TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2016;31(4):149-159
doi: 10.5505/tjo.2017.1532

REVIEW

Molecular Biomarkers in Ovarian Carcinoma

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SUMMARY

Ovarian cancer is the most lethal of the gynecological cancers because its etiology is not well understood and majority of ovarian cancers are detected at advanced stage, at which point it is typically incurable. Effective screening protocols and earlier disease detection and diagnosis could result in decreased morbidity for women with ovarian cancer. Cancer antigen 125 (CA-125) is the most frequently used diagnostic biomarker for ovarian cancer; however, it is not overexpressed in the early stage of the disease. Moreover, levels of CA-125 are also elevated in other instances, such as benign ovarian tumors and gynecological inflammation. Investigators are searching for new, specific, and sensitive biomarkers to replace or complement CA-125 in detection of ovarian cancer at an early stage. This review discusses current status and new biomarkers, algorithms for screening, and risk assessment for ovarian cancer.

Keywords: Biomarkers; ovarian carcinoma; risk estimation; therapeutics.

Introduction

Ovarian cancer (OC) is the sixth most common cancer in women in the United States. Khalil et al.[1] estimated that about 21.550 new ovarian cancer cases would be diagnosed in 2009 in the United States, and 14.600 women would die of the disease. Ovarian cancers are usually seen in peri- or postmenopausal women (mean age, 63 years).[2] Although the lifetime risk of developing ovarian cancer is 1.4% in Western countries, the risk increases 3.3% when a first-degree relative has the disease. Thus, a positive family history is the most significant risk factor. Nulliparity increases the risk of ovarian cancer, whereas pregnancy, lactation, use of oral contraceptives, and tubal ligation are associated with a reduced risk. Ovarian carcinomas are morphologically heterogeneous, and different histopathologic subtypes have distinct molecular characteristics and diverse response to treatment. Ovarian carcinomas can be classified as serous, endometrioid, clear cell or mucinous. Differences in chemotherapy response and patient outcomes probably relate to the molecular heterogeneity of these morphologically distinct ovarian carcinoma.[3,4] Insight into the pathogenesis of ovarian cancer comes from known factors that increase risk. These include inherited mutations in the BRCA1/2 genes in a minority of cases, and more generally, a range of hormone and/or reproduction-related factors.[5,6] Unfortunately, the majority of women are diagnosed with advanced-stage disease because of the asymptomatic nature of early-stage disease and the lackof an adequate early detection screening method. [7] Currently, there is no proven single biomarker for physicians to detect ovarian carcinoma at an early stage with adequate sensitivity and specificity. To solve this problem, researchers have aimed at the identification and validation of novel biomarkers for the early detection of ovarian carcinoma using new technologies. Di-

Received: January 09, 2017
Accepted: January 13, 2017
Online: January 17, 2017

Accessible online at:
www.onkder.org

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Turk J Oncol 2016;31(4):149-159
doi: 10.5505/tjo.2017.1532

agnostic markers for population screening would be a simple blood test with 95%specifcity and sesitivity.

In this review article, we will discuss current and promosing markers fordiagnosis, prognosis, and treatment of ovarian carcinoma in the clinic.

Methods

A PubMed search was performed using the keywords novel biomarkers in ovarian cancer to prepare a comprehensive literature review. Some 637 articles were observed for the initial search. The results were filtered by species, languages (English), article type, manuscripts published in the past five years, and with free full text and extracted miRNA and Long and non-coding RNA publications. Three hundred fifty three associated papers and 18 review articles appered after the filter process. Additional searches and selection were performedusing the keywords genetic markers in ovarian cancer, multidrug resistance in ovarian cancer and prognostic markers to supplement the information. Finally, 70 papers were selected for inclusion in the manuscript following a careful review of the abstracts. These papers consisted of 3 meta-analyses, 8 reviews, and 57 original papers.

Serum and Tissue Markers in Ovarian Carcinoma

CA125: Early detection of ovarian cancer greatly increases the chances for successful treatment. CA-125is the most sensitive and used marker in the management ofovarian cancerat every stage of the disease. CA-125 is used at the time of diagnosis of the disease, to evaluate the possibility of complete resection during surgery, to estimate sensibility for adjuvant or neo-adjuvant chemotherapy, and for diagnosis of recurrence. CA-125has a diagnostic and therapeutic value and could be of help during therapeutic evaluation, and could also be used to estimate global and progression-free survival. Low preoperative rates, half-life, and fast normalization of CA-125 during adjuvant chemotherapy are correlated with optimal surgery and better global and progression-free survival. The normal range of CA-125 is a strong predictive factor for disease recurrence, even if its role in survival has not yet been determined. The level of CA-125 and its dynamic interpretation is an indispensable approach for the diagnosis, therapeutics, and follow-up of ovarian cancer. Although serum CA-125 is still a very important prognostic and predictive factor for personalized care in ovarian carcinoma, CA-125 exhibits poor sensitivity for detecting early disease stages and low specificity to malignancy.

HE4: HE4 is a novel biomarker expressed in serous ovarian carcinoma and can be measured in serum, urine, and other body fluids using enzyme-linked immunosorbent assays (ELISA).HE4 protein is frequently overexpressed in serous and endometrioid histologic types of ovarian cancer.[8–14] However, HE4 is not specific for ovariancancer,HE4 expression has also been found in other malignancies such as pulmonary and endometrial adenocarcinomas.[15,16] It is reported in the majority of published papers that serum HE4 sensitivity and specificity in gynaecologic diseases are better than CA-125. The results of Molina et al. confirmed these previous studies by clearly showing that the use of HE4 may be important in the differential diagnosis of ovarian cancers with other gynecologic conditions including premenopausal women.[17–25] The authors also remarked that HE4 had a better utility in the differential diagnosis of ovarian cancer, and abnormal levels were found in only one third of patients with endometrial or endocervical cancer, and none with squamouscervical cancer. By contrast, CA-125 is frequently abnormal in all these malignancies. Molina et al. concluded that HE4 was the tumor marker of choice inovarian cancer, with a higher sensitivity, specificity, and efficiency in early stages than CA-125.[26]

Two markers have been Food and Drug Administration (FDA) approved: cancer antigen125 (CA-125) in 1987 and more recently, human epididymis protein-4 (HE4) in 2008 with limited application of monitoring disease recurrence and therapeutic response.[19,27–30]

RECAF: RECAF is an alphafetoprotein receptor that is a wide-spectrum oncofetal antigen with clinical potential for cancer diagnosis, prognosis, and screening. Tcherkassova et al. reported that serum RECAF was detected in elevated levels in patients ovarian cancer when compared with normal individuals. They also showed that the level of RECAF protein was higher in stage III/IV than stage I/II. Both RECAF and CA-125 were able to discriminate between healthy patients and those with cancer. More importantly, RECAF had beter performace to detect early-stage disease. Moreover, the specificity of the RECAF test was high at early and late stages of ovarian cancer, whereas the sensitivity of CA-125 was lower in earlier stages than in advance disease. Using the combination of RECAF and CA-125 serum values provides the specificity and the sensitivity necessary to screen for ovarian cancer, especially at early stages.[31]

Osteopontin (OPN): Osteopontin, a soluble protein present in all body fluids related to adhesion and extracellular matrix interactions, affects multiple cellular functions, includingin flammation, angiogenesis,

and tumor metastasis. Alternative splicing and post-translational modificationsof OPN result in a variable molecular weight of 41 to 75kd. Higher tissue mRNA and proteinlevel of OPN were reported in borderline tumors compared with ovarian adenocarcinomas, whereas Kim et al. reported on higher OPN tissue expression in OC and borderline tumors compared with benign tumors and normal tissue, as well as higher serum levels in ovarian cancer patients compared with healthy subjects and patients with benign ovarian disease or other gynecologic cancers.[32,33] The use of serum OPN in combination with leptin, prolactin, and insulin-like growth factor II as a diagnostic test for ovarian cancer was associated with 95% sensitivity and specificity.[34] It is suggested that CA-125 and macrophage inhibitory factor were added to the panel by this group.[35] As serum marker, 95% sensitivity and specificity for OPN were similarly observed in combination with CA-125 and kallikrein 10.[36]OPN level rose earlier compared with CA-125 marker in patients with recurrent disease.[37] Osteopontin expression was more frequent in effusions from patients with high-grade tumors, but was significantly associated with better debulking at primary surgery and complete response to chemotherapy at diagnosis. Unexpectedly, Davidson et al. showed that the presence of OPN in ovarian cancer cells in effusions was associated with less aggressive clinical course. OPN is frequently expressed in ovarian carcinoma effusions, but its presence is associated with less aggressive clinical course.[38]

Netrin-1: Netrin-1 (NTN1) is a diffusible laminin-related protein that has been shown to play a major role in the developing nervous system.[39,40] NTN1 is aberrantly overexpressed in the majority of malignant ovarian tumors but not in benign tumors. Moreover, high NTN1 expression was correlated with both tumor stage and grade. The differences in NTN1 expression upon progression to malignancy canbe used safely in malignant tumors, because NTN1 is barely expressed in normal and benign tissues. Lack of expression in normal/benign tissue is a desired but rare feature of cancer biomarkers. Therefore, Papanastasiou et al. suggested that NTN1 expression could possibly be used asa biomarker to distinguish benign from malignant ovarian-tumors.[41] NTN1 expression should also be evaluated in larger prospective studies as a promising candidate biomarker to distinguish early-stage ovarian cancer.

Nidogen-2 (Nid2): The nidogen family consists of two isoforms, nidogen-1 and nidogen-2, which are ubiquitous basement membrane (BM) proteins in mammals that are broadly expressed in various tissues. Nidogens have an important role in BM formation as integrating elements for BM assembly.[42,43]

Kuk C et al. showed that nidogen-2 was elevated in the serum of patients with ovarian carcinoma as compared with patients with benign gynecologic diseases and healthy controls. ROC curve analysis demonstrated that nidogen-2 had potential diagnostic value. Spearman correlation showed that nidogen-2 correlates highly with CA-125. Similar to CA-125, level of serum nidogen-2 is more frequently elevated in serous adenocarcinoma compared with other histotypes and late-stage of disease. It is reported that there was close correlation between nidogen 2 and CA-125 and these two markers mimic each other, therefore nidogen-2 could not be an additional marker for ovarian cancer.[44]

Kallikrens: The human kallikrein-related peptidase family is a family of serine proteases, which has been identified onhuman chromosome 19q13.[45] The family consists of 15 genes, of which 12 (KLK2, KLK3, KLK4, KLK5,KLK6, KLK7, KLK8, KLK10, KLK11, KLK13, KLK14, and KLK15) appear to be overexpressed in ovarian cancer. It has been shown that mRNA expression of KLK6 and KLK13 increased in ovarian cancer compared with normal ovarian tissues. High KLK6 or KLK13 expression in primary ovarian tumors can significantly predict prognosis in terms of recurrence-free survival and overall survival. All study have suggested that KLK6 and KLK13 could be potential biomarkers and therapeutic targets for treatment of ovarian cancer in the future.[46]

In another study, it was found that serum KLK6 and KLK10 had much lower overall sensitivities than serum CA125, whereas serum KLK10 may have higher specificity among these 3 markers.[47] Magdolen et al. showed that a high level of KLK5 protein is released into serum and ascitic fluids in patients with ovarian cancer, whereas KLK5 is very low in benign ovarian tumors. Thus, it is suggested that elevated KLK5 levels in serum and ascitic fluid could be used as a biomarker for early detection as well as for disease management in ovarian cancer.[48] Furthermore, Bayani et al. demonstrated that the KLK locus at 19q13.3/4 was subject to high genomic instability and copy number heterogeneity, mediated by structural rearrangements of19q. Moreover, structural rearrangements on 19q are associated with tumor grade, and may be associated with, or a marker of the differential pathogenesis thereby distinguishing low-grade and high-grade serous cancers.[49]

Claudins: Claudins are tight junction proteins that are involved in tight junction formation and function. Previous studies have shown that Claudin-7 is fre-

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doi: 10.5505/tjo.2017.1532

quently upregulated in epithelial ovarian cancer (EOC) along with Claudin-3 and Claudin-4. CLDN7 is elevated in all major subtypes of ovarian cancer: serous, endometrioid, clear cell and mucinous at both the mRNA and protein levels. Claudin-7 could be functionally involved in the invasion of ovarian carcinoma, but is inversely correlated with migration. Claudin-7plays important roles in a number of signaling pathwaysinvolved in cancer, cellular growth, proliferation, and cell cycle. Therefore, it will be important for ovarian carcinogenesis and have significant potential in diagnostic and therapeutic applications. Thus, futher research is needed to discoverits diagnostic and therapeutic potential.[50]

Folate Receptor Alpha (FRα): The folate receptor a (FRa), a 38–40 kDa molecule, is a well characterized member of the folate receptor (FR) family. FRa is anchored to cell membranes through a glycosylphosphatidylinositol moiety and transports folates via an endocytic process.[51] FRa expression has limited distribution in normal tissue, including few epithelia, predominantly in the lung, kidney, and choroid plexus, but is overexpressed in a spectrum of solid tumors, including ovarian cancer, non-small cell lung cancer, breast cancer, kidney cancer, and in high-grade osteosarcoma.[52–55] Thus, it has been suggested as a promising molecule as a biomarker for ovarian carcinoma. Functional intact FRa is elevated in ovarian carcinomain comparison with healthy controls. FRa levels should be researched in larger cohorts uncluding those with early-stage ovarian cancerto testify as to whether FRa is a feasible marker for ovarian cancer.[56]

Genetic and Epigenetic Markers in Ovarian Carcinoma

HYL-1 (Hyaluronidase-1): Mammalian hyaluronidases are endo-N-acetylhexosaminidases that hydrolyze the glycosaminoglycan hyaluronan. The gene family has 6–7 different genes which are about 40% identity among each others.[57,58] Allelic imbalance of three members of the gene family (HYAL1, HYAL2 and HYAL3) has been shown in tumors and stroma tissues of ovarian cancers.[59] It was shown that HYAL1 mRNA levels are inversely correlated with those of ERα specifically in clear cell and mucinous ovarian cancertissue samples, suggesting a role for ERα in regulating HYAL1 gene expression in ovarian cancer. It was suggested that levels of hyaluronidase expression may vary depending on tumor type and on aggressive tumor behavior and the expression of HYAL-1 in ovarian cancer tissue samples representing four different histopathological subtypes. Elevated levels of this enzyme has been demonstrated in clear cell and mucinous ovarian cancer, but not in serous or endometrioid cancer. It was also demonstrated that levels of HYAL1 mRNA in clear cell and mucinous ovarian cancers were inversely correlated with those of ERα. It was thought that HYAL-1 might play a role in tumor proliferation and cell cycle progression in ERnegative clear cell and mucinous ovarian cancer. Helena et al. proposed hyaluronidase-1 as a potential target/biomarker for clear cell and mucinous ovarian cancer, especially in tumors with low ERα levels or Erα-negative ovarian cancer.[60]

Myofibrillogenesis regulator 1 (MR1): MR-1 is a protein with 142 amino acid residues located on chromosomes 2q35.[61–63] MR-1 may promote cancer cell proliferation by binding to specific proteins such as eukaryon initiation factor 3, which is highly associated with the regulation of tumor cell growth and invasion.[64] Expression of MR-1 is increased both in mRNA and protein levels in tumor tissues from patients with ovarian cancer with serous papillary histology compared with benign control tissues. Knockdown of MR-1 expression inhibits cell adhesion and invasion, and anti-cancer drugs decrease the expression levels of MR-1 in cancer cells. Thus, MR-1 may be a novel biologic marker and potential therapeutic target for the treatment of ovarian cancer. It could also be used to monitor the effect of anti-cancer therapies. Further studies are needed to clarify whether MR-1 is an early diagnostic marker for ovarian cancer and to develop its full therapeutic potential.[65]

Lysosome-associated protein transmembrane-4 beta (LAMPM4B): LAPTM4B is a novel tumor-associated gene, which was first cloned in hepatocellular carcinomas (HCCs).[66,67] LAPTM4B is highly overexpressed in ovaries and the uterus.[68] Yin et al. initially shown the association between LAPTM4B expression and metastasis of epitelial ovarian carcinoma. They found that the sensitivity and specificity of LAPTM4B overexpression was 48.7% and 90.9% for intraperitoneal metastasis, and 73.8%% and 71.1% for lymph node metastasis, respectively.[69] According the results, the authors suggested that LAPTM4B overexpression may be a novel predictor of epithelial ovarian carcinoma metastasis and an important potential biomarker for early diagnosis of ovarian carcinoma.

Opioid-binding protein/cell adhesion molecule-like gene (OPCML): OPCML, a recently-identified tumorsuppressor, is frequently inactivated by allele loss and CpG island promoter methylation in epithelial

ovarian cancer. Genetic analysis revealed that OPCML was frequently inactivated somatically in epithelial ovarian cancer via allele loss and CpG island methylation, although inactivation mutation of OPCML is rare. Gene expression studies further demonstrated that OPCML expression was completely abolished in more than 80% of primary ovarian tumors as well as ovarian cancer cells.

IFFO1-M: Campan et al. investigated serum DNA of patients with ovarian carcinoma usingthe Illumina Infinium platform to analyze the DNA methylation status of more than 27.000 CpG islands. They identified one marker called IFFO1-M (IFFO1 promoter methylation), which is frequently methylatedin ovarian tumors and that is rarely detected in the blood of the normal population.[70] It is thought that IFFO1-M will be a blood-based candidate marker for sensitive detection of ovarian cancer after future validation stages of the marker development process.

miRNAs: MicroRNAs (miRNAs), a recently-discovered class of regulatory RNAs, are frequently deregulated in carcinogenesis. In ovarian tumorigenesis, numerous miRNAs have been found altered and some of these genes may represent ideal targets for diagnosis, prognosis, and treatment.[71]

EAG CHANNELS: Asher et al. demostrated for the first time that high expression of Eag potassium channels in patients with ovarian cancer was significantly associated with poor survival. There was also a significant association of Eag staining with high tumor grade and presence of residual disease. Proliferation of SK-OV-3 cells was significantly inhibited after treatment with voltage gated K+ channel blockers. Therefore, this novel finding demonstrates a role for Eag as a prognostic marker for survival in patients with ovarian cancer.[72]

Molecular Markers in Hereditary Ovarian Carcinoma

Hereditary Breast and OvarianCancer Syndrome (HBOC): HBCO is associated with a significantly increased risk for breast and ovarian cancer compared with that of the general population. Mutations in BRCA1 and BRCA2 account for 80–90% of HBOCcases. Hereditary breast-ovarian cancer syndromeis characterized by early-onset breast and ovarian cancers, bilateral breast cancer, both breast and ovarian cancer in the same person, and male breast cancer. Cancer in families that have the syndrome is seen in several generations. Both BRCA1 and BRCA2 genes have a tumor suppressor function and both are inherited as autosomal dominant with incomplete penetrance. Both genes play integral roles in genomic stability and integrity, cell cycle control, apoptosis, and DNA repair. The lifetime risk of developing ovarian cancer is about 20%–50% in patients carrying BRCA mutations.[73] Some 85% of female breast cancer and 40% of ovarian cancer is associated with BRCA1 syndrome, whereas male breast cancer and 20% of ovarian cancer is associated with BRCA2 syndrome. BRCA-associated ovarian cancers are characterized by higher patient survival rates and a better response to platinum-based chemotherapy.[74] The median survival time is 53.4 months for BRCA carriers versus 37.8 months fornon carrriers.[75]

Hereditary Nonpolyposis Colon Carcinoma (HNPCC) syndrome: HNPCC, also known Lynch II syndrome, is an autosomal dominant disorder characterized by an increased predilection for right colon cancer (without polyps) and endometrial-ovarian cancer (serous and endometrioid variants). Lynch II syndrome is characterized by germ-line mutations of DNA mismatch repair genes hMLH1, hMSH2, hMSH6 and PMS2. To date, most germline mutations have been identified in the MSH2 or MLH1 genes. Altered mismatch repair genes lead to microsatellite instability and inactivation of genes that the control cell cycle and DNA repair. Women with HNPCC syndrome have a lifetime risk of about 12% for developing ovarian cancer.[76]

Tools for Risk Estimation of Ovarian Cancer

CA-125 isa frequently used marker for initial diagnosis in ovarian cancer. However, the performance of CA-125 varies depending onthe cut-off selected, and the patient population, with sensitivities ranging from 29–100%. CA-125 gives many false positives in a wide variety of normal, benign, andother malignancies, leading to low specificity.[30,77,78] To improve the performance of CA-125, retrospective studies have reported using serial CA-125 measurements combined with other markers and te results wereinterpreted using a Risk of Ovarian Cancer Algorithm (ROCA). Many other risk assesment strategies have sought to combine CA-125 with additional markers.[79,80] The OvaCheckH test includes a CA-125 test with seven other markers and has 81.1% sensitivity and 85.4% specificity.[81] However, the test performance needs to be validated. The Risk of Ovarian Malignancy Algorithm (ROMA) combines measurements of both CA-125 and HE4.[17] The Risk ofMalignancy Index (RMI) was designed to improve specificity by combining CA-125 with an imaging score and menopausal status.[82] Unfortunately,

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doi: 10.5505/tjo.2017.1532

risk estimation tools, ROMA and RMI do not appear to increase performance significantly over CA-125 alone.[20,24] Another multimarker test, OvPlexTM, which combines CA-125 with C-reactive protein, serum amyloid A (SAA), interleukin 6 (IL-6), andIL-8, was shown to have 94.1% sensitivity and 93.1% specificity.[83] The test had biases whereby the case and control samples were not from the same population. Another test, OvaSureTM, combines leptin, prolactin, osteopontin, insulin-like growth factor II, and macrophage inhibitory factorwith CA-125. The test'ssensitivity and specificity were 95.3% and 99.4%, respectively.[35] However, there are multiple concerns about thestudy design and validation population.[84,85] One of the newest serum-based tests is the OVA1 test, which was approved in 2011. The key purpose of this test was to identify ovarian cancer risk in women who presented with an adnexal mass and were planning surgery.[86,87] The test measures transthyretin, apolipoprotein AI, transferrin, and β2 microglobulin combined with CA-125. The performance of OVA1 depends on the source of the surgicalpatient population and the menopausal status of the patient.[87,88] A new marker was identified by Yip et al. that was capable of discriminating between samples drawn from women with benign ovarian conditions and those from women with ovarian cancer. In their study, a preliminary multivariate analysis, using a logistic regression model on the nine most informative biomarkers appeared to have significantly improved performance over OVA1 biomarkers.[89]

Novel Therapeutics in Ovarian Carcinoma

TRAP1: TRAP1 (TNF receptor-associated protein 1) is a mitochondrial heath shock protein 75 that has antioxidant and antiapoptotic functions.[90,91] It is evident that mitochondrial defects and dysfunctions of oxidative phosphorylation and energy production inovarian cancercells are directly related to their resistanceto platinum drugs. Landriscina et al. demostrated for the fist time that TRAP1 is upregulated in osterosarcoma.[19] mRNA expression of TRAP1 is increased in tumor cells resistant to 5-fluorouracil and platin derivatives.[20] Resistance to platinum-based chemotherapy (CDDP) is the major obstacle to successful treatment of ovarian cancer. High level of TRAP1 expression is showned estrogen receptor-positive and CDDP-resistant ovarian carcinomas. Therefore, TRAP1 could be a prognostic marker predicting drug resistance and a therapeutic target to protectagainst drug resistance forpatients with ovarian cancer. Also, the fact that expression levels of TRAP1 proteins in ovarian cancers are estrogen regulated could helpto identify patients who would benefit from endocrine therapy.

Folate Receptor α inhibitor: Folate receptor α expression is highly restricted in normal adult tissues but upregulated in a wide range of human cancer types, including epithelial ovarian cancer. Farletuzumab, a humanized monoclonal antibody against folate receptor α has shown antitumor activity and favorable toxicityin preclinical evaluation. In aphase I study, Farletuzumab administered as an i.v. infusion at doses of 12.5 to 400 mg/m^2 was generally safe and well tolerated in the management of heavily pretreated patients with epithelial ovarian cancer. Farletuzumab will be an altenative agent in patients with platinum-sensitive and platinum-resistant epithelial ovarian cancer.

K+ Channel Blockers: Eag and HERG K+channels are overexpressed in ovarian cancer and high Eag staining is associated with significantly poorer survival, which identifes Eag as a putative prognostic marker. Asher et al. demostrated that K+channel blockers could be used to inhibit proliferating ovarian cancer cells as a therapeutic.

Antiangiogenic agents, VEGFR inhibitors: Cediranib is an oral tyrosine kinase inhibitor of VEGFR1, 2, and 3, and c-Kit, which interacts with the ATP-binding site within kinase domainof the receptor.[92,93] Cediranib is an effective moleculefor the prevention of tumor progression by inhibiting VEGFR-2 activity and angiogenesis, and concomitantly inhibiting VEGFR-3 activity and lymphangiogenesis. Therefore, Cediranib has been shown to be an active drug in recurrent ovarian cancer. A phaseIII randomized study (ICON6) on patients with ovarian, fallopian tube, and primary peritoneal carcinoma isongoing with three different combination therapies. Moreover, another phase I/II trial is ongoing for VEGF Trap, which is afusion protein that combines the Fc region of IgG1 withdomain two of VEGFR1, and domain three of VEGFR2 (VEGFRδ1R2) in combination with Docetaxel in patients with recurrent ovarian cancer, primary peritoneal cancer, and fallopian tube cancer.

PDGF inhibitors: PDGF magnifies the proliferation of human ovarian surface epithelial cells and ovarian cancercells.[94,95] High expression levels of PDGF and PDGFα were found in73.3% and 35.6% of malignant ovarian tumors, respectively.[96] It was shown that the elevated expression of PDGFRα is an independent poor prognostic factor in patients with ovarian cancer. Therefore, PDGF signaling pathways migth be novel targets forovarian cancer therapy.

Tyrosine kinase inhibitors (EGFR): Pertuzumab, a recombinant, humanized monoclonal antibody that binds to HER2, induces activation ofantibody-dependent cellular cytotoxicity without blocking the truncation of HER2 with the difference of Trastuzumab.[97] Combination therapy of pertuzumab with gemcitabine was assayed in a randomized phase II trial in 130 patients with platinum-resistant ovarian, fallopian tube, or primaryperitoneal cancer.[98] An increased treatment benefit was observed in the gemcitabine + pertuzumab combination in patients with low HER3 mRNA expression in their tumors. Therefore, pertuzumab maybe effective in platinum-resistant ovarian cancer, and low HER3 mRNA expression may predict a pertuzumab clinicalbenefit.

PARP-1 inhibitors: The poly (ADP-ribose) polymerases (PARPs) enzyme family has the most abundant isoform playing a key role in the repair of DNAsingle-strand breaks (SSBs) through the base excision repair pathway. Olaparib (AZD2281), an oral smallmolecule PARP inhibitor, was tested in BRCA-mutated patients with ovarian, primary peritoneal, and fallopian tube cancer.[99,100] In thestudy, 20 patients (40%) responded to therapy. Currently, randomized trials of olaparib and other PARP inhibitors in patients with ovarian cancer are underway.

DNMTinhibitors: Azacytdine and 5-aza-2'-deoxycytidine (decitabine) are approved to treat myelodysplastic syndrome. Phase Iand IIclinical trials are ongoing to examine treatment of ovarian cancer.[101] A phase Istudy has been completed recently of decitabine combined with carboplatin in patients with recurrent platinum-resistant ovarian carcinoma.[102]

Cancer Testis Antigens (CTA): There are currently nine Cancer Testis Antigens, SPAG9, OY-TES-1, Piwil2, LAGE-1, NY-ESO-1, SSX, AKAP-3, SCP-1, and Sp17. These antigens are the most suitable for a vaccine of ovarian cancer and immunotherapy, although they are not used in clinical practice now. Among these, CTA, SPAG9, NY-ESO-1, Sp17, and AKAP-3 have been examined in detail for diagostic and therapeutic approaches. Phase I clinical trials have been completed by Odunsi and Diefenbach et al. for the CTA NY-ESO-1, which demonstrated thepotential for the vaccination approach for advanced and high-risk ovarian cancer.[103,104] In the study by Diefenbach et al.,[100] vaccination with the HLA-A0201-restrictedNY-ESO-1b peptide was performed to patients at high risk for ovarian cancer in first remission, following conventional surgery and chemotherapy. No serious adverse effects were seen after vaccinations. Concordantly, strong CD4 and CD8 positive T-cell responses indicatedthat the NY-ESO-1-based vaccine was effective in eliciting specific anti-tumoractivities. However, the authors pointed out that ovarian tumor cells could escape from the vaccine because there was a lack of NY-ESO-1 expression in recurrent tumors. The results based on the NY-ESO-1 vaccine are very promising for ovarian cancer clinical trials.

Conclusions

Tumor biomarkers have been important in the management of ovarian cancer. Biomarkers are useful tools in early diagnosis of disease, monitoring treatment responses, detecting recurrent disease, and determining prognosis. The consideration of any single tumor marker assay has limited sensitivity and specificity in distinguishing malignant from benign tissue masses. Molecular markers are now becoming increasingly important for risk assessment to determine malignant and benign ovarian diseases and persons at high risk. Improvements will be needed to detect ovarian carcinoma at an early stage. Combinations of complementary serum or urine markers have proven useful in improving the sensitivity and specificity of assays used to identify invasive ovarian cancer at early stages because ovarian carcinomas have differential expression of various biomarkers. The data presented in the review suggest that further investigations are needed to identify new biomarkers for screening and early diagnosis of ovarian carcinoma.

Disclosure Statement

The authors declare no conflicts of interest.

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