Genomic and Molecular Characteristics of Ovarian Carcinosarcoma

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Abstract: Ovarian carcinosarcoma (OCS) is a rare malignancy with a poor prognosis. It is a biphasic tumor with malignant epithelial and mesenchymal components. A few mutations commonly seen in cancer have been identified in OCS, including TP53, PIK3CA, c-myc, ZNF217, ARID1A, and CTNNB1. Some OCS tumors have shown vascular endothelial growth factor positivity and limited HER2 expression. There is evidence of homologous recombination deficiency in OCS. This malignancy can be categorized as copy number high but has not been shown to have a high tumor mutational burden. There are mixed findings regarding the presence of biomarkers targeted by immune checkpoint inhibitors in OCS. For treatments other than systemic chemotherapy, the data available are largely based on in vitro and in vivo studies. In addition, there are case reports citing the use of poly-ADP ribose polymerase inhibitors, vascular endothelial growth factor inhibitors, and immunotherapy with varying degrees of success. This review paper will discuss the molecular and genomic characteristics of OCS, which can guide future treatment strategies.

Key Words: ovarian neoplasms, carcinosarcoma, review

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INTRODUCTION AND CLINICAL CHARACTERISTICS

Ovarian cancer is the eighth most common form of cancer among women worldwide. Within primary malignancies of the ovary, carcinosarcoma (ovarian carcinosarcoma [OCS] and malignant mixed Mullerian tumor) accounts for 1% to 4% of cases.[1–3] When compared with other ovarian cancer histologies, women with OCS are more likely to be diagnosed at an older age and typically have a worse performance status. In addition, OCS carries an overall worse prognosis.[4–8] Like most who present with advanced ovarian cancer, women with OCS often present with abdominal or pelvic pain, early satiety, bloating, gastrointestinal issues, or ascites. OCS is generally diagnosed at later stages (stage III or stage IV) when compared with other forms of ovarian cancer.[9,10] As with advanced ovarian cancers, otherwise, treatment for OCS generally involves cytoreductive surgery with adjuvant platinum-based chemotherapy.[11] When compared with other forms of ovarian cancer, carcinosarcoma has lower sensitivity to treatment with platinum-based chemotherapy.[7]

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Histology

OCS is a biphasic tumor consisting of malignant epithelial (carcinomatous) and mesenchymal (sarcomatous) components. The epithelial portion is often serous, endometrioid, or undifferentiated adenocarcinoma. The mesenchymal component is further categorized as homologous or heterogenous. Homologous differentiation includes stromal sarcomatous, fibrosarcomatous, or leiomyosarcomatous elements native to Mullerian organs. Heterogenous sarcomatous differentiation toward non-Mullerian structures most often takes the form of cartilaginous, osseous, or rhabdomyoblastic elements. Thus, OCS is a histologically diverse malignancy.

MOLECULAR PROFILE OF OVARIAN CARCINOSARCOMA

OCS is a rare malignancy with a paucity of data regarding its molecular makeup. Most of the research in this area has been conducted in small retrospective cohorts of patients. Data regarding potential drug targets are mostly confined to in vivo studies, which have revealed potential future therapeutic combinations.

TP53

TP53, which codes for the p53 protein, is one of the most frequently mutated genes in human cancers, including gynecologic malignancies.[12] TP53 mutations are commonly detected in OCS.[13–16] Although data are limited, TP53 mutations seem to be present in the majority of OCS with over 80% harboring this mutation in some studies. In addition, p53 showed similar expression patterns in both the epithelial and mesenchymal components, which supports a monoclonal origin of this tumor.[17,18] It is not clear what the prognostic significance of this is in the ovary, but in uterine carcinosarcoma, TP53 mutations were found to be associated with decreased overall survival.[15] Another study demonstrated a trend toward greater overall survival in OCS patients with p53 overexpression; however, this difference did not reach statistical significance.[18] Further research is needed to investigate the association between TP53 mutations and prognosis in OCS.

HER2/Neu

HER2/neu is an oncogene that, when mutated, leads to malignant transformation of healthy cells and has been investigated in OCS.[19] In a study using OCS cell lines derived from the biopsies of metastatic sites, one cell line showed low positivity (1+) for HER2/neu while the other cell line showed strong (3+) HER2/neu positivity by immunohistochemistry. This study also demonstrated HER2/neu gene (ErbB2) amplification by fluorescence in situ hybridization (FISH).[20] However, other studies failed to detect frequent HER2/neu positivity in OCS.[18,21]

ZNF217

Another oncogene of relevance to OCS is ZNF217. Its overexpression has been shown to contribute to tumor progression by preventing apoptosis due to telomere dysfunction. It is also known to promote chemoresistance in breast tumors.[22,23] ZNF217 is an upstream regulator of ErbB3 (HER3) expression and promotes signaling of the PI3K-AKT pathway.[24,25] The transcription factor ZNF217 has been targeted by the AKT inhibitor triciribine in mouse models.[26] Schipf et al[27] identified ZNF217 amplification by FISH in both the sarcomatous and carcinomatous tumor components of OCS.

RAS-RAF-MAPK Pathway

The RAS-RAF-MAPK pathway has been evaluated in OCS, given mutations are commonly identified across solid tumors, and there is potential for identifying multiple new therapeutic targets. The c-myc gene of this pathway is disrupted in over 50% of human cancers.[28] One study looked at c-myc in OCS by comparative genomic hybridization and FISH and reported amplification of c-myc specifically in the carcinomatous tumor component.[27] In addition, there was a higher proliferation index in the carcinomatous tumor component compared with the sarcomatous areas, measured by the expression of Ki67 antigen. On the basis of these findings, the authors concluded that the carcinomatous component seemed to be the more aggressive region of these tumors. Mutations in KRAS, the first signaling element of the RAS-RAF-MAPK pathway, have been detected in uterine carcinosarcoma in other studies but were not found in OCS or were only present at low frequencies.[15,16,29]

PI3K/AKT Pathway

The PI3K/AKT signaling pathway is commonly disrupted in cancer, although the data are sparse in OCS. Using next-generation sequencing (NGS), Jones and colleagues analyzed whole genomes of matched normal specimens and tumor samples for carcinosarcoma patients. Of the primary carcinosarcoma tumors originating in the ovary, 40% exhibited PIK3CA missense mutations. This study also detected a nonsense mutation in the PTEN gene in 1 of the 5 OCS specimens.[30] In another study, DNA was extracted from OCS tumors for whole exome sequencing. In this study, mutations of the PIK3CA gene were detected in 23% of OCS samples.[16] These study results are in contrast to other studies, which were only able to detect PIK3CA mutations in uterine carcinosarcoma as opposed to in OCS.[15,29]

Wnt/beta-catenin Pathway

Mutation of the β-catenin gene, CTNNB1, is the most common genetic alteration in the Wnt/β-catenin pathway in epithelial ovarian cancer, with mutations found frequently in endometrioid ovarian cancers.[31,32] Mutations in CTNNB1 have been detected in OCS. Jones and colleagues found a missense mutation of CTNNB1 in 1 of 5 OCS specimens using NGS sequencing. In another study, which performed genotyping on primary gynecologic carcinosarcomas, a CTNNB1 mutation was found in an OCS tumor with endometrioid histology, consistent with previous studies that CTNNB1 mutations are common in ovarian endometrioid tumors.[15,30]

Vascular Endothelial Growth Factor

Angiogenesis is essential for tumor growth, and vascular endothelial growth factor (VEGF) is the main regulator of this process. In a study inclusive of carcinosarcomas of the ovary (7) or fallopian tube (2), VEGF reactivity was detected by immunohistochemistry via the detection of monoclonal antibodies in 44% of tumor specimens. In this study, there was no association between VEGF expression and length of survival.[18] In a separate study inclusive of 5 ovarian and 20 uterine carcinosarcoma specimens, staining via labeled antibodies targeting VEGF was higher in carcinomatous areas of tumors, and higher expression of VEGF was associated with decreased survival. Further supporting these findings, higher numbers of small blood vessels as measured by an automated image analyzer were associated with shorter survival.[33]

Chromatin-Remodeling Genes

Mutations in chromatin-remodeling genes have been detected in OCS, including ARID1A. Mutations of ARID1A are prevalent in ovarian clear cell carcinoma and are also seen in endometrioid ovarian carcinoma.[34] Jones et al[30] detected ARID1A mutations in 80% of OCS samples using NGS. In a separate study analyzing the molecular subtypes of ovarian and uterine carcinosarcoma, ARID1A mutations were correlated with poor outcomes specifically for the copy number high phenotype. Tumors in this study were characterized as copy number high if they possessed very aberrant copy number alterations.[35] Another study analyzing chromatin-remodeling genes found amplification of the histone gene locus chr6p in 70% of OCS specimens. This study, inclusive of ovarian and uterine carcinosarcoma, detected frequent mutations in H2A/H2B histone genes, which are contained in the HIST1H gene cluster within the chr6p segment.[16]

TMB

High tumor mutational burden (TMB) refers to having many nonsynonymous mutations. TMB has been shown to be relevant in predicting response to immune checkpoint inhibitors (ICIs).[36,37] However, cancers originating from the ovary are typically low in terms of TMB.[38,39] More studies are needed to fully understand the extent of TMB in OCS. Gotoh et al[35] found almost all OCSs included in their study to be of the copy number high subtype. This was in comparison to uterine carcinosarcoma, which can be characterized by multiple genomic subtypes, including copy number high, copy number low, and the ultramutated phenotype, resulting from mutations in DNA polymerase ε. Uterine carcinosarcoma also exhibited microsatellite instability, unlike OCS. These differences in phenotypes were further supported by analysis of transcriptome patterns where OCS better resembled high-grade serous ovarian carcinomas than uterine carcinosarcoma.[35]

Homologous Recombination Deficiency

Homologous recombination deficiency (HRD) is a state of genomic instability due to defective repair of DNA damage. HRD is strongly associated with somatic or germline mutations of the BRCA1 and BRCA2 genes. The presence of HRD in ovarian cancer is of particular interest because these tumors may be sensitive to platinum chemotherapy and poly-ADP ribose polymerase (PARP) inhibitors. One study, which included mainly ovarian cancers, found loss-of-function homologous recombination mutations in 4 out of 12 (33%) carcinosarcomas.[13] BRCA mutations have been detected at low frequencies in patients with OCS.[40–42] Another study using whole exome sequencing detected signature-3, a genetic signature associated with HRD, in 15 of 25 (60%) of OCS cell lines. Furthermore, HRD+ cell lines were sensitive to treatment with olaparib.[43]

Role of ICIs

Immunotherapy is emerging as a standard of care in cancer treatment. These agents are ICIs, which target the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) pathways. There are mixed findings regarding the presence of these biomarkers in OCS. In a study inclusive of both adnexal and uterine carcinosarcoma, CTLA-4 expression was detected at low frequency, while no PD-L1 expression was found. Furthermore, CTLA-4 expression was higher at the carcinomatous component than the sarcomatous component of the primary tumors studied.[44] Hacking et al[45] found 87% of cases to be positive for > 1% PD-1 expression and 67% of cases with > 1% PD-L1 expression in their study of gynecologic carcinosarcomas, including cases of uterine, ovarian, peritoneal, and cervical origin. Another study of 19 OCS cases detected PD-L1 positivity in ~50% of the tumors. There was a significant negative correlation between PD-L1 expression and $CD8^+$ T lymphocyte count in the mesenchymal components. Three-year postoperative survival rate was significantly higher for mesenchymal PD-L1 negative patients. If mesenchymal PD-L1–positive patients have poorer survival, this may support the use of ICI in OCS to improve outcomes.[46]

CONCLUSIONS AND FUTURE DIRECTIONS

Because of the rare occurrence of OCS, there is a lack of randomized controlled trials specific to this histologic subtype to guide treatment. Cytoreductive surgery is the initial treatment followed by adjuvant chemotherapy. Systemic therapy for this patient population has largely been extrapolated from randomized trials performed in other ovarian cancer subtypes. Because of its poor prognosis and limited therapeutic options, there is a critical need for the development of new treatment strategies for OCS.

Targeting the HER2/neu pathway has emerged as a potential therapeutic focus. Although HER2/neu expression is variable in OCS, Guzzo et al[20] demonstrated in vitro sensitivity to trastuzumab-dependent cell-mediated cytotoxicity using a cell line of OCS overexpressing HER2/neu. The tyrosine kinase inhibitor of HER2/neu, Neratinib, has also shown successful results in vitro when exposed to a HER2/neu amplified OCS cell line via signaling inhibition and cell cycle arrest.[47] In addition, there are multiple studies that test the efficacy of HER2-directed antibody-drug conjugates (ADCs) in vitro and in vivo. Trastuzumab emtansine (T-DM1) was more effective than trastuzumab alone in inhibiting cell proliferation and in causing cell death in OCS cells overexpressing HER2 and achieved complete treatment response in vivo using mouse models.[48] A subsequent study compared the HER2-targeting ADC SYD985 to T-DM1 using uterine and OCS cell lines. Unlike T-DM1, SYD985 demonstrated activity against both cell lines with strong (3+) as well as low (1+) HER2/neu expression and showed significantly better tumor growth inhibition and higher overall survival in vivo.[49] A recent study demonstrated significant cell death induction when treating uterine and OCS cell lines with HER2/neu overexpression with another HER2-directed ADC, trastuzumab deruxtecan (DS-8201a).[50]

Targeting VEGF to inhibit angiogenesis could be a potential treatment strategy for OCS. Multiple case reports cite the use of bevacizumab as a treatment for OCS.[51–53] One study analyzed retrospective data for patients with a gynecologic carcinosarcoma treated with Pazopanib, a tyrosine kinase inhibitor of vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and receptor tyrosine kinase c-KIT. Of the 2 patients included with OCS, 1 patient had progression-free survival (PFS) of 11 months and an overall survival of 12.4 months, similar to prognosis for OCS patients treated with chemotherapy.[54]

Tumors with HRD may be sensitive to treatment with PARP inhibitors. In a patient with OCS with a germline mutation of the homologous recombination repair gene RAD51D, treatment with the PARP inhibitor olaparib resulted in immediate clinical improvement and tumor sensitivity with no reported tumor regrowth. Before starting treatment with olaparib, this patient failed treatment with multiple lines of chemotherapy and was previously enrolled in a phase I clinical trial using a PD-1 inhibitor.[55] In another case report, olaparib was used in a patient with OCS with a germline BRCA1 mutation who ultimately required third-line chemotherapy. After treatment with olaparib, PFS was at least 64 months without any adverse events due to olaparib.[56] Another case reported the use of niraparib as maintenance therapy in combination with bevacizumab for a patient with OCS after receiving multiple lines of chemotherapy.[52]

Because of the rarity of OCS, the response to treatment with ICI largely remains unknown. The association of ovarian cancer and lower TMB may predict poorer responses to treatment with ICI. However, there is evidence of PD-L1 expression in OCS, which may represent certain patients who can benefit from immunotherapy. In a case report, a patient with OCS who had recurrence after multiple lines of chemotherapy was treated with pembrolizumab. Positron emission tomography /computed tomography showed partial response in affected lymph nodes after multiple cycles of pembrolizumab, with only thyroiditis grade 1 reported as an adverse event. Of note, this patient was not tested for microsatellite instability, mutational load, or PD-L1 expression.[51] Another female with Lynch syndrome and stage III OCS was started on pembrolizumab after previously showing disease progression on chemotherapy and bevacizumab. After initiation of pembrolizumab, she showed improved functional status with stabilization of disease except for multiple episodes of small bowel obstruction and a temporary elevation in CA 125 levels after ~3 years of treatment.[53] The recent phase 3 RUBY clinical trial, a randomized, double-blind, multicenter study, investigated the efficacy of dostarlimab, a PD-1 inhibitor, compared with placebo in combination with carboplatin and paclitaxel in patients with endometrial cancer. This study was inclusive of patients with uterine carcinosarcoma and showed improved PFS for patients treated with dostarlimab, with significant improvement seen in patients with mismatch repair–deficient, microsatellite instability–high tumors. These results support investigating treatment of OCS with this PD-1 inhibitor as well as testing for mismatch repair deficiency and microsatellite instability in these tumors.[57]

There are limited studies focused on OCS due to its low incidence, and the available studies often have small sample sizes. Studies are often inclusive of both uterine carcinosarcoma and OCS as uterine carcinosarcoma is more common. However, the molecular and mutational profile of uterine carcinosarcoma differs from OCS, which supports this malignancy being treated as a separate and distinct cancer. We should aim to better understand the genomic and molecular characteristics of OCS to tailor future treatment options.

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