should be confirmed histologically and patients are treated with neoadjuvant chemotherapy and considered for interval debulking surgery [31].

The option of secondary surgery should be considered in patients with late relapse (treatment-free interval for platinum-based chemotherapy > 6 months) of LGSOC. Secondary cytoreductive surgery (SCS) in patients with low-grade tumors improved overall survival after first relapse (93.6 after complete resection vs 45.8 months in case of residual disease) if complete resection was achieved ($p = 0.04$) [32]. A recent retrospective analysis showed a complete resection rate at SCS of 38.1% in low-grade tumors, which was slightly lower than in high-grade tumors (48.3% complete resection) [33]. The lower complete resection rate might be explained by the infiltrative nature of the disease, desmoplastic reaction, and calcifications [32]. However, if SCS seems feasible in relapsed low-grade serous ovarian carcinoma, this option should be discussed with the patient. In patients with third, fourth, or fifth relapse, surgery can be considered on an individual basis. Retrospective series suggest that repeat surgery is feasible and possibly beneficial [34].

Chemotherapy

Adjuvant chemotherapy can be safely omitted in completely staged FIGO IA LGSOC. In completely staged patients with FIGO IB/C LGSOC, the indication for adjuvant chemotherapy should be discussed with the patients. Based on the available evidence from ICON/ACTION, adjuvant chemotherapy can improve survival. In general, adjuvant chemotherapy in early-stage ovarian cancer can improve 5-year overall survival from approximately 74 to 82% (HR 0.67, 95% CI 0.50–0.80, $p = 0.008$). Subanalysis of well-differentiated carcinomas was also in benefit of adjuvant chemotherapy [35]. From FIGO IIA upwards, adjuvant chemotherapy is recommended [23]. Patients with advanced LGSOC (FIGO III–IV) should be treated with combination chemotherapy: carboplatin-paclitaxel [36]. LGSOC is considered less sensitive to chemotherapy as high-grade serous tumors [37–39]. The objective response rate of LGSOC to carboplatin-paclitaxel in first-line setting is reported to be between 23 and 25% [27, 39]. In retrospective series on recurrent LGSOC, objective response rates of 4.9% for platinum-based chemotherapy and 2.1% for platinum-free regimens were reported. Regardless of the objective response rate, more than half of patients achieved stable disease and median time-to-progression was 34.7 and 26.4 weeks respectively [38]. Pegylated liposomal doxorubicin showed promising results with two patients reported to have obtained a complete remission in a retrospective series. In addition, nine patients had a stable disease for a median duration of 9 months [40].

Hormonal Treatment

Based on the known strong hormone receptor positivity and the results of retrospective trials, patients with LGSOC often receive anti-hormonal treatment [41]. Patients with LGSOC can be offered maintenance therapy in accordance with the retrospective series of Gershenson et al. who observed a significant lower risk of relapse in patients who received hormonal treatment (HR 0.44, 95% CI 0.31–0.64, $p < 0.001$). A trend towards a longer overall survival was longer in patients who were treated with hormonal maintenance therapy ($p = 0.056$) [42••]. Fader et al. investigated the possibility of a hormonal treatment with tamoxifen, letrozole, or anastrozole in patients who did not receive chemotherapy after debulking surgery. In this study, 22.2% have relapsed after a median follow-up of 41 months. The authors reported a 3-year progression-free survival (PFS) of 79.0%. Median PFS and OS were not reached at the time of publication [43]. In recurrent LGSOC, a retrospective analysis on hormonal treatment (letrozole, anastrozole, tamoxifen, leuprolide, etc.) showed an objective response rate of 9%. In this population, 61.8% of patients achieved stable disease [44]. Paragon was a prospective randomized phase II trial to study the role of anastrozole as a hormonal treatment in hormone receptor–positive (ER and/or PR) recurrent or metastatic LGSOC. An objective response rate of 14% was achieved after 6 months. At this time point, the clinical benefit rate was 61% [45]. These results confirm the activity of aromatase inhibition in relapsed LGSOC.

Anti-angiogenic Treatment

The synergistic effect of bevacizumab in combination with chemotherapy does not seem to be restricted to high-grade tumors. There are no appropriately designed/powered trials to evaluate the use of bevacizumab in first-line setting. In accordance with the current guidelines, LGSOC are treated in parallel to other epithelial ovarian cancer subtypes. The indication for anti-angiogenic treatment is identical [23]. In ICON7, 80 patients with advanced LGSOC were included; the results favored the addition of bevacizumab (HR 0.78, 95% CI 0.31–1.97, $p = 0.07$) [46]. In relapsed LGSOC, the combination of standard chemotherapy and bevacizumab is a possibly beneficial combination with 5 out of 13 patients achieving a partial remission in a trial by Schmeler et al. [47]. These findings were confirmed in a larger series in which the addition of bevacizumab led to an objective response rate of 47.5% [48]. Case reports have even suggested the activity of bevacizumab as a monotherapy in LGSOC [49, 50].

Targeted Treatment

Oncogenic mutations, such as those in the *RAS-RAF-MEK-ERK* pathway, can be suitable targets for therapy. Several case reports have demonstrated a potential role for MEK inhibitors in LGSOC [51, 52]. A phase II trial on selumetinib in LGSOC showed stable disease in 65% of patients with an objective response rate of 15% [53]. In addition, a phase Ib study with binimetinib in combination with paclitaxel weekly demonstrated an overall response rate of 14% [54]. The phase III trial on binimetinib (MILO/ENGOT-ov11) showed an objective response rate of 24% with a median PFS of 11.2 months. In this study, patients with a mutation in the *RAS-RAF-MEK-ERK* pathway had a higher response rate and a longer PFS (17.7 months) [55]. Recently, a randomized phase II/III trial was presented at ESMO 2019 meeting, studying the efficacy of trametinib, a MEK inhibitor, in comparison with standard of care (letrozole, pegliposomal doxorubicin, weekly paclitaxel, tamoxifen, or topotecan) in patients with recurrent LGSOC. In this study, patients treated with trametinib had a median progression-free survival of 13.0 months in comparison with 7.2 months in the control arm (HR 0.48, 95% CI 0.36–0.64, $p < 0.0001$) [56••]. An association between *KRAS* mutations and response to MEK inhibitor treatment has been observed; in addition, *EGFR* activity might lead to resistance to MEK inhibitors. Patients with known *KRAS* mutations would be good candidates for MEK inhibitor treatment, while patients with a *EGFR* mutation might not benefit from this therapy approach [57].

Conclusion

LGSOC is a relatively rare subtype of ovarian cancer, which is only partially sensitive to standard chemotherapy. Surgery plays an important role in the treatment of LGSOC, but systemic treatments are becoming increasingly important. Through extensive studies on the biology of LGSOC novel targets are discovered. The results of trametinib in recurrent LGSOC are very encouraging. We hope that in the future, studies will define novel treatment strategies for LGSOC.

Compliance with Ethical Standards

Conflict of Interest Nina Pauly declares that she has no conflict of interest.

Sarah Ehmann has received non-financial research support from Tesaro.

Enzo Ricciardi declares that he has no conflict of interest.

Beyhan Ataseven has received non-financial research support from Roche, Tesaro, and PharmaMar, and has received compensation from Roche, Amgen, AstraZeneca, Tesaro, Clovis Oncology, and Celgene for service as a consultant.

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- • Of importance
- •• Of major importance

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