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Review

Ovarian low-grade serous carcinoma: A comprehensive update ☆,☆☆

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ABSTRACT

Ovarian low-grade serous ovarian carcinoma (OvLGSCa) comprises a minority within the heterogeneous group of ovarian carcinomas. Despite biological differences with their high-grade serous counterparts, current treatment guidelines do not distinguish between these two entities. OvLGSCas are characterized by an indolent clinical course. They usually develop from serous tumors of low malignant potential, although they can also arise *de novo*. When compared with patients with ovarian high grade serous carcinoma (OvHGSCa) patients with OvLGSCa are younger and have better survival outcomes. Current clinical and treatment data available for OvLGSCa come from retrospective studies, suggesting that optimal cytoreductive surgery remains the cornerstone in treatment, whereas chemotherapy has a limited role. Molecular studies have revealed the preponderance of the RAS–RAF–MAPK signaling pathway in the pathogenesis of OvLGSCa, thereby representing an attractive therapeutic target for patients affected by this disease. Improved clinical trial designs and international collaboration are required to optimally address the unmet medical treatment needs of patients affected by this disease.

Contents

Introduction

Ovarian cancer is the leading cause of death from gynecological cancer in the western world [1]. It comprises though a heterogeneous group of tumors with distinctly different histological characteristics, molecular features, and clinical behavior [2–5]. Among the epithelial ovarian cancers the most common subtype is serous carcinoma [6,7]. Histologic grade has been recognized as an important prognostic factor [8–10]. To that end, ovarian serous ovarian carcinoma

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(OvSCa) has been traditionally graded according to three major 3-tier grading systems:1) the FIGO (the International Federation of Gynecology and Obstetrics) system, which assesses the architectural features of the tumor [11]; 2) the World Health Organization (WHO) system, which is based on both architectural and cytologic features [12]; and 3) the Shimizu/Silverberg system, which analyzes three parameters: glandular architecture, degree of nuclear atypia, and mitotic index [13]. In 2004, Malpica et al. described a novel 2-tier system for grading OvSCa as either high-grade (usually former grades 2 and 3) or low-grade (usually former grade 1 tumors), based primarily on the degree of nuclear atypia, and using the mitotic rate as a secondary feature (Fig. 1) [14]. This 2-tier grading system was further validated allowing its universal use [15,16], with the subsequent benefits for standardizing the design and interpretation of clinical trials. In addition, this 2-tier grading system has allowed the meaningful segregation of cases of OvSCas as it has been found that the differences between the low and high grade cases are not limited to the pathology but also detected at the pathogenic and molecular levels, as well as in the epidemiologic and clinical features [17,18].

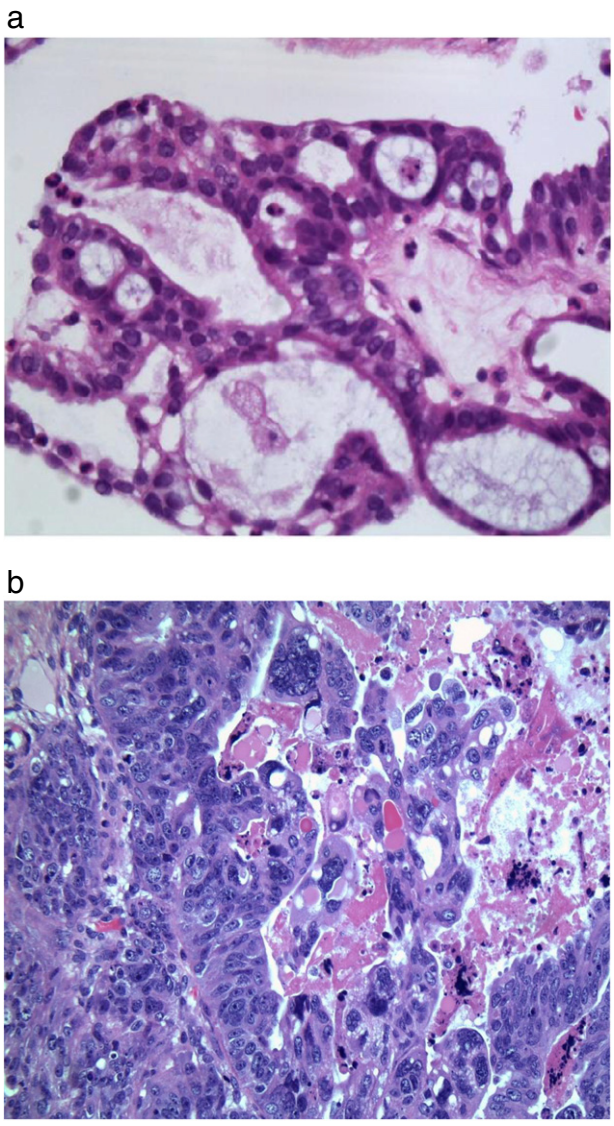

Fig. 1. Histopathology of serous ovarian cancer according to the two-tier grading system. a) Low-grade serous ovarian carcinoma: uniform nuclei and infrequent mitotic figures, in keeping with low nuclear atypia of well-differentiated tumors. b) High-grade serous ovarian carcinoma: nuclear pleomorphism and frequent mitotic figures. Nuclear atypia is characteristic of high-grade tumors.
Courtesy of Dr. Blaise A. Clarke, University of Toronto.

Despite the aforementioned differences, current treatment guidelines for ovarian carcinoma do not clearly distinguish between OvLGSCa and OvHGSCa thereby making uniform treatment recommendations for advanced disease (stages II–IV) [19,20]. Patients with OvLGSCa, usually have an indolent clinical course; however, they experience multiple recurrences and may ultimately die from disease [17]. The treatment of advanced-stage disease is a difficult and challenging situation for the clinician, whereby effective and high-quality evidence-based treatment options for this specific patient population are lacking. It is therefore relevant to improve our understanding of the singularities of OvLGSCa in order to offer better therapeutic options to these patients.

This review will provide an update regarding the distinctive epidemiologic, clinical, histological, and molecular features of OvLGSCa. It will also evaluate the current treatment options, focusing on advanced-stage disease, and the role of new targeted agents in OvLGSCa. We will also discuss methods in clinical study design that can potentially overcome the limitations of prior studies on this type of cases.

Clinical epidemiology

Data from representative population-based cancer registries (e.g. National Cancer Institute's Surveillance Epidemiology and End Results [SEER]) suggests that OvLGSCa represents a minority within the group of invasive serous tumors [21]. Plaxe et al. reported on a descriptive epidemiologic study that the median age at diagnosis for patients with OvLGSCa is 56 years, as opposed to 63 years for patients with OvHGSCa. The difference between these two groups was statistically significant (mean 7.2 years, confidence interval [CI] 6.0–8.2, $p = 0.0001$). Moreover, in the OvLGSCa population there was no significant difference between the age at diagnosis for patients with early or advanced-stage disease, whereas this difference did reach statistical significance for the OvHGSCa group (patients with advanced disease were an average of 2.5 years older than those diagnosed at early stage, CI 1.7–3–3, $p = 0.0001$). Over the period from 1992 to 2003, the annual incidence rate of OvLGSCa decreased by an average of 3.8% each year (CI −0.8% to −6.6%, $p = 0.02$), whereas this rate increased an average of 1.4% each year (CI 0.3–1.6%, $p = 0.02$) for OvHGSCa. No significant differences in the incidence of low-grade and high-grade tumors were seen among ethnicities. In this study, mean overall survival (OS) for OvLGSCa was significantly higher than that for OvHGSCa (99 versus 57 months, log-rank test $p = 0.001$). It is also worth noting that OvLGSCas were more likely to be confined to the ovary at the time of diagnosis. The rate ratio of advanced to early disease was 1.9 for OvLGSCa, whereas it was 10.2 for OvHGSCa. A major limitation of this study lies on its lack of central pathology review. Moreover, tumors were graded on a scale of 1 to 4, where grade 1 tumors were considered “well differentiated”, whereas grades 2, 3 and 4 were grouped as high-grade tumors. More recently, it has been suggested that the incidence of OvLGSCa might be slightly lower (3.4%) than previously reported. In their large retrospective series, Kobel et al. reported on the histopathology of a rigorously annotated database registry of ovarian cancer cases [22]. Major strengths of this study were, on the one hand, that all cases were centrally reviewed by experienced gynecological pathologists; on the other hand, the differentiation between low-grade and high-grade tumors of serous subtype applied the revised two-tier diagnostic criteria.

Population studies have also shown that different patterns of cancer incidence rate can unmask qualitative age interactions relevant to the pathogenesis or the outcome of a given tumor [23,24]. Grimley et al. analyzed the age-adjusted and age-specific incidence rate patterns of OvSCas using a comprehensive dataset from the SEER program [25]. The age-adjusted incidence rate ratio of high to low-grade

($IRR^{H/L}$) tumors was <1.0 before the age of 40, and >1.0 thereafter. Importantly, the distinction between age-specific rates for low-grade and high-grade tumors was irrespective of stage, supporting the hypothesis of morphologic grade as an age-specific effect modifier.

Histopathology

An accurate pathologic assessment of the tumor specimen is crucial for an optimal management of patients with OvLGSCa. The 2-tier grading system for OvSCa has demonstrated to have good inter-observer and intra-observer reproducibility [14,16], supporting its implementation in the routine practice. OvLGSCas have some key histopathologic features that make them distinctive from their high-grade counterparts.

The invasive component of OvLGSCa can display small papillae, micropapillae, macropapillae, small nests and less commonly large nests of cells that infiltrate the stroma, usually surrounded by a clear space or cleft. The micropapillae are elongated structures supported by a very thin (sometimes absent) fibrovascular core. However, the small papillae are round or oval, and might or might not contain a fibrovascular core. The macropapillary form of invasion may be misleading and prompt the erroneous diagnosis of serous adenofibroma. In contrast to the micropapillae commonly observed in conventional OvLGSCa, the macropapillae contain a fibrous stromal core which is lined by a minimal amount of serous epithelium [26]. Psammoma bodies are common in OvLGSCa and may be numerous, whereas necrosis or multinucleated tumor giant cells are not commonly seen. The nuclei of the tumor cells mildly vary in size and shape. It is generally accepted that OvSCas with cells showing more than 3:1 variation in nuclear size and shape are classified as high-grade tumors [14]. In addition, OvLGSCas have a low mitotic activity (below 12 mitoses per 10 high power fields).

Immunohistochemical features can aid in distinguishing low-grade and high-grade serous carcinomas, but a certain degree of overlap also occurs. The Ki-67 proliferation index, not unexpectedly, tends to be higher in OvHGSCa compared with OvLGSCa [27]. Differences in the extent of immunohistochemical expression of p53 between low-grade and high-grade tumors can also be useful in the differential diagnosis. O'Neill et al. reported that p53 intense staining was observed in 18% of OvLGSCa, as opposed to 64% in OvHGSCa [27]. In contrast, weak staining was seen in 64% and 28% of low-grade and high-grade lesions, respectively. Overexpression of p16 is now frequently used as a surrogate marker of high-risk human papillomavirus associated lesions [28]. Its role in ovarian cancer has not been investigated that extensively. However, two studies reported that p16 expression was more frequently observed in high-grade lesions than in low-grade tumors, making this marker also of potential diagnostic utility [29,30].

There is a common association between OvLGSCa and different non-invasive tumors such as serous adenofibroma, and serous tumors of low malignant potential with or without a micropapillary/cribiform pattern. This association is exceedingly rare in cases of OvHGSCa [14]. It has been then hypothesized that OvLGSCa develops from the aforementioned non-invasive components. Molecular studies (discussed below) and clinical observations have further confirmed this association [31,32], suggesting that ovarian serous tumors of low malignant potential tumors and OvLGSCa likely share common tumorigenic pathways.

Molecular pathology

The kinase cascade involving RAS, RAF, mitogen/extracellular signal-regulated kinase (MEK), extracellular signal regulated kinase (ERK), and mitogen-activated protein kinase (MAPK) is one of the major biologic pathways frequently altered in human cancer [33,34]. Mutations of either *BRAF* or *KRAS* lead to constitutive activation of MAPK, which subsequently activates downstream a variety of cellular and nuclear targets (Fig. 2) [35]. Singer et al. reported on the role of *BRAF* and *KRAS* mutations in ovarian carcinoma [36]. They found mutations in *BRAF* (codon 599) in 33% of OvLGSCa samples, whereas *KRAS* mutations (codons 12 and 13) were found in 35% of the cases. Consistent with what has been observed in melanoma and colorectal cancer [33], none of the OvLGSCa specimens analyzed had a mutation in both *BRAF* and *KRAS*. These mutations were seen in similar proportion (28% for *KRAS*, 33% for *BRAF*) in a subset of serous tumors of low malignant potential. In contrast, none of the OvHGSCa samples had *BRAF* or *KRAS* mutations. A recent study by Wong et al. has found that *BRAF* or *KRAS* mutations do not seem to be that frequent in advanced-stage OvLGSCa [37]. Samples from 43 patients with OvLGSCa (39 cases FIGO stage III) were analyzed and *KRAS* mutations were detected in eight samples (19%), whereas *BRAF* mutation was only detected in one sample (2%). Consistent with the study by Singer et al., no *BRAF* or *KRAS* mutations were detected in any of the OvHGSCa. Since the activation of MAPK is regulated by upstream kinases including KRAS and BRAF, it has been hypothesized that the activation of MAPK in ovarian cancer specimens would be associated with tumor grade and with the mutational status of either *KRAS* or *BRAF*. Actually, low-grade serous tumors, including serous neoplasms of low malignant potential and OvLGSCa exhibit a higher frequency of active (phosphorylated) MAPK than OvHGSCa [38].

The mutational status of the p53 gene, *TP53*, as well as its protein expression pattern has been thoroughly studied in ovarian carcinoma over the past decade [39]. Based on the three-tier grading system, overall estimates of *TP53* mutation prevalence are 28% for grade 1 serous carcinomas and 52% and 51% for grade 2 and grade 3 carcinomas, respectively [39]. Singer et al., using the 2-tier grading system and stringent criteria in the molecular genetic analysis (using direct nucleotide sequencing), demonstrated functional *TP53* mutations in 51% of OvHGSCa and 8% in OvLGSCa [40]. Serous neoplasms of low malignant potential showed a similar frequency of *TP53* mutations as those observed in the OvLGSCa group. There was no significant correlation between *TP53* mutational status and p53 overexpression in the samples analyzed. Recent data from a large prospectively annotated cohort of OvHGSCa confirm that *TP53* mutations are almost ubiquitous (96%) in the pathogenesis of high-grade tumors [41].

Gene expression can further help delineate the distinct molecular features of malignant tumors. In that regard, Bonome et al. examined a series of microdissected serous tumors of low malignant potential, OvLGSCa and OvHGSCa [5]. Their results demonstrated a collective clustering of the majority of the serous neoplasms of low malignant potential with OvLGSCa, separate from the OvHGSCa. These data gave further support to the concept of a continuum of tumor progression between tumors of low-malignant potential and OvLGSCa. More recently, May et al. have reported on the differences in gene profiling among low-malignant potential tumors and OvLGSCa, identifying a subset of genes potentially involved in OvLGSCa carcinogenesis. Four differentially expressed gene products (TANK, PARP1, CDK2, and PEA15) may act co-ordinately and modulate the ERK–MAPK pathway, thereby affecting cell proliferation and apoptosis [42].

There is also evidence suggesting that the insulin-like growth factor (IGF)–insulin pathway may play an important role in ovarian carcinogenesis [43]. Gene expression profiling has shown an association between individual genes in the IGF pathway and outcome in OvHGSCa [44]. In OvLGSCa samples, *IGF-1* is also frequently overexpressed. Cell proliferation assays demonstrated that low-grade cell lines are more sensitive to IGF-1R inhibition than high-grade cell lines [45]. Collectively, these data suggest that interfering with the IGF pathway may represent an attractive therapeutic approach in OvLGSCa.

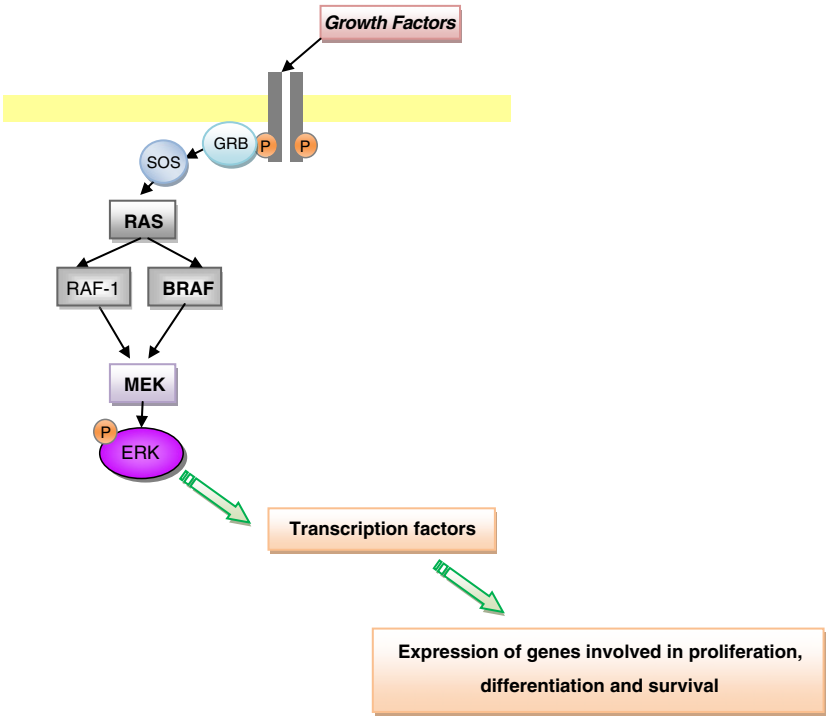

Fig. 2. Schematic representation of the RAF–RAS–MEK pathway. The binding of different extracellular growth factors (e.g. epidermal growth factor) to their cognate transmembrane tyrosine-kinase receptors stimulate autophosphorylation of tyrosine residues. This subsequently stimulates a downstream cascade of events mediated by signaling molecules such as GBR and SOS. Through the interaction with the GBR–SOS complex RAS undergoes a conformational change, which subsequently enables it to bind to RAF-1 and recruit it from the cytosol to the cell membrane, where RAF-1 activation takes place. Activated RAF-1 phosphorylates and activates MEK (MAPK–ERK kinase), which in turn phosphorylates and activates extracellular-signal-regulated kinase (ERK). Ultimately, ERK can enter the nucleus to control gene expression of key genes involved in cell proliferation by phosphorylating transcription factors. Activating mutations in *BRAF* can lead to constitutive activation of MAPK–ERK. GRB, growth-factor-receptor-binding protein; SOS, "son of sevenless". Courtesy of Dr. Irene Brana, University of Toronto.

Clinical features and therapeutic management

Available data regarding the clinical course of OvLGSCa come from single-institutions' retrospective studies. Gershenson et al. reported on the clinical outcome of a cohort (n = 112) of advanced-stage (FIGO stages II to IV) OvLGSCa patients [46]. Median age at diagnosis was 43 years, and most patients (90%) had stage III disease. All patients underwent primary cytoreductive surgery. Optimal debulking was defined as a surgical procedure that left ≤2 cm of residual disease, and was achieved in 82% of patients for whom postoperative information was available. Only 50% of patients had either cisplatin or carboplatin combined with paclitaxel as the primary chemotherapy regimen. At the completion of chemotherapy, 48% of patients had persistent disease. The median PFS for the entire cohort was 19.5 months, and the median OS time was 81.8 months. Multivariate analysis adjusted for clinical variables such as residual disease (none versus any), taxane-based chemotherapy (non-taxane versus taxane-based regimen), and age (younger than 45 years versus older than 45), showed that persistent disease after primary chemotherapy was the most important factor associated with shorter PFS (HR 2.6, CI 1.6–4.2, p = 0.01).

In order to assess whether OvLGSCa is as responsive to primary chemotherapy as OvHGSCa, Schmeler et al. retrospectively reviewed the response rate of a series of 25 patients with OvLGSCa treated with platinum-based neoadjuvant chemotherapy (72% were treated with a platinum drug and a taxane) [47]. Response was evaluated by WHO criteria. Patients received a median of six cycles of therapy. Most patients (88%) had stable disease (SD) as their best response. One patient (4%) had a complete response (CR). No partial responses were seen, and in two patients (8%) their disease progressed. Nineteen patients (76%) had interval debulking surgery, which was optimal (defined as ≤2 cm of residual disease), in 63% of cases. In this study, the median PFS and OS times were 21 and 56 months, respectively.

To the best of our knowledge, only three single-institution studies have reported on the management and clinical outcome of recurrent OvLGSCa. Bristow et al. reported on the role of secondary cytoreductive surgery in a hospital-based series of 26 patients with recurrent OvLGSCa [48]. Most patients (n = 24, 92%) with recurrent disease had FIGO stages III and IV at diagnosis, and the majority of them (n = 21, 86%) had received adjuvant platinum-based chemotherapy after primary surgery. Twenty-one patients with recurrent OvLGSCa underwent surgical exploration for the purpose of cytoreduction, whereas 5 patients were treated with salvage chemotherapy alone upon the diagnosis of relapse. Of the 21 patients undergoing secondary cytoreductive surgery, 15 (71%) had optimal debulking (≤1 cm residual disease). Age ≥ 46 years was the only independent predictive factor for an optimal secondary surgical outcome (OR 0.06, CI 0.01–0.7, p = 0.02). The median OS post-recurrence was 56 months, and optimal secondary debulking was the strongest predictor of survival after recurrence (HR 0.06, CI 0.01–0.5, p = 0.01). Only 12 patients that received chemotherapy had measurable disease. Of those, two patients had a CR, and one patient had a PR, for an overall response rate of 25% (3 of 12 patients). Six patients (50%) experienced disease progression. Gershenson et al. reported on a retrospective study (n = 58) of recurrent OvLGSCa (of whom 10 patients had measurable disease) an overall response rate of 3.7% [49], evaluated by modified Response Evaluation Criteria in Solid Tumors (RECIST) [50]. There were no significant differences in response between platinum-sensitive and platinum-resistant patients. Patients were treated with a wide variety of regimens, of which 64% were platinum-based. More recently, the M.D. Anderson group reported on their retrospective series (n = 64) with different hormonal treatments (mostly aromatase inhibitors and tamoxifen) in recurrent OvLGSCa [51].

The overall RR was 9% (6 complete responses and 2 partial responses). Most patients with an objective response had platinum-sensitive disease. Patients' median time to progression (TTP) was 7.4 months. Fifty patients for which tissue was available were assessed for estrogen receptor (ER) and progesterone receptor (PR) expression status. Interestingly, ER+/PR− disease was associated with shorter TTP (HR 1.96, 95% CI, 1.1–3.6, p = 0.03).

Targeted therapies

A better understanding of the molecular pathogenesis of OvLGSCa would lead to rational evaluation of new targeted agents for the treatment of this disease. Initial reports pointed towards a high frequency of *KRAS* and *BRAF* mutations in OvLGSCa [36,52], making this pathway an attractive therapeutic target by interfering with its downstream effectors (i.e. MEK–MAPK) [38,53,54]. To that end, the preliminary results of a phase II clinical trial evaluating AZD6244 (selumetenib), a MEK-1/2 inhibitor, in patients with recurrent OvLGSCa (n = 53) have been reported [55]. A majority of patients (58%) had received at least three prior cytotoxic regimens. Overall response rate to AZD6244 therapy was 15% and 34 patients (65%) had SD. The median PFS was 11 months. Only 6% of patients for whom sufficient tumor material was available had mutations in *BRAF*, whereas 41% and 15% of patients had mutations in *KRAS* and *NRAS*, respectively. No correlation between response and the mutational status was observed.

Angiogenesis has shown to play a central role in the pathogenesis and clinical behavior of ovarian carcinoma. In this regard, the monoclonal antibody directed against the vascular endothelial growth factor (VEGF) bevacizumab has demonstrated significant activity in recurrent ovarian cancer [56–58], and it has also been evaluated in the first-line setting (GOG218 and ICON7) [59,60]. Bidus et al. reported on two heavily pre-treated patients with recurrent OvLGSCa who achieved sustained complete responses with bevacizumab [61]. It is then conceivable that antiangiogenic agents may also have activity against well-differentiated ovarian neoplasms, such as OvLGSCa, and should be further investigated, with focus on recurrent disease.

The IGF pathway has recently emerged as another potential therapeutic target for ovarian cancer, including OvLGSCa [45,62,63]. There are currently three active clinical trials investigating the efficacy of IGF-1R-directed therapy in ovarian cancer. AMG 479 is a fully human anti-IGF-1R monoclonal antibody that is being tested in combination with standard chemotherapy in the front-line setting after optimal cytoreduction (clinicaltrials.gov identifier: NCT00718523). A second study is examining AMG 479 as a single agent in recurrent platinum-sensitive disease (clinicaltrials.gov identifier: NCT00719212). OSI-906 is a small molecule dual tyrosine kinase inhibitor targeting both IGF-1R and the insulin receptor (IR). It is currently being evaluated in combination with paclitaxel for patients with recurrent ovarian cancer (clinicaltrials.gov identifier: NCT00889382).

Conclusions

Ovarian cancer can no longer be considered a single disease. Although high-grade serous carcinomas represent the vast majority of ovarian cancer, there are profound clinical and molecular differences among the various histologic subtypes [64–66]. This review has focused on OvLGSCa as a unique disease entity within the serous ovarian cancer spectrum.

Clinical epidemiological studies have put into context the findings from clinical and molecular studies. Firstly, OvLGSCas present at a younger age and have longer survival than HGSOC [21,46]. Secondly, annual incidence rate estimates for low-grade and high-grade tumors are diverging, which can potentially be explained by differences in exposure to risk factors [21]. And thirdly, the increased incidence of serous carcinoma in postmenopausal women is much more pronounced in high-grade tumors when compared to OvLGSCa. This observation is consistent with a potential differential impact of aging and differences in sensitivities or exposures to hormonal influences on carcinogenesis [25].

To date, there are no prospective clinical studies published in OvLGSCa. Therefore, retrospective case-series from large institutions represent the only source of clinical and treatment data for this patient population. Upfront debulking surgery with maximal cytoreductive intent is the strongest factor that correlates with prolonged survival across studies. Responsiveness of OvLGSCa to chemotherapy appears clearly inferior (<5%) to that of OvHGSCa [47,49,67–69]. Retrospective studies have some limitations: i) a relatively small number of patients treated; ii) a variety of regimens used; iii) differences in length and timing of follow up; and iv) distinct methods used for assessing clinical response. However, the low response of OvLGSCa to cytotoxic chemotherapy again underlines the importance of an accurate histologic assessment of the tumor specimen, in particular at its initial presentation. In the context of neoadjuvant chemotherapy becoming an increasingly accepted alternative treatment in the front-line setting of advanced ovarian cancer, caution should be exercised with non-responsive patients who sometimes are spared from cytoreductive surgery, being referred to palliative second-line chemotherapy. Thus, it is likely that advanced OvLGSCa should preferably be managed with aggressive upfront debulking surgery whenever possible.

Advances in the molecular biology of OvSCa, coupled with comprehensive morphological studies, have shed light into the distinctive molecular characteristics of low-grade tumors. As opposed to their high-grade counterparts, OvLGSCa shares common morphologic and molecular features with serous neoplasms of low malignant potential [70]. Epidemiological and clinical data have further corroborated this association [21]. This gain in knowledge in the molecular pathology of OvLGSCa represents a window of opportunity for evaluating new targeted agents. On the one hand, preliminary results of MEK inhibition in OvLGSCa are promising and warrant further clinical testing [55]. On the other hand, both the angiogenesis pathway and the IGF/insulin axis are allegedly attractive molecular targets also worth exploring in OvLGSCa.

Future directions

Rare tumors (such as OvLGSCa) merit further attention from the international community and pharmaceutical companies. Joint initiatives (e.g. the Rare Cancers Europe Committee) have been recently launched to address the scientific and clinical challenges faced by physicians when dealing with rare cancers. At the international, cooperative group level, both the Gynecologic Oncology Group (GOG) and the Gynecological Cancer Intergroup (GCIG) have also created working committees focused on rare gynecological tumors [71]. These efforts must be acknowledged.

Multi-institutional prospective population-based registries, as well as updated epidemiological studies, using uniform pathological criteria (using the two-tier grading system) and more accurate clinical staging information will help in better understand the real incidence and prevalence of OvLGSCa nowadays. In clinical protocols, a clear definition regarding the methods and timing of surveillance of patients in clinical remission is key for an unbiased assessment of patient and treatment outcomes. Central pathology review (with the implementation of the two-tier grading system), data mining and post-hoc analyses (focused on the OvLGSCa subpopulation) from large randomized phase III studies (e.g. GOG218, ICON7, OCEANS3) in ovarian carcinoma would provide valuable information on the outcomes and impact of new therapeutic interventions in the OvLGSCa population.

Future trial design should consider the clinical and molecular differences among ovarian cancer subtypes. While the conduct of large phase III studies in OvLGSCa can be certainly challenging, a shift

towards proof-of-concept early phase I and II studies with rationale-based targeted therapies could potentially expedite the approval of new drugs with demonstrable activity, thereby allowing a prompt access to effective treatment options.

Conflict of interest statement
None of the authors declare any conflict of interest relevant to the present manuscript.

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