Ovarian cancer: Diagnosis and treatment strategies (Review)

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Abstract. Ovarian cancer is a malignant tumor that seriously endangers health. Early ovarian cancer symptoms are frequently challenging to detect, resulting in a large proportion of patients reaching an advanced stage when diagnosed. Conventional diagnosis relies heavily on serum biomarkers and pathological examination, but their sensitivity and specificity require improvement. Targeted therapy inhibits tumor growth by targeting certain characteristics of tumor cells, such as signaling pathways and gene mutations. However, the effectiveness of targeted therapy varies among individuals due to differences in their unique biological characteristics and requires individualized strategies. Immunotherapy is a promising treatment for ovarian cancer due to its long-lasting antitumor effect. Nevertheless, issues such as variable efficacy, immune-associated adverse effects and drug resistance remain to be resolved. The present review discusses the diagnostic strategies, rationale, treatment strategies and prospects of targeted therapy and immunotherapy for ovarian cancer.

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1. Introduction

Ovarian cancer is a major malignancy of the female reproductive system and currently the eighth most frequently diagnosed cancer globally (1). Due to the concealed location of ovarian cancer within the body and the absence of reliable early screening techniques, coupled with the subtle nature of initial symptoms, most patients are typically diagnosed with advanced-stage disease upon presentation. However, developments in liquid biopsy and imaging technology are expected to improve the early diagnostic rate of ovarian cancer and provide greater treatment opportunities. Ovarian cancer frequently exhibits primary or secondary drug resistance, rendering treatment challenging and resulting in 5-year survival rates of only 30-45% (2). Deepening biomedical research has resulted in targeted therapy and immunotherapy gradually becoming new options for the treatment of ovarian cancer. Targeted therapies achieve antitumor effects by specifically interfering with signaling pathways critical to tumor cell growth and proliferation. Currently, targeted ovarian cancer therapy mainly includes anti-angiogenesis therapy and poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors. Immunotherapy, notably immune checkpoint inhibitors (ICI) and adoptive T-cell therapy, has demonstrated notable efficacy in the treatment of melanoma (3), non-small cell lung cancer (4) and various other malignancies, offering distinct therapeutic benefits. However, the value of immune therapy for the treatment of ovarian cancer (5) has not yet been realized, as it is still at the research stage. Researchers have recently begun to focus on the issue of drug resistance (6) and integrate targeted therapy and immunotherapy with other treatments to improve the survival and quality of life (QOL) of patients with ovarian cancer. The present review focuses on the most recent research progress in ovarian cancer diagnosis, targeted therapy and immunotherapy to provide clinicians with the latest available research results and treatment directions.

2. Diagnosis

Pathological classification and molecular characteristics. Ovarian cancer is a heterogeneous disease with varying histological, morphological and molecular characteristics. Understanding these molecular features can be used to guide ovarian cancer diagnosis, prognosis and treatment strategies. Ovarian cancers are categorized according to their origin and

histological characteristics, with the predominant type being epithelial ovarian cancer (7), constituting ~90% of diagnosed cases. Epithelial ovarian cancer has subtypes including high-grade serous carcinoma (HGSOC) comprising 70% of cases and low-grade serous carcinoma (LGSOC) comprising 3% of cases, along with endometrioid, clear cell, mucinous and other subtypes. Other less common types of ovarian cancer include those that originate from primitive germ cells, known as germ cell tumors, and ovarian stroma cells, known as sex cord-stromal tumors. Although these common subtypes are derived from epithelial tissue, their clinical presentation, molecular features and prognosis differ markedly. Although HGSOC and LGSOC are both derived from the serous epithelium, HGSOC is more invasive than LGSOC and often accompanied by tumor protein p53 (TP53) gene mutations (8), whereas LGSOC is mainly associated with KRAS and BRAF mutations (9). By contrast, endometrioid ovarian cancer shares molecular features with endometrial cancer, such as PTEN and catenin β1 gene mutations; clear-cell ovarian cancer often resembles renal cell carcinoma and is characterized by AR-rich interaction domain 1A and phosphatidylinositol-4, 5-bisphosphonate 3-kinase catalytic subunit α gene mutations; and mucinous ovarian cancer has mucin-secreting characteristics and is mainly associated with KRAS mutations (10,11). Personalized treatment strategies may be required for different ovarian cancer subtypes according to their specific molecular characteristics.

Serum biomarkers. Currently, the ovarian cancer molecular markers routinely detected in clinical practice are cancer antigen 125 (CA125) (12), carcinoembryonic antigen (CEA) (13), human epididymis protein 4 (HE4) (14), carbohydrate antigen 19-9 (CA19-9) (15), mesothelin (16), α-fetoprotein (17), PARP (18), FRα (19), TP53 (20), HRD (21), BRCA1/2 (22) and AXL (23) (Table I); however, the detection of only one of these markers often provides an inaccurate result (24). CA125 is the most frequently used biomarker in the diagnosis of ovarian cancer (25), while HE4 was introduced as a biomarker more recently. CA125 has been reported to exhibit low sensitivity during the early stages of ovarian cancer, during menstruation or in patients with endometriosis, as these are also associated with elevated CA125 levels in some cases. However, the analysis of HE4 in combination with CA125 can be used to improve diagnostic accuracy (24). A clinical investigation involving 458 participants, in which electrochemiluminescence immunoassays were used to evaluate the serum levels of HE4, CA125, CA19-9 and CEA, demonstrated that the joint assessment of HE4 and CA125 yielded the most optimal outcomes. This combination exhibited a sensitivity of 80.10% and specificity of 69.08%. Notably, increasing the number of tumor markers to three or four did not increase diagnostic accuracy beyond the efficacy achieved by the HE4 and CA125 combination (26).

Nanotechnology has recently demonstrated great potential for the diagnosis of ovarian cancer due to its high accuracy and low invasiveness. However, the cost and technical requirements are high, which might limit its clinical applications (27). In addition, autoantibodies such as anti-TP53 and anti-New York esophageal squamous cell carcinoma 1 (NY-ESO-1) have been found to have diagnostic value, although their sensitivity and specificity require further study. Specifically, it was reported that a combination of tripartite motif containing 21, NY-ESO-1, TP53 and paired box 8 exhibited 67% sensitivity and 94% specificity for HGSOC (28). Other new markers and detection methods are also under investigation, including the CytoSaLPs scoring tool (29), circ-DENN domain containing 4 C circular RNA (30) and lysophosphatidic acid (31). In addition, a blood extracellular vesicle microRNA (miRNA) microarray has been developed, which has been demonstrated to enhance the specificity of early ovarian cancer diagnosis, reduce false positives and exhibit clear clinical utility in distinguishing malignant ovarian tumors (32).

Pathological examination. Histopathological examination is key in the diagnosis of ovarian cancer. The microscopic observation of tissue samples enables pathologists to accurately diagnose cancer and observe its biological characteristics. The precise diagnosis of ovarian cancer, particularly when the ovarian tumor is large, relies on the histopathological findings of the resected specimen. Fine-needle aspiration is a commonly used biopsy technique for ovarian cancer; however, the amount of tissue obtained may be insufficient to enable a definite diagnosis in some cases (33). The currently emerging diagnostic method is liquid biopsy, which is non-invasive, low-trauma and low-risk, and enables continuous sampling (34). Circulating tumor DNA (ctDNA) is an important element of the liquid biopsy. ctDNA has been demonstrated to have an improved diagnostic performance compared with conventional CA125 for early cancer detection (35). For example, TP53 mutant ctDNA is a promising tumor-specific biomarker for tracking the treatment response of HGSOC. Notably, it exhibits greater sensitivity compared with CA125, with a superior ability to monitor disease progression and therapeutic efficacy (36). In addition, a meta-analysis demonstrated that the mutation spectrum of a solid tumor and its ctDNA are consistent, which indicates the potential application of the ctDNA in the diagnosis of ovarian cancer (37). However, this field is currently only in clinical development. Therefore, the available methods for the early diagnosis of ovarian cancer are limited in sensitivity and specificity, and the ability to evaluate the multifactorial processes associated with chemoresistance development is restricted (38). Immunohistochemical testing is another important method used in the diagnosis of ovarian cancer. It can be used to evaluate the proteins expressed by tumor cells, thereby providing information about the tumor origin, degree of differentiation and prognosis (39). A recent cross-sectional study determined that ovarian masses exhibiting a high neutrophil-to-lymphocyte ratio and elevated tumor marker levels, are likely to be malignant; however, substantial clinical data are required to validate the diagnostic accuracy of these indicators (40).

Genetic diagnosis. Gene expression profiling is useful in ovarian cancer, as it can provide deeper insights into the molecular mechanisms underlying this multifaceted condition. Microarray technology (41) or RNA sequencing (42-44) can be used analyze the expression levels of thousands of gene simultaneously, and are able to identify the different molecular signatures associated with ovarian cancer subtypes (45). Furthermore, gene expression profiling can be used to detect

Table I. Predictive and prognostic capabilities of common tumor biomarkers and their clinical effectiveness.

First author, year	Biomarker	Predictive/ prognostic biomarker	Sensitivity and specificity	Clinical effectiveness	(Refs.)
Samborski, 2022	CA125	Predictive	Low sensitivity and specificity	Often used for the detection and efficacy evaluation of patients with epithelial ovarian tumors (serous tumors)	(12)
Turner, 2021	CEA	Predictive and prognostic	High sensitivity and low specificity	Not specific to malignant tumors; mainly used as an auxiliary in diagnosis; valuable in the judgement of prognosis and treatment evaluation	(13)
Anastasi, 2023	HE4	Predictive	Low sensitivity and high specificity	FDA approved as a marker for monitoring disease progression and recurrence; important for differentiating pelvic masses, benign and malignant tumors	(14)
Ali, 2022	CA19-9	Predictive	-	Highly expressed in mucinous ovarian cancer and gastrointestinal metastatic ovarian cancer	(15)
Lv, 2019	Mesothelin	Predictive and prognostic	High sensitivity and low specificity	Novel tumor marker for ovarian cancer; candidate for targeted therapy	(16)
Rath, 2022	AFP	Predictive	-	Mostly used in liver cancer diagnosis; can also be increased in ovarian immature teratoma and endoembryonic sinus tumor	(17)
Wu, 2023	PARP	Predictive and prognostic	-	Benefits patients with recurrent platinum-sensitive ovarian cancer, regardless of BRCA mutation	(18)
Dilawari, 2023	FRα	Predictive	-	FDA-approved for FRα-positive, platinum-resistant epithelial ovarian cancer	(19)
Borcoman, 2023	TP53	Predictive and prognostic	-	Can be used for tumor diagnosis, treatment evaluation, and prognosis; targeted intervention against TP53 can significantly inhibit tumor growth and improve survival	(20)
Magliacane, 2022	HRD	Predictive	-	Positive HRD is a clinical predictor of PARPi sensitivity	(21)
Grafodatskaya, 2022	BRCA1/2	Predictive and prognostic	-	Used to assess prognostic outcomes, develop treatment options and predict response to PARPi treatment	(22)
Umemura, 2020	AXL	Prognostic	-	Upregulation indicates a poor prognosis and is also a potential therapeutic target	(23)

CA125, cancer antigen 12; HE4, human epididymis protein 4; FDA, Food and Drug Administration; CEA, carcinoembryonic antigen; AFP, α-fetoprotein; CA19-9, carbohydrate antigen 19-9; FRα, folate receptor α; TP53, tumor protein 53; HRD, homologous recombination deficiency; PARP, poly (adenosine diphosphate-ribose) polymerase; PARPi, PARP inhibitor.

persistently overexpressed or downregulated genes in ovarian cancer, thereby revealing potential therapeutic targets. Nevertheless, gene expression profiling has limitations, such as high cost and impracticality in small-sample experiments (46). Gene expression profiling can also be used to monitor treatment response and detect resistance mechanisms (47). This information may be used to guide personalized treatment strategies.

Next-generation sequencing (NGS) technology offers the capability to sequence vast amounts of nucleotides quickly and at a cost that is significantly lower than that of traditional methods, such as Sanger sequencing. Despite its widespread use, the scientific community has made no clear recommendations regarding the use of NGS in oncology (48). NGS is a high-throughput sequencing technology that can comprehensively evaluate various types of genomic variations, including point mutations, copy number variations and gene fusions. NGS has successfully identified gene mutations that are suitable for use as therapeutic targets and provided insights into the molecular mechanisms of disease development and progression (49). For example, a study indicated that holliday junction recognition protein (HJURP) accelerates tumor progression and increases resistance to chemotherapy in patients with ovarian cancer, suggesting that HJURP is potentially a novel treatment target. This was supported by *in vitro* experiments, which suggested that HJURP silencing used in conjunction with cisplatin and AZD1775 offers a potential strategy for the management of ovarian cancer (50). NGS technologies such as whole-exome or whole-genome sequencing may be used to identify prognostic and predictive biomarkers associated with ovarian cancer and promote the development of personalized medicine. In addition, the combined detection of miRNA-205, HE4 and CA125 in exosomes extracted from the plasma of patients with ovarian cancer, using healthy controls as a reference, yielded an area under the curve of 0.951, 100% sensitivity and 86.1% specificity in the early detection of ovarian cancer (51).

Epigenetic factors are important in the occurrence, development and prognosis of ovarian cancer. Epigenetic studies have focused on non-coding changes, such as DNA methylation (52,53), histone modifications (54) and non-coding RNAs (55), that might lead to the silencing of tumor-suppressor genes or the overexpression of oncogenes. For example, in a study that aimed to develop a novel panel of methylation-specific genes for use in a TaqMan-based qPCR assay, promoter methylation of high homeobox A9 (HOXA9) and hypermethylation in cancer 1 (HIC1) was detected ≥80% of ovarian cancer tissues, but no hypermethylation was found in the serum of matched cancer-free women. Thus, the study confirmed the excellent performance of combined HOXA9 and HIC1 methylation analysis in the screening of ovarian cancer samples (56).

3. Targeted therapy

Targeted therapy for ovarian cancer involves the specific binding of targeted drugs to molecular markers on the surface of tumor cells, effectively blocking their signaling pathways and inhibiting the proliferation and survival of the cells. Various targeted drugs are currently employed in the treatment of ovarian cancer, including PARP (57-61), vascular endothelial growth factor (VEGF) (62), tyrosine kinase inhibitors (TKIs) and FRα (63) as listed in Table II. The introduction of these drugs has improved the survival rates and QOL of patients with ovarian cancer, and also expanded the therapeutic options available to physicians. With ongoing advancements in biomarker research, more effective targeted drugs are likely to be developed, further enhancing the treatment landscape for ovarian cancer.

PARP inhibitors. PARP inhibitors function via the mechanism of targeted synthetic lethality. PARP inhibitors inhibit the repair of DNA damage in tumor cells and promote apoptosis, thereby enhancing the curative effect of radiotherapy and platinum drug-based chemotherapy (18). In a number of clinical trials, PARP inhibitors significantly prolonged the progression-free survival (PFS) of patients with ovarian cancer in first-line maintenance therapy as well as in platinum-sensitive relapsed maintenance therapy. Therefore, the use of PARP inhibitors as a maintenance therapy has been introduced for ovarian cancer (64-66). Additionally, treatments with PARP inhibitors have shown encouraging outcomes in various solid tumors with BRCA1/2 mutations, including HER2-negative breast cancer, metastatic pancreatic cancer and prostate cancer resistant to conventional therapies (67). At present, the US Food and Drug Administration has sanctioned the use of three PARP inhibitors, namely olaparib, niraparib and rucaparib, for the management of ovarian cancer.

Olaparib, developed by AstraZeneca, has been endorsed for initial maintenance therapy in ovarian cancer and as a maintenance treatment for recurrent ovarian cancer that responds to platinum-based chemotherapy. The SOLO2/ENGOT-Ov21 phase III trial used olaparib as platinum-sensitive maintenance therapy in patients with recurrent ovarian cancer (68). The results indicated that olaparib exerted an obvious curative effect on patients with recurrent ovarian cancer and BRCA1/2 mutation compared with placebo, where the patients experienced an increase in median overall survival (OS) of 12.9 months compared with placebo-treated controls. However, in August 2022, based on extensive clinical data, the manufacturer of olaparib voluntarily withdrew the indication of this drug as a single agent for the treatment of relapsed advanced ovarian cancer with BRCA mutation after third-line or more prior chemotherapy. Nakazawa *et al* (69) reported that patients with platinum-sensitive recurrent ovarian cancer with disease progression after olaparib maintenance therapy had a very poor response to subsequent platinum-based chemotherapy. Nevertheless, the continued use of olaparib following platinum-based chemotherapy remains the preferred approach for individuals newly diagnosed with BRCA-mutated advanced ovarian cancer, as well as for those with platinum-responsive recurrent disease. However, further studies are required to support the use of this drug in posterior-line therapy, and more findings are expected.

Rucaparib is the second PARP inhibitor, after olaparib, to be FDA-approved for the treatment of ovarian cancer. In 2018, the FDA approved rucaparib for use in platinum chemotherapy-sensitive recurrent epithelial ovarian cancer and fallopian tube carcinoma, or as maintenance therapy in primary peritoneal carcinoma. Evaluations of participants in

Table II. Overview of clinical trials and therapeutic targets for ovarian cancer therapies.

First author, year	Targeted drug	Clinical trial	Target	Date to market, yyyy/mm/dd	Company	Condition	(Refs.)
Washington, 2019	Lynparza/ olaparib	NCT01844986	PARP	2018/12/19	AstraZeneca	Maintenance therapy for advanced ovarian cancer with BRCA1/2 mutation and platinum-sensitive recurrent ovarian cancer after response to chemotherapy	(57)
Shirley, 2019	Rubraca/ rucaparib	NCT02855944	PARP	2018/06/13	Clovis Oncology	Advanced BRCA-mutated ovarian cancer with receipt of ≥2 prior chemotherapy regiments	(58)
Essel, 2018	Zejula/ niraparib	NCT02655016	PARP	2017/03/27	Glaxo Smith Kline	Used in combination with some chemotherapy agents to treat platinum-resistant recurrent ovarian cancer	(59)
Lee, 2021	AiRuiYi/ fuzuloparib	NCT03509636	PARP	2020/12/11	Jiangsu Hengrui Pharmaceuticals Co., Ltd.	Treatment after second-line chemotherapy for platinum-sensitive recurrent ovarian cancer with BRCA1/2 mutation, and maintenance therapy after effective chemotherapy for platinum-sensitive recurrent cancer	(60)
Luo, 2022	Baihuize/ pamiparib	NCT03333915	PARP	2021/05/07	BeiGene, Ltd.	Recurrent ovarian cancer with germline BRCA1/2 mutation after prior second-line or higher chemotherapy	(61)
Guan, 2018	Avastin/ bevacizumab	NCT00262847 and NCT00483782	VEGF	2018/06/13	Genentech, Inc.	Combined with chemotherapeutics, such as paclitaxel and topotecan, to treat platinum-resistant recurrent ovarian cancer	(62)
Matulonis, 2023	Elahere/ Mirvetuximab soravtansine-gynx	NCT04209855	FRα	2022/11/14	ImmunoGen	Platinum-resistant, FRα-positive epithelial ovarian cancer prior to 1-3 line systemic therapy	(63)

GOG, Gynecologic Oncology Group; VEGF, vascular endothelial growth factor; FRα, folate receptor α.

two phase I/II studies and a phase II clinical trial have shown that rucaparib is effective as a third-line therapy for ovarian cancer with BRCA mutations, with an overall response rate (ORR) of 80% in patients who underwent treatment in the phase II trial (70). In addition, the phase III ARIEL3 clinical trial used rucaparib in the maintenance treatment of platinum-sensitive ovarian cancer, and the results revealed that the treatment significantly improved the PFS of the patients (71). These trial results indicate that rucaparib is a promising treatment option that may extend the lifespan of the patient and reduce adverse reactions, such as aminotransferase levels, inflammation and elevated serum creatinine.

Niraparib has received authorization for use as a maintenance treatment in adult individuals with recurrent epithelial ovarian cancer, cancer of the fallopian tube or primary peritoneal cancer that is sensitive to platinum, following initial platinum-based chemotherapy. The NOVA trial demonstrated the efficacy of niraparib maintenance chemotherapy in patients with a partial response to platinum-based therapy, with and without a germline BRCA mutation (gBRCAm), as their PFS was longer than that of the patients treated with placebo (72). In patients achieving a complete response, niraparib was associated with greater PFS improvement relative to placebo in patients with a gBRCAm compared with those without. Niraparib exhibited controllable tolerance during adverse drug reaction monitoring, and dose reduction was possible to limit the possibility of adverse drug reactions (73). However, data on the cost-effectiveness of niraparib as a maintenance therapy are limited, particularly due to the lack of mature OS data. Furthermore, it is unclear whether the advantage of niraparib over placebo in PFS will lead to a confirmed improvement in OS (73,74).

In addition to the use of PARP inhibitors as monotherapy, other ongoing clinical trials (75-77) are focusing on their combinations with other agents, including platinum-based chemotherapy, anti-angiogenic agents and ICIs, with specific examples being carboplatin and bevacizumab. Patient-derived organoids (PDOs) have been recognized as an effective tumor model for the screening of PARP inhibitors and for addressing drug resistance in ovarian cancer, with patients experiencing improved results when treated according to recommendations derived from these models (78,79). However, the use of PDOs faces challenges, such as ensuring high-quality biopsies and navigating the intricacies of the tumor microenvironment. Consequently, the identification of PARP inhibitors that more accurately meet patient requirements necessitates further investigation and study.

Generally, PARP inhibitors demonstrate positive efficacy in the first- and second-line maintenance treatment of ovarian cancer, but their use in post-line treatment requires further study. A subgroup analysis demonstrated that patients with BRCA mutations or with homologous recombination deficiency (HRD) benefited more than those without BRCA mutations or HRD, respectively (66). Thus, genetic testing can guide accurate treatment, and follow-up requires further research.

VEGF inhibitors. VEGF is important in new blood vessel formation, tumor growth and metastasis in ovarian cancer, as it stimulates endothelial cell proliferation, division and migration, and increases vascular permeability (80,81). VEGF prevents tumor neovascularization by hindering the interaction between VEGF and its receptor, VEGFR, thereby contributing to its anticancer activity. Currently, the most studied targeted therapy is bevacizumab, a recombinant humanized monoclonal antibody targeting VEGF, which has been shown to prolong median PFS effectively when added to chemotherapy (81). Two randomized phase III trials, namely Gynecologic Oncology Group (GOG)-0218 and ICON7, resulted in the inclusion of upfront bevacizumab in the National Comprehensive Cancer Network (NCCN) ovarian cancer guidelines (82). The first-line approval was based on the results of the pivotal GOG-0218 study, which demonstrated that adding bevacizumab to carboplatin and paclitaxel chemotherapy significantly prolonged the median PFS by 3.8 months and that this combination did not reduce the QOL of the patients (80,83). Following this rationale, the European Medicines Agency sanctioned the use of bevacizumab with platinum and paclitaxel as an initial chemotherapy combination for ovarian cancer (62). The ICON7 trial used a lower bevacizumab dose and shorter maintenance period. This significantly improved the median PFS by 2.7 months, with a greater benefit for patients with high-risk disease. This finding might be explained by the greater demand for angiogenesis in the patients with a high risk of progression, causing them to be more susceptible to antiangiogenic therapies (62,82). Studies have also shown that additional treatment with bevacizumab significantly prolonged PFS, but not OS, in patients regardless of their resistance or sensitivity to platinum-based chemotherapy (81,84). In short, bevacizumab significantly improved the PFS and ORR of patients with platinum-resistant ovarian cancer. However, the inclusion of bevacizumab in chemotherapy regimens should be tailored to the specific circumstances of patients with platinum-sensitive ovarian cancer, with its addition being contingent upon the clinical status of the patient. The use of bevacizumab in maintenance therapy should be based on treatment with this agent during first- or second-line chemotherapy and the HRD and BRCA status of the patient. Although the GOG-0218 and ICON7 clinical trials reported that bevacizumab prolonged the PFS by several months, it did not effectively extend OS. Therefore, bevacizumab does not currently fulfill the necessary criteria for being an optimal treatment option for patients with advanced ovarian cancer.

TKIs. In addition to bevacizumab, certain TKIs also serve as anti-angiogenic drugs targeting VEGF and VEGFR, and may be added to the treatment regimen according to the condition of the patient.

VEGFR signaling pathways are typically inhibited by TKIs that target receptor tyrosine kinases (RTKs). RTKs are typically imbalanced in most cases of HGSOC (85) and frequently excessively activated in tumors, which can lead to recurrence, progression and metastasis. Therefore, RTKs have long been considered a therapeutic target for endometrial ovarian cancer. The AGO-OVAR 12, ICON6 and AGO-OVAR 16 phase III trials used nintedanib, cediranib and pazopanib, respectively, to target TKIs (86-88). Numerous studies have reported that these drugs are more effective when used in combination therapies, and exhibit little activity as single drugs (87-89). Pazopanib targets VEGFR and platelet-derived growth factor receptor, which regulate tumor cell growth,

metabolism and angiogenesis, and demonstrates good activity when used as a single agent. However, the AGO-OVAR 16 study found that although pazopanib prolonged PFS, it did not improve the median OS significantly, and had a reduced effect on prolonging PFS in East Asian patients compared with patients of other ethnicities (88). Based on these results, the US FDA did not approve pazopanib for the treatment of advanced ovarian cancer, and the NCCN guidelines do not recommend pazopanib as a maintenance therapy after initial ovarian cancer treatment. However, this drug can be used for the treatment of platinum-resistant recurrent ovarian cancer.

Cediranib exerts good antitumor effects in recurrent ovarian cancer; the ICON6 study reported that cediranib chemotherapy combined with maintenance therapy extended the PFS by 2.3 months compared with simple chemotherapy and did not reduce the QOL of patients (87). Additionally, the anti-angiogenic properties of anlotinib have been reported to be superior to those of sunitinib, sorafenib and nintedanib (84). Notably, individuals receiving only anlotinib had a PFS period of 7.7 months, demonstrating that the efficacy of anlotinib was comparable to that of bevacizumab. Additionally, anlotinib is associated with a reduced rate of toxic reactions compared with sunitinib, especially in terms of hematological toxicities (90). Therefore, anlotinib appears to be a potential anti-angiogenic agent that is safe to use in ovarian cancer.

Overall, the TKIs nintedanib, cediranib and pazopanib effectively prolong the PFS but not the OS of patients with ovarian cancer, and are not used in routine clinical practice. Therefore, it is urgently necessary for more clinical trials to evaluate the effectiveness of TKIs and discover more effective combination therapies. Furthermore, anlotinib may be a potential treatment option with low toxicity for patients with ovarian cancer that is resistant or refractory to platinum-based therapies. However, few studies of anlotinib have been performed, and its mechanisms of action have not been fully elucidated. Thus, further trials are required to verify its specific efficacy.

Epidermal growth factor inhibitors. The epidermal growth factor receptor (EGFR), a member of the ErbB group of cell surface receptors, is highly expressed in 30-70% of ovarian cancers, a condition that is often associated with a less favorable outcome (85). Current evidence (91,92) suggests that single-agent anti-EGFR biotherapy with EGFR TKIs or anti-EGFR antibodies, either as maintenance therapy after first-line chemotherapy or combined with chemotherapy, has little effect on the survival of patients with recurrent cancer. New-generation EGFR inhibitors interfere with the interaction of multiple ErbB family members. These include lapatinib, an EGFR and ErbR-2 dual inhibitor, which is currently undergoing a GOG phase II study in the US for the treatment of advanced ovarian cancer (93).

Activation of PI3K-AKT-mTOR signaling and other pathogenic pathways. The PI3K-AKT-mTOR signaling pathway is involved in various cellular processes, including regulation of the cell cycle, the production of proteins that precede apoptosis, the regulation of angiogenesis, and the promotion of cancer cell invasion and metastasis. In addition, mutations and hyperactivation of this pathway are observed in the majority of patients with ovarian cancer. Therefore, targeting this signaling pathway is important to inhibit cancer cell proliferation and apoptosis (94-96). In addition to its involvement in ovarian cancer, the PI3K-AKT-mTOR pathway prevents oocyte maturation in ovarian follicular dysplasia (94). In an *in vitro* study, the dual PI3K/mTOR inhibitor PKI-402 significantly reduced cell proliferation and cell viability compared that achieved with single PI3K or mTOR inhibitors. By reducing the activity of this survival signaling pathway, PKI-402 may have the potential to suppress tumor formation, migration and invasion, and overcome chemotherapy and radiotherapy resistance (97). However, although this dual mTOR/PI3K inhibitor yielded good antitumor effects, it nevertheless exerts toxic and adverse effects on normal cells. Therefore, much additional research is necessary to develop improved mTOR/PI3K dual inhibitors and single PI3K/AKT/mTOR inhibitors.

The RAS-RAF-MEK-ERK pathway, a key MAPK pathway, is involved in cell proliferation, differentiation and development, growth factor signaling, and the apoptosis pathway. Clinical studies have explored the use of MAPK inhibitors both as monotherapies and in combination therapies, focusing on the selective inhibition of proteins within the MAPK pathway, known as vertical inhibition, or targeting multiple signaling pathways to reduce their activity (98,99). There is considerable evidence that MEK inhibitors are only potentially curative in patients with LGSOC, while dual inhibition of this MAPK pathway using RAF and MEK inhibitors has greater potential (98,99). Additionally, the simultaneous inhibition of MEK and PARP has been shown to result in increased DNA damage, potentially leading to cell death. Specifically, MEK inhibition augments the effectiveness of the PARP inhibitor, with an extended duration of effect and broadened therapeutic potential (18,100).

The folate receptor (FR)-mediated signaling pathway is involved in tumor division and migration, and the inhibition of FRα has been demonstrated to have direct anticancer activity. Therefore, FRα is a novel therapeutic target in ovarian cancer research. The employment of FRα antibody-drug conjugates (ADCs) and small-molecule drug conjugates, which increase the targeted delivery of anticancer treatments directly to the tumor site, has improved the outlook of patients with cancer exhibiting high levels of FRα expression (101). In November 2022, the US FDA approved mirvetuximab soravtansine, the first-ever FAα target in the ADC field. This ADC has been approved used as a systemic treatment for adult patients with platinum-resistant epithelial ovarian cancer, fallopian tube carcinoma or primary peritoneal carcinoma (102).

A phase II trial of mirvetuximab soravtansine for platinum-resistant ovarian cancer, conducted as a single-arm study, demonstrated uniform antitumor effects, along with favorable tolerability and safety profiles in patients with FRa-high tumors (63). In summary, mirvetuximab soravtansine is a promising treatment for patients who have ovarian cancer with high FRα expression levels, and may stimulate the development of new targeted therapy methods for the further improvement of prognosis and survival.

4. Immunotherapy

Cancer vaccines. Tumors escape the immune system through various mechanisms. It is generally thought that epithelial ovarian cancer is immunogenic (103). Ovarian

cancer immunotherapy using cancer vaccines is a treatment strategy that aims to stimulate the immune system of the patient to recognize and attack cancer cells, thereby killing tumor cells and inhibiting their proliferation. A number of cancer vaccines have been developed based on the delivery of selected tumor-specific antibodies, including tumor antigens, tumor cells, peptides and genetic vaccines. However, various factors influence the generation of an autoimmune response. Dendritic cell (DC) vaccines increase DC uptake and the presentation of tumor-associated antigens and so are a particularly attractive option for immunotherapy (104). Human conventional type 1 DCs have the ability to activate natural killer (NK) and NK T cells (105). Numerous clinical trials have investigated the treatment of ovarian cancer using therapeutic vaccines, and indicated that a single application of a vaccine does not have an obvious effect (106), possibly due to the tumor interfering with the effectiveness of the vaccine. Therefore, it may be necessary to use a vaccine in combination with other therapies (107). Furthermore, recent studies have demonstrated that novel ovarian cancer vaccines, such as a formulation comprising cancer antigen and adjuvants (108), and cancer stem cell vaccines (109), have potential as a direction for further investigation. However, the limitations of these studies are that they were only conducted in mouse models and cannot be directly generalized to humans.

ICIs. Evasion of the immune response presents a significant obstacle in the treatment of ovarian cancer. At present, the ICIs showing the most potential target cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). This protein is expressed on the surface of activated lymphocytes and resembles the protein CD28; however, while CD28 promotes T-cell activation, CTLA-4 suppresses the immune response. Anti-CTLA-4 treatment is associated with some adverse reactions, include fatigue, mild infusion reaction and inflammatory skin reaction (110). However, data on anti-CTLA-4 as a single-agent therapy for ovarian cancer are limited, and anti-CTLA-4 agents are being explored in combination with other ICIs, such as anti-programmed death 1 (PD-1) and anti-PD-1 ligand (PD-L1) agents, in an attempt to improve efficacy (111). Furthermore, the use of anti-CTLA-4 drugs with other treatments such as chemotherapy, targeted therapy or cancer vaccines has potential in the treatment of ovarian cancer (112).

Immune cells, especially activated T lymphocytes, express PD-1 and PD-L1 on the cell surface. As interaction between PD-1 and PD-L1 impedes the activity in the target cell, blocking the signal transduction between the two proteins effectively alters tumor activity. Currently, several commonly used PD-1/PD-L1 inhibitors are undergoing clinical trials in ovarian cancer (113,114). In a clinical trial, patients with uncommon serous tumors resistant to PD-1/PD-L1 inhibitors demonstrated significantly better responses compared to those with other, typically more responsive, ovarian cancer subtypes (115). Another trial observed that poor prognosis was significantly associated with the tumor cell PD-L1 level in ovarian cancer (90). Overall, PD-1/PD-L1 inhibitors have found to be effective in a smaller proportion of patients with ovarian cancer than in patients with other tumors.

ICIs have been combined with other treatments for ovarian cancer (116-119). However, the incidence and severity of adverse events are much higher with combined treatment than with single treatments (120,121). There are various clinical situations with unmet clinical demands, particularly for recurrent platinum-resistant ovarian cancer. Furthermore, there is evidence that the gut microbiome influences the efficacy of ICIs, with different bacterial strains varying in their influence on immune regulation (122).

Adoptive cell therapy. Cellular immunotherapy, also known as adoptive cell therapy, is a personalized immunotherapy. It involves the *ex vivo* expansion and manipulation of lymphocytes from the patient, and their reinfusion into the patient to promote an immune response to cancer. This novel method is an potential cure with multiple strategies (123,124), such as the use of tumor-infiltrating lymphocytes, NK cells or modified immune components, such as chimeric antigen receptors (CARs) and engineered T cell receptors, for adoptive cell transfer. Continuous advances in genomics and immune engineering technology have facilitated the development and use of CAR-T cells; however, they have several challenges, including limited activity in solid tumors, off-target effects, tumor antigen escape, ovarian tumor heterogeneity and immunosuppressed tumor cells (125,126). T-cell receptor therapy is an alternative cell-based therapy that has potential as a future option for the treatment of ovarian cancer. However, it is major histocompatibility complex (MHC)-restricted, as it relies on the presence of MHC molecules to identify antigenic targets and activate T-cell function (127). Based on data from the Cancer Genome Atlas, CD47 is amplified in HGSOC. The amplification of CD47 enhances its 'don't eat me' signal, which protects cancer cells from being phagocytized by macrophages. Therefore, targeting bone marrow immune checkpoints might also be an attractive therapy option (128).

5. Conclusions

Despite remarkable progress in the diagnosis, targeted therapy and immunotherapy of ovarian cancer, early detection and accurate diagnosis are the key to successful treatment. The emergence of novel biomarkers combined with artificial intelligence-based imaging technologies is expected to revolutionize diagnostic capabilities. With the advent of personalized precision medicine, targeted therapy enables a personalized and precise treatment regimen by selectively focusing on the molecular alterations driving ovarian cancer progression. However, it currently does not alter OS, highlighting the need for more effective maintenance therapies. Immunotherapy is a promising means of harnessing the immune system to fight the cancer. Recent advances in ICIs, adoptive T-cell therapy, oncolytic viruses, DCs, cancer vaccines and cytokines have provided promising prospects for the current and future treatment of ovarian cancer. Future strategies may involve the design of therapies that limit the production of inflammatory cytokines while preserving antitumor efficacy. This approach could significantly mitigate the side effects typically associated with conventional treatments.

Despite these major achievements, challenges remain in the optimization of treatment strategies and overcoming drug resistance mechanisms in ovarian cancer.

As research continues into the complex tumor microenvironment and tumor-host interactions, a complete understanding of the molecular and immunological underpinnings of ovarian cancer is critical. Furthermore, a single approach is not generally advantageous in the treatment of ovarian cancer, and future research efforts that focus on combining targeted therapy with immunotherapy and selecting the appropriate combination therapy according to the ovarian cancer type are recommended. Given the complex relationship between the response to different combination therapies and treatment effects, additional biomarkers might be necessary for use in response prediction. Furthermore, it is necessary to develop uniform standards for combination drugs in the treatment of ovarian cancer. Despite novel therapies offering new hope, their high costs and uncertain efficacy limit their acceptability and widespread use. Moreover, the recurrence rate of ovarian cancer remains high, and the options for post-recurrence treatment are limited, which presents a significant challenge for current treatment protocols. Therefore, future research focusing on the identification of new therapeutic targets and the development of more effective strategies for post-recurrence treatment is necessary. In terms of future directions, improvements in personalized treatment and precision medicine are likely to be crucial. Tailoring treatment plans that are optimally suited for each patient, based on an analysis of the genetic and molecular profiles of the tumor, may be key to improving the therapeutic outcomes and QOL of patients with ovarian cancer.

With the knowledge and insights presented in the present review, it is expected that the scientific community will progress greatly in the advancement of ovarian cancer diagnosis, treatment and management. This may ultimately herald a new era of precision medicine and improved patient care.

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Authors' contributions

XJL and ZCL performed the literature search and drafted the manuscript. HLM and XWL were primarily responsible for writing the section on targeted therapy. HXZ, XXL, XFC, XHZ, ZLZ and ZHH were major contributors to revision of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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