The article was received on December 2, 2020, and accepted for publishing on May 23, 2021.

ORIGINAL ARTICLES

Ovarian cancer under the magnifying glass

Ionut M. Cobec[1], Roxana Popescu[2], Aurica E. Moatar[3,4], Doina Verdes[2]

Abstract: *Cancer is a pathology generating problem to the public health systems all over the world.*

The etiology and pathogenesis of ovarian cancer are still partially unknown. It is still a challenge when it comes to the origin, the molecular basis of ovarian carcinogenesis, tumor progression, and therapy options of ovarian cancer.

This paper brings an overview of ovarian cancer, starting with the pathogenesis, histopathological forms, and molecular biology of ovarian cancer, and follows the growth factors as molecular targets for specific therapy.

Keywords: *ovarian cancer, pathogenesis, molecular biology, growth factors*

INTRODUCTION

Ovarian cancer is a pathology that throughout history has sparked both controversy and questions, some of which remain unanswered to this day. Over time we have been working hard towards laying the foundation for the current therapeutic standard in addressing existing ovarian tumors.

Following the epidemiological data and the steps taken gradually by our forerunners in their pioneering work in both surgical as well as drug therapy, but also the new findings in the field and the literature developed, overall representing a rich scientific dowry, we realize that we are faced with pathology that over time rose many difficulties for clinicians, researchers, and patients under therapy.

EPIDEMIOLOGY AND PATHOGENESIS DATA

Cancer is a pathology generating problem to the public health systems in Romania, its incidence being among the lowest in Central and South-East Europe, whilst having a higher mortality rate [1]. Both body functions and immune response are involved in the pathogenesis of cancer and angiogenesis, hypoxia and inflammation can be identified at the cellular level [2].

The etiology and pathogenesis of ovarian cancer are still partially unknown [3, 4].

When determining the origin of ovarian cancer, there are several theories including the theory of the de novo ovarian cancer [5], the hypothesis of the inclusion of cysts [6, 7, 8] based on a Mullerian phenotype causing the malignant transformation of the mesothelial ovarian cortex corresponding to the serous, endometroid, mucinous, clear cell, transition types, but also to the Mullerian epithelium found outside the uterus, fallopian tube, cervix [7, 8, 9, 10, 11]. The fallopian tube may be more or less involved in the origin of serous ovarian cancer, both through the proliferation of fallopian secretion cells and through its vicinity, causing dysplastic lesions, the inclusion cysts formed at the time of ovulation near the fimbria causing the

Corresponding author: Cobec Ionut Marcel
cobec_i@yahoo.com

[1] Clinic of Obstetrics and Gynecology, Diakonie Klinikum, Schwäbisch Hall, Germany
[2] Department of Cell and Molecular Biology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[3] Clinic of Internal Medicine, Hohenloher Krankenhaus, Öhringen, Germany
[4] Department of Pharmacology and Biochemistry, "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania

formation of endosalpingiosis [6, 12, 13], the transformation of epithelial ovarian inclusions, of the serous adenomatous cyst into an ovarian borderline serous tumor which may become invasive carcinoma [14, 15, 16].

PECULIARITIES OF HISTOPATHOLOGICAL FORMS OF OVARIAN CANCER

Ovarian cancer has the following histological types according to WHO (World Health Organization): serous, endometrioid, mucinous (most common), clear cell, transitional cell, squamous cell, and undifferentiated and mixed epithelial. Tumors can be benign, malignant, or borderline, and, depending on the subtype, they can be low grade or high grade (depending on nuclear atypia and mitosis) [17, 18]. Borderline tumors are considered potentially indolent and weakly malignant [19, 20, 21].

Ovarian cancer can be classified as follows: type I consisting of low-grade carcinomas -serous, endometrioid, clear cell, mucinous, and Brenner tumors, they are generally indolent, may have originated in borderline tumors and endometriosis, showing molecular entities such as KRAS, BRAF, ERBB2, PTEN, CTNNB1, PIK3CA, and type II consisting of high-grade carcinomas, serous, endometrioid, mixed mesodermal malignant tumors (carcinosarcomas) and undifferentiated carcinomas, they are generally aggressive, characterized by genetic instability, may have originated in intraepithelial carcinoma of the uterine tube, their molecular entity presented as mutations at the TP53 level [19, 20, 21, 22, 23, 24]. Both types may have originated in the extra ovarian tissue that can be implanted in the ovary [25].

Following the changes made in the FIGO staging, a new staging resulted. As recommended by FIGO, it is indicated that histology, including the grading, should be part of the staging process and also that the primary site (ovary, fallopian tube, peritoneum) should be mentioned where possible, and if this is not possible, this also must be mentioned. The damage to the retroperitoneal lymph nodes must be proven histologically or cytologically and stage I tumors with dense adhesions can be classified as stage II if malignant cells are proven to be histologically present [6, 26]. According to the International Agency for Research on Cancer (IARC), from histology's point of view, we can differentiate between carcinomas (serous carcinomas, mucinous carcinomas endometrioid carcinomas, clear cell carcinoma, NOS adenocarcinoma, other specific carcinomas, nonspecific carcinomas), sex-cord stromal tumors, germ cells tumors, other specific cancers (these including malignant Brenner tumors, carcinosarcomas, mixed Mullerian tumors), non-specific cancers [27, 28].

MOLECULAR BIOLOGY OF OVARIAN CANCER

The molecular basis of ovarian carcinogenesis and progression are not yet fully elucidated, considering the genetic and epigenetic alterations that translate into alterations of the molecular signaling pathways involved in survival, proliferation and cell death, adhesion, and angiogenesis.

Carcinogenesis involves inadequate adjustment mechanisms of the signaling pathways governing cell cycle, differentiation, apoptosis, expression of oncogenes and/or antioncogens, the action of transcription, and growth factors [29, 30, 31].

Amongst the RB family members, the RB gene (retinoblastoma gene) is involved in ovarian carcinogenesis. The majority of malignant ovarian tumors have had a strong expression of the pRb about a normal ovary where the protein is barely detectable [32, 33]. It was demonstrated that overall survival was positively influenced by the positive expression of p21 and p27 in patients with negative p53 only [34]. The p53 is the most relevant oncosupressor gene. Inactivation of the p53 oncosupressor gene's function appears to be an early event in hereditary ovarian cancer induction characterized by germ mutations of the BRCA1 tumor suppressor gene. The somatic mutation of p53 is the most common molecular change that occurs in epithelial ovarian cancer. The immune-histochemical expression of p53 protein was associated with the highly differentiated serous type, positive cytology, residual tumor, and stage of disease [4, 35, 36, 37, 38].

Studies in the specific literature suggest that the expression of Bcl-2 and Bax is an important prognostic marker [39].

The ovary is subject to cyclical changes where the angiogenesis process is continuous [3]. VEGF (vascular endothelial growth factor) is a growth factor that stimulates the angiogenesis process and increases microvascular permeability [40]. Ovarian cancer causes the release of VEGF in response to conditions of hypoxia and acidity, the serum and ascitic fluid VEGF values being elevated with malignant tumors as opposed to benign [40, 41, 42 43]. Type I and II ovarian tumors differ in molecular-genetic evidence just as much as they differ morphologically [44].

High-grade serous ovarian cancer, which is part of type II tumors, has frequently known mutations of TP53 (in more than 80% of cases) and amplification of CCNE1, which are characteristic of type II tumors, but rarely mutations that characterize type I tumors such as KRAS, BRAF, ERBB2, PTEN, CTNNB1 and PIK3CA [44, 45, 46, 47]. Type I tumors are more stable genetically and show distinctive pattern mutations

that happen in a particular cell type, as opposed to type II which present morphological and molecular homogeneity, are genetically unstable with a high-frequency mutation of TP53, thus suggesting that ovarian tumors develop on different molecular pathways [44, 48]. The mutations in the KRAS or BRAF lead to subsequent activation of the MAPK signaling pathway (mitogen-activated protein-kinase) [49, 50]. It was shown that some inflammatory markers, glucose protein transporter 1 (Glut-1), iNOS, cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), nuclear factor kappa B (NF-kB) are involved in the initiation and progression of cancer [51, 52]. Immunohistochemical analyses showed statistically increased levels of expression of Glut-1, iNOS, COX-1, COX-2 in type II ovarian tumors, but no statistical difference of expression of NF-kB in ovarian tumors type I and II [52].

Researchers have identified five molecular subtypes presenting clinicopathological characteristics and survival rates for ovarian epithelial cancer, which are: Epi-A, Epi-B, Mes and Stem-A, and Stem-B. Epi-B and Stem-A subtypes are independent prognosis factors [53].

The BRCA1 gene was often studied because of the proven implications in the transmission of hereditary breast and ovarian cancer. In molecular terms, we distinguish as follows: low-grade serous ovarian carcinoma presents KRAS and BRAF mutations, and the high-grade present mutations of TP53 and abnormalities of BRCA. Serous high-grade ovarian carcinoma shows an increased nuclear expression of Ki-67 and has immunoreactions for p53, BRCA1, WT1, p16. Mucinous ovarian carcinoma presents KRAS mutations in its tumorigenesis, which are immunoreactive for CK7 and CK20. Endometrioid ovarian carcinoma shows mutations of the β-catenin (CTNNB1), PTEN, and ARID1A. Endometrioid ovarian carcinoma is immunoreactive for vimentin, CK7, CK20, the epithelial membrane antigen, estrogen, and progesterone receptors. Ovarian clear cell carcinoma presents ARID1A mutations, lack of protein BAF250, is positive for HNF1-β, and is negative for ER and WT1 [5, 54, 55, 56, 57, 58].

GROWTH FACTORS AS MOLECULAR TARGETS FOR SPECIFIC THERAPY

Knowing that VEGF is involved in tumor growth, invasion, and dissemination to the lymph nodes, liver, lungs, numerous drug agents are being used with the target role occupied by VEGF in ovarian cancer, especially when peritoneal carcinomatosis and/or ascites are present. One of the agents used in neutralizing the VEGF is bevacizumab, a recombinant humanized monoclonal antibody that stops the binding of VEGFRs on all the VEGF isoforms, thus preventing tumor growth and ascites production. Paclitaxel can be used in combination with bevacizumab acting synergistically and with the same effects. Bevacizumab used in combination with cisplatin increases the survival rate [59, 60, 61].

Agents acting as inhibitors of tyrosine kinase receptors are counted as VEGFR antagonists (Ramucirumab, Cediranib, Semaxanib) and agents that have as target multiple tyrosine kinase receptors (Sunitinib, Sorafenib, Vatalanib, Intedanib, Pazopanib, Motesanib, Vandetanib, AEE788) [62, 63].

VEGF overexpression in ovarian cancer makes it a therapeutic target, thus aiming at the inhibition of neo-vascularization, but also anti-angiogenic agents. VEGF is a dimeric protein, a member of the VEGF/PDGF, including VEGF-B, VEGF-C, VEGF-D, PIGF, and PDGF, involved in angiogenesis, proliferation, survival, migration of endothelial cells and stimulated by hypoxic conditions [12, 60, 64, 65].

Anti-VEGF therapy has been shown to play an important role in female patients with primary and recurrent ovarian cancer [60, 61, 66]. The use of bevacizumab can have aggressive complications that can lead to death, the risk is even higher when used in combination with chemotherapy, particularly platinum-based (cisplatin, carboplatin, oxaliplatin) or taxanes (paclitaxel, docetaxel) [66, 67, 68, 69]. As standard therapy in advanced ovarian cancer, cytoreduction surgery followed by platinum-based chemotherapy is used with a fairly good response, but sometimes resulting in tumor recurrence within 5 years and therapeutic resistance [66]. In case of resistance to platinum other chemotherapeutics are used such as metronomic paclitaxel, docetaxel, topotecan, liposomal doxorubicin, etoposide, gemcitabine, but the response is quite limited with a fairly low survival rate [50]. Attempts have been made to develop different therapies aiming at the interruption of angiogenesis, molecular target, inhibition of the Poly- (ADP) Ribose polymerase function (PARP), growth factors such as insulin-like growth factor (IGF) [70, 71]. Treatments often target the vascular endothelial growth factor pathway (using bevacizumab or aflibercept), the mechanisms of DNA repair (using iniparib or olaparib), or are guided against folate ways (using pemetrexed farletuzumab, vintafolid) [61].

Oral therapy with olaparib is currently being used as maintenance therapy, this being a PARP inhibitor used on patients with recurrent serous ovarian cancer sensitive to the platinum-based therapy, where the existence of mutations in BRCA has been proven and where the patient had two or more courses of platinum-based chemotherapy and showed a partial or complete response to the most recently used platinum-based chemotherapy [22, 71, 72, 73, 74, 75, 76].

References:

1. Vrdoljak E, Bodoky G, Jassem J, et al. Cancer Control in Central and Eastern Europe: Current Situation and Recommendations for Improvement. Oncologist. 2016;21(10):1183-1190.

2. Singh N, Baby D, Rajguru JP, et al. Inflammation and cancer. Ann Afr Med. 2019;18(3):121-126.

3. Klymenko Y, Nephew KP. Epigenetic Crosstalk between the Tumor Microenvironment and Ovarian Cancer Cells: A Therapeutic Road Less Traveled. Cancers (Basel). 2018;10(9):295.

4. Qian F, Rookus MA, Leslie G, et al. Mendelian randomisation study of height and body mass index as modifiers of ovarian cancer risk in 22,588 BRCA1 and BRCA2 mutation carriers. Br J Cancer. 2019;121(2):180-192.

5. Singh A, Gupta S, Sachan M. Epigenetic Biomarkers in the Management of Ovarian Cancer: Current Prospectives. Front Cell Dev Biol. 2019;7:182.

6. Testa U, Petrucci E, Pasquini L, at al. Ovarian Cancers: Genetic Abnormalities, Tumor Heterogeneity and Progression, Clonal Evolution and Cancer Stem Cells. Medicines (Basel). 2018;5(1):16.

7. Escalona RM, Chan E, Kannourakis G, et al. The Many Facets of Metzincins and Their Endogenous Inhibitors: Perspectives on Ovarian Cancer Progression. Int J Mol Sci. 2018;19(2):450.

8. Yang WL, Lu Z, Bast RC Jr. The role of biomarkers in the management of epithelial ovarian cancer. Expert Rev Mol Diagn. 2017;17(6):577-591.

9. Farra R, Maruna M, Perrone F, et al. Strategies for Delivery of siRNAs to Ovarian Cancer Cells. Pharmaceutics. 2019;11(10):547.

10. Kim J, Park EY, Kim O, et al. Cell Origins of High-Grade Serous Ovarian Cancer. Cancers (Basel). 2018;10(11):433.

11. Motohara T, Masuda K, Morotti M, et al. An evolving story of the metastatic voyage of ovarian cancer cells: cellular and molecular orchestration of the adipose-rich metastatic microenvironment. Oncogene. 2019;38(16):2885-2898.

12. Bregenzer ME, Horst EN, Mehta P, et al. The Role of Cancer Stem Cells and Mechanical Forces in Ovarian Cancer Metastasis. Cancers (Basel). 2019;11(7):1008.

13. Phelan CM, Kuchenbaecker KB, Tyrer JP, et al. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017;49(5):680-691.

14. Vang R, Hannibal CG, Junge J, et al. Long-term Behavior of Serous Borderline Tumors Subdivided Into Atypical Proliferative Tumors and Noninvasive Low-grade Carcinomas: A Population-based Clinicopathologic Study of 942 Cases. Am J Surg Pathol. 2017;41(6):725-737.

15. Soslow RA, Murali R. A guided tour of selected issues pertaining to metastatic carcinomas involving or originating from the gynecologic tract. Semin Diagn Pathol. 2018;35(2):95-107.

16. Wang Y, Hong S, Mu J, et al. Tubal Origin of "Ovarian" Low-Grade Serous Carcinoma: A Gene Expression Profile Study. J Oncol. 2019;2019:8659754.

17. Mathieu KB, Bedi DG, Thrower SL, et al. Screening for ovarian cancer: imaging challenges and opportunities for improvement. Ultrasound Obstet Gynecol. 2018;51(3):293-303.

18. Kulbe H, Otto R, Darb-Esfahani S, et al. Discovery and Validation of Novel Biomarkers for Detection of Epithelial Ovarian Cancer. Cells. 2019;8(7):713.

19. Suh DH, Chang SJ, Song T, et al. Practice guidelines for management of ovarian cancer in Korea: a Korean Society of Gynecologic Oncology Consensus Statement. J Gynecol Oncol. 2018;29(4):e56.

20. Lalwani N, Prasad SR, Vikram R, et al . Histologic, Molecular and Cytogenetic Features of Ovarian Cancers: Implications for Diagnosis and Treatment. RadioGraphics. 2011; 31:625–646.

21. Karst AM, Drapkin R. Ovarian Cancer Pathogenesis: A Model in Evolution. Hindawi Publishing Corporation Journal of Oncology. 2010; 2010:1-13.

22. Cobec IM, Sas I, Pirtea L, et al. Podoplanin as Key Player of Tumor Progression and Lymph Vessel Proliferation in Ovarian Cancer. Anticancer Res. 2016; 36(10):5265-5272.

23. Temkin SM, Bergstrom J, Samimi G, et al. Ovarian Cancer Prevention in High-risk Women. Clin Obstet Gynecol. 2017;60(4):738-757.

24. Ahmed N, Kadife E, Raza A, et al. Ovarian Cancer, Cancer Stem Cells and Current Treatment Strategies: A Potential Role of Magmas in the Current Treatment Methods. Cells. 2020;9(3):719.

25. Castro PT, Aranda OL, Marchiori E, et al. Proportional vascularization along the fallopian tubes and ovarian fimbria: assessment by confocal microtomography. Radiol Bras. 2020;53(3):161-166.

26. Zoung RH. A brief history of the pathology of the gonads. Modern Pathology. 2005; 18: S3-S17.

27. Wahab NA, Othman Z, Nasri NWM, et al. Inhibition of miR-141 and miR-200a Increase DLC-1 and ZEB2 Expression, Enhance Migration and Invasion in Metastatic Serous Ovarian Cancer. Int J Environ Res Public Health. 2020;17(8):2766.

28. Chen VW, Ruiz B, Killeen JL, et al. Pathology and Classification of Ovarian Tumors. Cancer Supplement. 2003; 97(10): 2631-2642.

29. Müllerová Z, Müller T, Křivánková K, et al. Molekulární podstata kancerogeneze epiteliálních ovariálních karcinomů [Molecular Mechanisms of Carcinogenesis of Epithelial Ovarian Cancers]. Klin Onkol. 2016;29 Suppl 4(Suppl 4):46-53.

30. Lisio MA, Fu L, Goyeneche A, et al. High-Grade Serous Ovarian Cancer: Basic Sciences, Clinical and Therapeutic Standpoints. Int J Mol Sci. 2019;20(4):952.

31. Keyvani V, Farshchian M, Esmaeili SA, et al. Ovarian cancer stem cells and targeted therapy. J Ovarian Res. 2019;12(1):120.

32. Patch AM, Christie EL, Etemadmoghadam D, et al. Whole-genome characterization of chemoresistant ovarian cancer [published correction appears in Nature. 2015 Nov 19;527(7578):398]. Nature. 2015;521(7553):489-494.

33. Iness AN, Litovchick L. MuvB: A Key to Cell Cycle Control in Ovarian Cancer. Front Oncol. 2018;8:223.

34. Plisiecka-Hałasa J, Karpińska G, Szymańska T, et al. P21WAF1, P27KIP1, TP53 and C-MYC analysis in 204 ovarian carcinomas treated with platinum-based regimens. Ann Oncol. 2003; 14(7):1078-85.

35. Wang Z, Liu H, Xu C. Cellular Senescence in the Treatment of Ovarian Cancer. Int J Gynecol Cancer. 2018;28(5):895-902.

36. Satapathy S, Kumar C, Singh RK. MicroRNAs as Key Regulators of Ovarian Cancers. Cell Med. 2019;11:2155179019873849.

37. Couch FJ, Wang X, McGuffog L, et al. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. PLoS Genet. 2013; 9(3):e1003212.

38. Prudnikova TY, Villamar-Cruz O, Rawat SJ, et al. Effects of p21-activated kinase 1 inhibition on 11q13-amplified ovarian cancer cells. Oncogene. 2016;35(17):2178-2185.

39. Carberry S, D'Orsi B, Monsefi N, et al. The BAX/BAK-like protein

BOK is a prognostic marker in colorectal cancer. Cell Death Dis. 2018;9(2):125.

40. Bekes I, Friedl TW, Köhler T, et al. Does VEGF facilitate local tumor growth and spread into the abdominal cavity by suppressing endothelial cell adhesion, thus increasing vascular peritoneal permeability followed by ascites production in ovarian cancer?. Mol Cancer. 2016;15:13.

41. Duncan TJ, Al-Attar A, Rolland P, et al. Cytoplasmic p27 expression is an independent prognostic factor in ovarian cancer. Int J Gynecol Pathol. 2010; 29(1):8-18.

42. Gómez-Raposo C, Mendiola M, Barriuso J, et al. Angiogenesis and ovarian cancer. Clin Transl Oncol. 2009; 11:564-571.

43. Sopo M, Anttila M, Hämäläinen K, et al. Expression profiles of VEGF-A, VEGF-D and VEGFR1 are higher in distant metastases than in matched primary high grade epithelial ovarian cancer. BMC Cancer. 2019;19(1):584.

44. Koshiyama M, Matsumura N, Konishi I. Recent concepts of ovarian carcinogenesis: type I and type II. Biomed Res Int. 2014;2014:934261.

45. Bowtell DD, Böhm S, Ahmed AA, et al. Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. Nat Rev Cancer. 2015;15(11):668-679.

46. Ishibashi T, Nakayama K, Razia S, et al. High Frequency of PIK3CA Mutations in Low-Grade Serous Ovarian Carcinomas of Japanese Patients. Diagnostics (Basel). 2019;10(1):13.

47. Prat J, D'Angelo E, Espinosa I. Ovarian carcinomas: at least five different diseases with distinct histological features and molecular genetics. Hum Pathol. 2018;80:11-27.

48. Smolle E, Taucher V, Pichler M, Petru E, Lax S, Haybaeck J. Targeting signaling pathways in epithelial ovarian cancer. Int J Mol Sci. 2013;14(5):9536-9555.

49. Vang R, Levine DA, Soslow RA, et al. Molecular Alterations of TP53 are a Defining Feature of Ovarian High-Grade Serous Carcinoma: A Rereview of Cases Lacking TP53 Mutations in The Cancer Genome Atlas Ovarian Study. Int J Gynecol Pathol. 2016;35(1):48-55.

50. Cho RK. Ovarian cancer update: Lessons from Morphology, Molecules and Mice. Arch Pathol Lab Med. 2009; 133(11):1775-1781.

51. Pratheeshkumar P, Sreekala C, Zhang Z, et al. Cancer prevention with promising natural products: mechanisms of action and molecular targets. Anticancer Agents Med Chem. 2012;12(10):1159-1184.

52. Ali-Fehmi R, Semaan A, Sethi S, et al. Molecular Typing of Epithelial Ovarian Carcinomas Using Inflammatory Markers. Cancer. 2011; 117:301-9.

53. Tan TZ, Miow QH, Huang RYJ, et al. Functional genomics identifies five distinct molecular subtypes with clinical relevance and pathways for growth control in epithelial ovarian cancer. EMBO Molecular Medicine. 2013; 5:983-998.

54. Cline MS, Liao RG, Parsons MT, et al. BRCA Challenge: BRCA Exchange as a global resource for variants in BRCA1 and BRCA2. PLoS Genet. 2018;14(12):e1007752.

55. Murthy P, Muggia F. Women's cancers: how the discovery of BRCA genes is driving current concepts of cancer biology and therapeutics. Ecancermedicalscience. 2019;13:904.

56. Hatano Y, Tamada M, Matsuo M, et al. Molecular Trajectory of BRCA1 and BRCA2 Mutations. Front Oncol. 2020;10:361.

57. Rein BJD, Gupta S, Dada R, et al. Potential Markers for Detection and Monitoring of Ovarian Cancer. Journal of Oncology. 2011 doi:10.1155/2011/475983.

58. Prat J. New insight into ovarian cancer pathology. Annals of Oncology. 2012; 23 (10):111- 117.

59. Zhang L, Zhou Q. Bevacizumab with dose-dense paclitaxel/carboplatin as first-line chemotherapy for advanced ovarian cancer. Eur J Pharmacol. 2018;837:64-71.

60. Moghaddam SM, Amini A, Morris DL, et al. Significance of vascular endothelial growth factor in growth and peritoneal dissemination of ovarian cancer. Cancer Metastasis Re. 2013; 31:143-162.

61. Leamon CP, Lovejoy CD, Nguyen B. Patient selection and targeted treatment in the management of platinum-resistant ovarian cancer. Pharmacogenomics and Personalized medicine. 2013; 6:113-125.

62. Mallmann-Gottschalk N, Sax Y, Kimmig R, et al. EGFR-Specific Tyrosine Kinase Inhibitor Modifies NK Cell-Mediated Antitumoral Activity against Ovarian Cancer Cells. Int J Mol Sci. 2019;20(19):4693.

63. Choi HJ, Armaiz Pena GN, Pradeep S, et al. Anti-vascular therapies in ovarian cancer: moving beyond anti-VEGF approaches. Cancer Metastasis Rev. 2015;34(1):19-40.

64. Paik ES, Kim TH, Cho YJ, et al. Preclinical assessment of the VEGFR inhibitor axitinib as a therapeutic agent for epithelial ovarian cancer. Sci Rep. 2020;10(1):4904.

65. Moghaddam SM, Amini A, Morris DL, et al. Significance of vascular endothelial growth factor in growth and peritoneal dissemination of ovarian cancer. Cancer Metastasis Rev. 2012; 31:143-162.

66. Sato S, Itamochi H. Neoadjuvant chemotherapy in advanced ovarian cancer: latest results and place in therapy. Therapeutic Advances in Medical Oncology. 2014; 6(6):293-304.

67. Li M, Kroetz DL. Bevacizumab-induced hypertension: Clinical presentation and molecular understanding. Pharmacol Ther. 2018;182:152-160.

68. Coleman RL, Spirtos NM, Enserro D, et al. Secondary Surgical Cytoreduction for Recurrent Ovarian Cancer. N Engl J Med. 2019;381(20):1929-1939.

69. Bottoni C, Scambia G, Fagotti A, et al. The safety of bevazicumab for the treatment of ovarian cancer. Expert Opin Drug Saf. 2018;17(11):1107-1113.

70. Liefers-Visser JAL, Meijering RAM, Reyners AKL, et al. IGF system targeted therapy: Therapeutic opportunities for ovarian cancer. Cancer Treat Rev. 2017;60:90-99.

71. Gomez MK, Illuzzi G, Colomer C, et al. Identifying and Overcoming Mechanisms of PARP Inhibitor Resistance in Homologous Recombination Repair-Deficient and Repair-Proficient High Grade Serous Ovarian Cancer Cells. Cancers (Basel). 2020;12(6):1503.

72. Hirotsu Y, Schmidt-Edelkraut U, Nakagomi H, et al. Consolidated BRCA1/2 Variant Interpretation by MH BRCA Correlates with Predicted PARP Inhibitor Efficacy Association by MH Guide. Int J Mol Sci. 2020;21(11):3895.

73. Ikegami M, Kohsaka S, Ueno T, et al. High-throughput functional evaluation of BRCA2 variants of unknown significance. Nat Commun. 2020;11(1):2573.

74. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patientins with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomized phase 2 trial. Lancet Oncol. 2014; 15:852-61.

75. Oza AM, Cibula D, Benzaquen AO, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a

randomised phase 2 trial. Lancet Oncol. 2015; 16(1):87-97.
76. Cimpean AM, Cobec IM, Ceauşu RA, et al. Platelet Derived Growth Factor BB: A "Must-have" Therapeutic Target "Redivivus" in Ovarian Cancer. Cancer Genomics Proteomics. 2016; 13(6):511-517.