Review Article

Pathogenesis, significant biomarkers and treatment strategies in ovarian cancer

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ABSTRACT

The aim of this paper is to study the pathogenesis, significant biomarkers and treatment strategies in ovarian cancer. Because of poor prognosis, ovarian cancer is usually diagnosed in final stages and although the first phase of treatment and chemotherapy usually seems to be a nice therapeutic approach but after a while, in many cases the disease will return. There are several biomarkers in order to diagnose the ovarian cancer but nowadays the combination of CA125 and HE4 are used and Pelvic examinations and diagnostic sonographies can also help early detection. Some factors such as using contraception pills, breastfeeding, early menopause and proper nutrition can decrease the risk of being involved with this malignancy, but instead late menopause, due to increasing the number of ovulation cycle, and also smoking tobacco can increase the risk of this disease. Several medicines are used to improve the inhibition of angiogenesis chemotherapy such as: bevacizumab and cediranib.

***Keywords*:** Ovarian cancer, biomarkers, risk factors, targeted therapies

INTRODUCTION

When we usually think about women malignancies, the breast cancer is often the first choice that comes in our mind, and also the ovarian cancer (OC) is recognized as a silent killer and because of poor prognosis, is usually diagnosed in final stages and therefore is recognized as 7th most common cancer among women over 50 years old [1-4]. Among developed regions, the epithelial type of ovarian cancer is more often with 5 main histotypes [5,6]. Pregnancy and hormones are two important factors that play role in getting this disease [7]. Ovarian tumors are divided into two classes, I and II, class I tumors develop slowly and they are just limited to ovary and have good prognosis therefore they are diagnosed in first stages but class II tumors behave completely different. They are so aggressive and have poor prognosis and develop rapidly [8]. In advanced V stages, surgery and chemotherapy can only guarantee 25 % patient survival. Although over the past 5 years the rate of response to chemotherapy has changed from 65 % to 80 % but unfortunately it returns again soon after [9,10]. Each year 239,000 new cases get involved with ovarian cancer and 152,000 of them die worldwide [11]. The highest incidence rate is 11.4 per 100,000 populations in Eastern Europe and 0.6 per 100,000 populations in central Europe and China has a lower incidence rate than other countries.

In 2015, among every 100.000 people in bog societies, 5200 new cases and 22500 death have been reported [12]. And in The United States 21290 new cases and 180 death were reported in 3 years [13]. The lowest rate in Asia and Africa is 3 per 100,000 people. Migration from low-rate countries increase the risk of getting this cancer by 33 % that confirms the importance of non-genetic risk factors in initiation of that [14,15]. The risk of OC in a woman lifetime is one in 75 and the mortality rate is 1 in 1004. Information about ovarian cancer is poor among human societies therefore it's emerging in the late stages that the relative survival rate in last five years is only 29 %.

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the mortality rate is 1 in 1004. Information about ovarian cancer is poor among human societies therefore it's emerging in the late stages that the relative survival rate in last five years is only 29 %.

Few of the cases, 15 %, with localized tumors (non-metastatic) diagnosed in stage 1, have a 5-year survival rate of 92 % [16]. In few of these cases, 15 % are with localized tumors (non-metastatic) and are diagnosed in stage 1 hand had a 5-year survival rate (92 %).

Remarkably, the relative 5 year survival rate generally varies between 30 and 40 % worldwide and since 1995 the disease has increased by 2-4 % [17]. White women have the highest incidence, white and Asian/Oceanic and African American and Native American Indians have been the most prevalent after whites [18-20]. This article investigates the pathological classification, genetic investigation, biomarkers, diagnostic algorithms, clinical and pathological heterogeneity and targeted therapies of ovarian cancer, and on the other hand, offers the multi-targeted drug to improve ovarian cancer progression.

Pathological classification

All benign and malignant ovarian tumors originate from these three types of cells: A) epithelial cells B) stromal cells C) germ cells. In developed countries, more than 90 % of malignant tumors have epithelial origin. 5-6 % of tumors (originating from umbilical cord) are stromal cells, such as granulosa cells and theca cells, which consist of ovarian follicles and 2-3 % of tumors are stem cells, such as teratomas that originate from multipotent stem cells [21]. Ovarian cancer reflects a heterogeneous disease with histological subgroups that differ in cellular origins pathogenesis molecular changes gene expression and prognosis. Malignant OC, known as a carcinoma, consists of 5 tissue subgroups [8,22-24]. 1) 70 % high grade ovarian cancer 2) 10 % endometrium 3) 10 % clear cell ovarian cancer 4) 3 % mucous cells 5) 5 % low grade ovarian cancer. The cellular origin and cause of OC pathogenesis is not well understood, and interestingly, most tumors originate from other genetic tissues and involve the ovary in the second degree. Morphological and genetic studies in ovarian cancer have led to the development of hypotheses for high-grade malignant tumors that usually lack an algorithm and pattern of progression [25,26]. Epidemiological research clearly highlights the hormonal and reproductive factors in the pathogenesis of OC. There are two hypotheses to prove the cause of ovulation [27].

The hypothesis of continuous ovulation

The number of ovulation cycles increase the rate of cell division and the repair of superficial epithelium after each ovulation and enhance the chance of spontaneous mutations [28]. The correlation between increasing the number of ovulations over a lifetime and higher risk of this cancer is consistent with this hypothesis [28-31].

The hypothesis of gonadotropins

Attribution of these gonadotropins leads to Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) [32]. Both of these hypotheses provide a framework for interpreting epidemiological data. A closer look is available by Riemann and his coworkers [33]. Ovarian cancer rates have declined in recent years with the increase in taking birth control pills. Despite awareness of ovarian cancer, the therapeutic process and survival rate have not been changed significantly since there is still an important challenge for early detection. Type I tumors are not as lethal as type II tumors and they are caused by a continuous cycle of ovulation, uterine ampoule and endometriosis and it is believed that endometriosis increases the risk of ovarian cancer in women [4,33,34]. The signs and symptoms of ovarian cancer have been unknown throughout history because they contain a number of symptoms that a woman may feel every day, such as: Abdominal flatulence abdominal pain frequent urination early satiety and changes in bowel habits. Genetic prediction shows that family history increases the risk of ovarian cancer. Mutations in the BRAC2 and BRAC1 (tumor suppressor genes) and MMR genes are primarily associated with genetic risk of ovarian cancer and they can increase the incidence risk from 1.6 % to 40 % [1,35-37]. If the number of ovulations increase, the tendency for ovarian cancer will increase and also some factors that cause ovulation to stop, such as: pregnancy control, premature menstruation, pregnancy, breast-feeding and premature menopause can reduce the risk of ovarian cancer [35,38,39]. The lack of a high-confidence screening in the early stages of ovarian cancer unfortunately cause this cancer to be diagnosed at last stage that only 15 % of patients have metastatic tumors [40].

Biomarkers and ovarian cancer detection algorithms

Early detection and prevention of the ovarian cancer development to an invasive and dangerous disease can be the most effective way to save lives. During consecutive years, measuring carbohydrate antigen 125 (CA 125) and ultrasonography and pelvic examinations have been used as diagnostic tests for the presence of endothelium ovarian

cancer (EOC) [41]. And since further evaluation usually involves non-invasive surgery, so false positive results can lead to intervention of unnecessary surgery [42]. Screening test in prostate, lung, colorectal, breast and ovarian cancers does not reduce mortality but only reduces unnecessary surgical interventions [43]. In laboratory tests, several tumor markers are evaluated which carbohydrate antigen 125 (CA125) is one of the diagnostic tests that first time was reported to be increase in ovarian cancer at serum in early 1980 [44]. This marker is less sensitive in the early stages of cancer [45]. The marker CA125 is elevated in physiological or pathological conditions such as menstruation-pregnancy and endometriosis and inflammatory diseases [46]. Carbohydrate Antigen 125 is a mucin-type glycoprotein produced by the MUG16 gene and associated with the cell membrane. This biomarker is often used in ovarian lesions [44]. In meta-analysis, Fara et al Showed that the sensitivity and reliability of this marker in the diagnosis of ovarian cancer was 78 % [47]. Also, due to the low sensitivity of this marker, it is possible to use other biomarkers such as the human epididymis protein (HE4) to improve ovarian cancer characteristics. HE4 is a novel marker that is currently is being evaluated for diagnosis of malignant tumors [48]. This glycoprotein belongs to the family of four disulfide nuclear proteins whose alternative name is WFDC2, and encoding the key genes of WAP protein is mainly done on chromosome 20q12-13.1 [49] and WAP consist of about 50 amino acids, whose biological function is still unclear [50]. Yanaranop et al reported that the sensitivity of HE4 in cancer detection is 86 % [51,52] and a study of 387 patients showed that the HE4 marker is more reliable for diagnosing ovarian epithelial cancer than CA125 [53]. Increasing the level of HE4 depends on two factors: 1) age increasing 2) using Tobacco [54-56] in smokers, the level of HE4 should always be interpreted with caution because false positive results may be reported [57]. And since other biomarkers such as the RMI (Risk of malignancy index) may be more sensitive, so they can be more reliable in detecting ovarian cancer. RMI was suggested by Jacobs et al in 1990 and its sensitivity for ovarian cancer detection is 92.4 % , so this sensitivity can be increased by altering the threshold level of malignancy [58]. To describe tumor markers and screening tests, the receiver operating characteristic (ROC) area under the curve (AUC) can be used, as it is a useful graphical tool for comparing biomarkers and algorithms. The ROC can evaluate the diagnosis between having and not having the disease, i.e., evaluating the

differentiating of a test [59]. In screening studies, the use of AUC can be a useful indicator for the diagnosis of ovarian cancer [60]. In a comparison between RMI and other biomarkers, it is shown that RMI is not the most useful diagnostic tool for ovarian cancer. By using CA125, sonography findings and menopausal status according to the formula: RMI U x M x CA125, we can calculate the rate of ovarian cancer malignancy by this algorithm [61]. In diagnosing ovarian cancer, CA125 is not evaluated alone and cannot provide a definitive opinion about ovarian cancer, but always should be used in comparison to patient data an appropriate imaging (sonography) and another tumor marker that can differentiate between Benign and malignant ovarian cancers [62]. The Food and Drug Administration in USA (FDA) has approved the HE4 marker as a more appropriate commercial marker for monitoring epithelial ovarian cancer patients [63]. This biomarker is expressed low in epithelium tissues of respiratory organs and reproductive organs, but is more expressed in ovarian tumors, especially in endometriosis ovarian cancer [64] and It is also highly expressed in the human trachea, salivary glands, lung, prostate, pituitary, thyroid and kidney [65]. HE4 has also been evaluated as an independent prognostic marker in abnormal lung cancer cells [64]. In 2009, Moore et al introduced another biomarker called Risk of Ovarian Malignancy Algorithm (ROMA) helped differentiate benign pelvic tumors from epithelial ovarian cancer and was able to predict ovarian masses with high sensitivity to other markers, as well as ROMA is calculated in women before and after menopause [60]. These markers are summarized in Table 1.

Table1. The sensitivity and reliability of significant ovarian cancer biomarkers: This table shows the sensitivity and reliability of all markers mentioned for ovarian cancer tests, their differences, and also the degree of satisfaction

Diagnostic markers	Satisfaction	Type of diagnosis	Reference
CA 125	78 %	Ovarian lesions	[47]
HE4	86 %	Diagnosis of malignant tumor	[51, 52]
RMI	92.4 %	Ovarian cancer diagnosis	[58]
ROMA	97 %	Differentiation of benign pelvic masses from ovarian cancer	[64]

Today the best biological diagnostic tool seems to be a combination of CA125 and HE4 levels to predict the risk of ovarian cancer in patients with suspected benign ovarian tumors. If the level of CA125 as well as the level of HE4 be elevated together, resolving the malignant lesion and therefore predicting surgical treatment for anatomopathological examination is essential. Serum HE4 levels are different in smokers and in users of hormonal contraceptives, so it seems necessary to always insert this information in the patient's clinical history. However, since the level of CA125 is independent on these variables, simultaneous measurement of these two markers makes it possible to correct any possible changes in such specific cases [61].

Clinical, pathological and molecular heterogeneity of ovarian cancer

The view taken from ovarian cancer is that the carcinoma begins in the ovary and spreads to the pelvic and abdominal cavities before metastasis to other sites [6]. One of the major problems in describing the pathogenesis of ovarian cancer is that it is a heterogeneous disease and it is composed of different types of tumors with different characteristics [5]. The traditional view of ovarian cancer is that, different tumors all originate from the epithelium of the ovarian surface (mesothelioma) and subsequent

metaplastic changes result in making different cell types (serous, endometrioid, clear, mucosal, and transitional) that morphologically resemble the epithelial of the fallopian tube, endometrium, digestive tract, endocrine, bladder, and urinary tract [8]. However, the normal ovary does not have any compounds that look like these cells. In addition, the cervix, endometrium, and fallopian tubes are arised from the molar ducts. While both ovaries are arised from mesoderm epithelium at the border of the genitourinary tract, separately from the molar ducts. Thus, an alternative theory suggests that tumors with a molar phenotype (serous, endometrioid, and clear cell) are derived from the mullerian tissue rather than the mesothelioma [66]. The most convincing evidences suggest that the most of the primary ovarian cancers, named serous, endometrioid, and clear cell cancer, originate from the fallopian tubes and endometrium, not directly from the ovary [67]. Unlike other solid tumors, it is thought that biological behavior of ovarian cancer is unique. Most patients with this cancer are usually diagnosed in late stages, and the disease is mainly found in the peritoneal cavity. In summarize, the dual model incorporates the nature of OC heterogeneity. The main histological types of ovarian cancer can be divided into groups I and II based on their distinct genetic characteristics. Genetically, type I tumors are stable and limited to one ovary and have a good prognosis, so called borderline tumors and are characterized by mutations in a number of different genes, including KRAS, BRAF, PTEN, CTNNB1, ARID1A, PP2R1A.On the other hand, type II tumors are aggressive and rapidly growing and in 75 % of cases are diagnosed in the late stage. They are not restricted to one ovary and have a poor prognosis and are mainly characterized by mutations in the TP53 gene. This group of tumors are genetically too unstable and include high-grade serous cancer, endometrioid and malignant mesodermal tumors [5,6,64]. The vast majority of what is considered ovarian cancer belongs to Type II that in terms of tissue subgroups, there are differences between ethnic and racial groups and particularly the prevalence of clear cells adenocarcinoma is high in Japan [68]. Heterogeneity in the tumor microenvironment is recognized as an important factor in the tumor. Ascites in ovarian cancer patients create a heterogeneous environment in the microenvironment of inhibitory tumors in vivo. In addition, Macrophage (M1) and unlike Macrophage (M2) increase ovarian cancer metastasis through activation of NFKB, these cases support the existence of clinical-pathological and molecular

heterogeneity in ovarian cancer caused by stromal cells, etc. in tumor microenvironment [69]. Intra-Tumor Heterogeneity of ovarian carcinoma (ITH) has been documented for several decades. Rudolph et al. Have investigated the tumor heterogeneity morphologically and by karyotyping and cytogenetic technologies in the 1980s and microenterprise technology in the late 1990s.It has led to numerous studies that confirm the heterogeneity of tumors in qualitative ways. The use of NGS technology in human tumors has shown that ITH is more common in many types of human cancers, including ovarian cancer. NGS is used for molecular characterization of tumors and identify new drug targets and select appropriate patients for clinical trials [70]. There is little accumulation of new mutations during metastasis and interestingly, only 6 % of the mutations are of the common type and most of them are somatic and these studies show that metastatic potential may be present in the early stage of ovarian cancer development [70]. In 1992, Jacob et al performed several analyzes to determine the clonal origin of metastasis in ovarian cancer. This study emphasizes that most ovarian cancer metastases are based on genetic alteration patterns involving the loss of heterozygotes mutation in p53 gene and inactivation of the mononuclear chromosome [64]. Numerous studies reported that early metastases are related to the same genomic alteration patterns and it supports this notion that major genetic changes in ovarian cancer occur in the primary tumor and also malignant cells of ovarian cancer exist in ascites cells [70]. In addition, Payne et al reported that ovarian cancer is both bilateral and monoclonal simultaneously. However, primary and metastatic tumors that developed after separation rarely show mutations found in type I tumors [71]. Interestingly, the most common mutated genes in all groups were PIK3A TP53 and KRAS, but there are differences between subgroups due to the frequency of these genetic mutations. Previous reports have shown that the PIC3A and KRAS mutations are respectively important mutations in clear cells and mucosal subgroups [68]. The endometrial histology subgroup of ovarian cancer is similar to endometrial cancer histologically and from molecular aspect. They express KRAS-ARID1-PTEN-PIK3A and CTNNB1 mutations but they are genetically different because the frequency of PTEN and CTNNB1 mutations is significantly different between these two malignancies [72]. Recent studies have highlighted the importance of molecular signaling pathways, for example, the MAPK signaling pathway is important for the cellular response to a variety of

growth and differentiation factors and to cause a mutation in KRAS or one of its downstream genes, called BRAF, (KRAS and BRAF mutations are separated), which has led to the activation of signaling constructs with MAPK-mediated in more than half of the APST, MPSC [73-76]. In addition, an adhesion mutant bp12 called ERBB2 encoding (HER2/NEU), which activates an upstream K-RAS regulator, has been identified in 9 % of these tumors. Interestingly, tumors with ERBB2 mutation lack the KRAS and BRAF mutations [77,78]. Accordingly, 60-70 % of APSTs, MPSCs, and LGSCs express active MAPK [79]. They rarely have a TP53 mutation. Recent studies have more elucidated the molecular pathogenesis of APST, MPSC and LGSC. Unlike LGSCs, HGSCs has TP53 mutation in 95 % of cases, but rarely contains a KRAS or BRAF mutation [80]. Aside from the TP53 mutations, there are no other mutations consistently found in scattered HGSCs (non-familial) except from BRCA1 and BRCA2 mutations, which are characteristic of familial HGSCs. On the other hand, inactivation of BRCA1 and BRCA2 genes by other mechanisms, such as BRCA1 promoter hyper methylation, occurs frequently and therefore Inactivation of BRCA1/2 by mutation or other mechanisms occurs in 40–50 % of dispersed HGSCs [81]. The most prominent molecular feature of HGSC is the extent of dispersal and high number or copies of DNA including cyclin CCNE1(E1, NOTCH3, AKT2, RSF1) and the PIK3CA sites [82]. Despite the molecular differentiation of ovarian cancer, LGSC and even an APST is sometimes occurred simultaneously with HGSCs and it shows that such progress rarely happens [83]. According to genome-wide mutation analysis, the most common molecular genetic alteration in clear cell carcinoma is a mutation in ARID1A gene [84,85]. There is a mutation in the PIK3CA gene activator in approximately 50 % of ovarian tumors, and deletion of PTEN gene, a tumor suppressor gene that is involved in the PI3K/PTEN signaling pathway and in the clear cell carcinoma progression [86]. Clear cell cancer, mutations that break down PI3K/PTEN signaling are common in low-grade endometrial carcinoma and indeed, mutations in the PTEN tumor suppressor gene, which rarely occur in other types of EOC, have been reported in approximately 20 % of low-grade ovarian endometrioid carcinomas [87,88]. Another mechanism where activation of PI3K signaling occurs is through activation of PIK3CA mutations [79]. The wnt/b-catenin signaling pathway, which is involved in the regulation of several important cellular processes including

proliferation, motility and survival (about 40 % of ovarian endometrial carcinomas) is are usually regulated by activation of CTNNB1 mutations (a gene encoding beta-catenin) [89]. The oncogenic mutations in KRAS-BRAF-ERBB2 lead to activation of the signaling transduction pathway MAPK mitogen activated kinase protein, which plays an important role in transmitting growth signals to the nucleus and help the variable evolution [73,90]. Previous studies have shown that the KRAS mutation at codon 12-13 occurs in 1/3 of invasive low-level MAPSCs and another 1/3 occurs in SBT Serous Borderline Tumor. Similarly, the BRAF gene at codon 600 occurs in 30 % of low-grade carcinomas and 28 % of SBTs [73]. Mutations in BRAF-KRAS-ERBB2 are cross-linked. Therefore, mutation in each gene is observed in about 2/3 of MPSCs and APSTs. In contrast, these genes do not mutate in high serous carcinoma [73,78,90]. The KRAS and BRAF mutations seem to occur very early in the development of low-grade MPSCs. It was found that the same KRAS and BRAF mutations in SBTs are detected in the adenoma cyst epithelium adjacent to the SBTs [80]. The mutation in TP53 is low. Studies show that most advanced-stage of high-grade serous carcinomas have mutated TP53 with a mutation frequency of over 80 % [91]. The TP53 mutation is present in 37 % of primary serous cancers [92]. Figure 1 lists a general summary of the types of ovarian cancer that include a general classification of the genetic features and cells involved in this malignancy, as well as the genes that cause the metastasis and incidence of the cancer. And most of the mutations that are expressed are somatic mutations that have been expressed in the early stages of cancer.

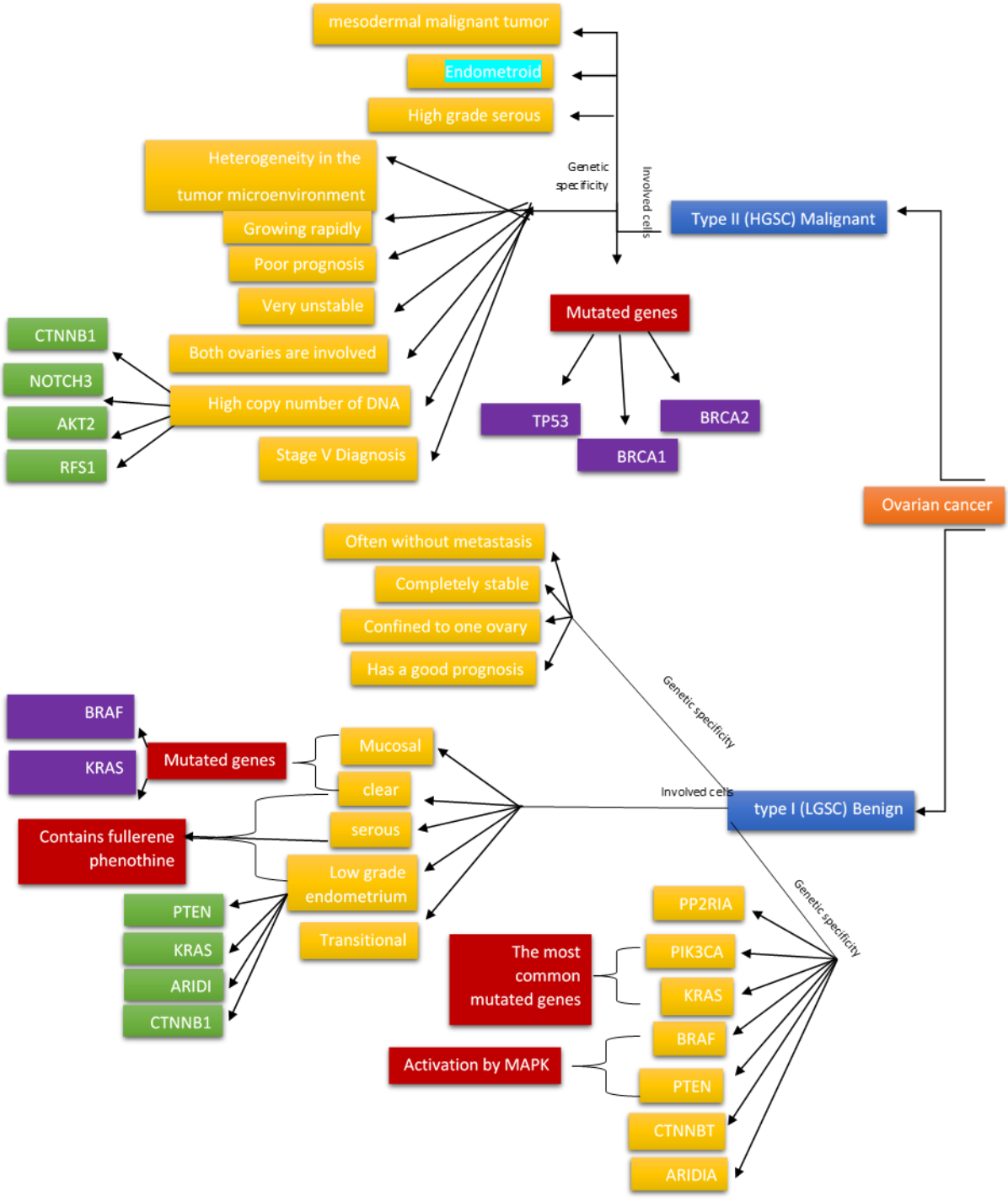

Figure1. Different type and characteristics of ovarian cancer: This figure summarizes the types of ovarian cancer tumors, along with the genetic characteristics of each group and the mutated genes that cause the malignancy.

Ovarian cancer treatment

Ovarian cancer is usually diagnosed in the late stages but recently with pharmaceutical advances and surgical technology and treatment regimens, the disease has been diagnosed shortly before its end stage. Many new drugs are currently being tested and they have been tested in clinical trials to evaluate their effectiveness in ovarian cancer. New drugs are mainly directed against molecular pathways and prevent the proliferation of cancer cells, tumor growth and release of death signals is essential. For example, angiogenesis factors are inhibitor of growth factor signaling, inhibitor of growth factor and inhibitor of Poly-ADP Ribose Polymerase (PARP). In addition, many therapeutic safety approaches have been tested. These new agents have not shown therapeutic approaches to treat ovarian cancer so far, but may lead to delayed relapse or fixation of the disease. However, the prospects for treating ovarian cancer with the heterogeneity of these tumors are complex. Different histological types of ovarian epithelial cancer have distinct cellular origins and diverse spectrum of mutations have different prognosis [68,93]. Even in one type of histology different molecular subgroups with different prognosis were found [94,95]. To address these cases, we need better description of these differences and find reliable biomarkers and develop therapeutic approaches. Many studies are done by focusing on the discovery of biomarkers, but few eventually enter the clinical phase [96].

Ovarian cancer treatment standards

For treatment of ovarian cancer, it should be attempted to determine the type of tumor tissue including its grading [97]. High-grade and low-grade scales are currently used for diagnosis. But in endometrial ovarian cancer, a triple scale (G1/G2/G3) is used [89]. The evaluation of staging in grades of pathologic surgery should be performed in accordance with current FIGO recommendations [98]. Therefore, according to the ESGO2017 ovarian cancer surgery guidelines, the goal of surgery is to obtain a tumor and remove it completely [99]. After surgery, patients are treated under first-line chemotherapy with intravenous injections of platinum and taxane for 21 days in 6 periods. In patients with stage IA/IB and G1/G2 tumors,

chemotherapy cannot be eliminated. In advanced stages III and IV, cytoreduction is not completely possible. The most common reason for that is a sudden attack on the small intestine and damage to the liver helium. Patients with non-surgical tumors are treated with induction chemotherapy initially because of poor performance, then if they respond to treatment, of the three courses of chemotherapy cycle, they can undergo IDS, then chemotherapy will continue for up to 6 periods [82]. The evaluation of the correct treatment process is determined after the first line of chemotherapy. Evaluation of response to treatment is performed based on imaging results and the recite criteria (response evaluation criteria in solid tumors) [100]. Most patients respond well to first-line chemotherapy, but many unfortunately have a recurrence. For patients with 1cm of tumor remaining, the risk of recurrence is estimated to be 70-60 % and for women with larger mass it is estimated to be 80-85 % [101]. Therefore, they should be periodically controlled. Elevated CA125 levels may be the first symptom of metastasis but if clinical symptoms are not present the second line therapy should not be started and postponing treatment until the clinical signs of the disease do not threaten the patient's survival [102]. This agreement qualifies for clinical trials if the patient has a high serum CA125 level [103]. Phase III clinical trials show that combination of anti-angiogenesis with bevacizumab and weekly dose of paclitaxel in first-line management of ovarian cancer can improve the survival, therefore, both methods can be considered as new standards of care for patient survival. However, they have significant economic consequences and impose different burdens on patients [99]. The results of a European trial for cancer research and treatment in 55971 patients showed that Patients with stage IIIC tumors and with less metastatic tumors than others had a higher survival rate with primary surgery. However, patients with stage 4 and large metastatic tumors were better [104]. Most patients have recurrence with chemotherapy despite high response rates to initial treatment [105]. The main option for treating ovarian cancer is chemotherapy returning which recently, a combination of cytoreductive surgery and intraperitoneal chemotherapy and elevated heat is increasingly being used to manage peritoneal metastases. This method is currently used as a standard treatment for peritoneal metastases from colorectal cancer and in some medical centers is used to treat ovarian cancer patients. In patients

with ovarian cancer, is done in combination with systemic therapy, which begins about 3 weeks after surgery [99].

New targeted therapies in ovarian cancer

Angiogenesis is a dynamic and powerful process that occurs primarily in embryo development-wound healing and in response to ovulation. At the same time, it can be inappropriately activated in many pathological conditions such as cancer diabetes as well as numerous disorders including ischemic-inflammatory-infection. Growth factor cytokines, integrins, matrix protein kinases are some of the well-known regulators of angiogenesis. Key factors in the development of the pathologic vascular network of the tumor are VEGF vascular endothelial growth factor and its signaling pathways. Initially, it is predicted that blocking VEGF signaling in cancer, due to decreased blood supply, inhibits angiogenesis and cause contraction in the tumor [106]. In epithelial ovarian cancer, increasing the expression of VEGF has a prognosis that correlates with tumor grade, tumor stage, and patient survival. Since VEGF receptors are present on the surface of ovarian cells, it seems that VEGF may be involved in the development of this malignancy. With increasing in permeability of intraperitoneal vessels, VEGF is responsible for the formation of ascetic fluids in patients with ovarian cancer, as a result, angiogenic inhibition is one of the new therapeutic options that is widely used in the treatment of ovarian cancer [99].

VEGF inhibition

Bevacizumab is a human recombinant monoclonal antibody against VEGF that blocks VEGF binding to its receptor. It was found that bevacizumab leads to normalization of tumor vessels, reduced tumor pressure, and improved efficacy of cancer treatment. In 2004, this drug was identified as the first clinical inhibitor of angiogenesis in the United States [107]. In 2011, based on GOGO218 and ICON7 trial data, bevacizumab obtained the European Commission's license for first-line treatment with standard chemotherapy in women with OFPC improve [108]. In 2014, the Food and Drug Administration (FDA) approved bevacizumab with paclitaxel and paclitaxel or PEGylated liposomal doxorubicin for the treatment of patients with epithelial ovarian cancer, who are resistance to platinum-fallopian tube, and primary peritoneal cancer [107]. Phase III clinical trials, examine bevacizumab in ovarian cancer and they are still ongoing

[109,110]. GOG218 designed a 3-step clinical trial to determine if incorporation of bevacizumab into standard chemotherapy improves first-line treatment and improves survival without progress in stages III and IV. Patients in the third phase received bevacizumab only with chemotherapy, which had better clinical results than patients treated without bevacizumab. The absence of a significant difference in PFS between the control group and the bevacizumab group suggests that bevacizumab should go beyond chemotherapy to prevent disease progression [111,112]. Other studies suggest that patients with recurrent ovarian cancer (metastasis) can benefit from bevacizumab, regardless of their sensitivity to platinum therapy [113]. Price reduction should be such that this product is affordable for most health services in the country [99].

VEGF Receptor Inhibitors

Cediranib is an anti-angiogenic multi-kinase inhibitor that acts against all three VEGF receptors. Several clinical trials have been done with cediranib against different cancers, which has produced disappointing results. However, it has shown hopeful results against ovarian cancer. In one treatment group with cediranib for 11 months with chemotherapy was observed that the toxic effect of cediranib was the most common cause of discontinuation, the most common ones were diarrhea, neurodegeneration, hypertension and sound changes. As a result, cediranib can improve the ovarian cancer but cannot prevent recurrence of the disease [114,116].

Pazopanib is a multikinase inhibitor of growth factor receptor VEGFR1-3 derived from platelet α-β and c-KIT. Randomized phase II clinical trials of Mito-11 have investigated the safety and efficacy of Pazopanib in combination with paclitaxel and platinum-resistant ovarian cancer patients and patients. Its side effects include neurotrophy, fatigue, leukopenia, hypertension and anemia. The first interim analysis showed no benefit. Toxicity induced by pazopanib was 4.4 % in the liver and 2.8 % in diarrhea which have been a major complication however, it was advantageous in the treatment of platinum-resistant ovarian cancer. However, further studies are available to investigate the efficacy of this drug [116].

Nintedanib is the next generation of potent triple angiokinase inhibitor of VEGF1-2-3 and FGFR1-2-3 and PDGFRα-β. It has less activity against FIT3-Src-RET. This has

shown significant antitumor activity in several types of tumors in clinical trials [99].

CONCLUSION

Ovarian cancer is the main cause of death worldwide. But with appropriate methods of prevention and development of screening tools it is predicted that this fatal disease may be slightly reduced. The best diagnostic tool is a combination of CA125 and HE4 to predict the risk of ovarian cancer in patients suspected benign tumors. If both CA125 and HE4 levels are elevated and a clinical examination is performed, the patient will undergo surgery. Epidemiological studies that identify genetic environmental and lifestyle factors may increase or decrease the risk of this deadly disease. The use of oral contraceptives has probably observed in the downward trend and it has been more involved in developed countries.

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