



Ovarian cancer: state of the art and perspectives of clinical research

Ovarian cancer is composed of three histological subtypes: epithelial (90%), germ cell (5%), and sex cord stromal cell (5%) (1). Epithelial ovarian cancer (EOC) is the most lethal gynecological disorder due to lack of effective early detection strategies (2). The forthcoming special series focuses on several key elements that are essential for an understanding of this heterogeneous group of malignancies.

More than one-fifth of EOC have been related to hereditary conditions (3). Particularly, in about 65–85% of hereditary ovarian tumors, the genetic abnormality is a germline mutation in breast cancer genes (BRCA) that causes DNA repair defects. Apart from *BRCA1/2*, several other suppressor genes and oncogenes have been associated with hereditary ovarian cancer (i.e., *TP53*, *BARD1*, *CHEK2*, *RAD51*, and *PALB2*). Screening efforts are likely to be the best way to detect early stage disease, and germline genetic testing should be offered to EOC patients. The analysis should be able to detect damaging variants in all genes associated to ovarian cancer susceptibility. The complexity of genetic testing increases with the high number of involved genes. Next-generation sequencing (NGS) represents a technology for simultaneous multi-gene analysis, by using very low amount of nucleic acids with rapid turn-around time. However, the incorporation of NGS into clinical practice is for several reasons still challenging. Firstly, the ovarian cancer risk is not clear for some of the included genes. Secondly, variant of uncertain significance rates increase as more genes are analyzed. Finally, beyond germline pathogenic variants, somatic mutations may also affect therapeutic choices, and as such upfront tumor sequencing may be equally important to NGS.

Notch pathway plays a crucial role in ovarian cancer and affects the prognosis. Along with vascular endothelial growth factor (VEGF), it is essential in ovarian cancer angiogenesis, whilst it is also related to chemoresistance. Notch targeting with small-molecule inhibitors or antibodies is a promising treatment in early stage of development. Most important targets for Notch blockade are gamma-secretase and Dll4. Navicixizumab is a bispecific anti-Dll4 and anti-VEGF dual antibody, developed in combination with weekly paclitaxel. Furthermore, xanthohumol and withaferin A had *in vitro* efficacy through downregulation of Notch1 and Notch3 (4,5).

High-grade serous is the most common histology of EOC. Homologous recombination (HR) is a mechanism of DNA repair important in the carcinogenesis of this subtype. There is mature evidence that poly (ADP-ribose) polymerase (PARP) inhibitors exploit HR deficiency, especially in *BRCA1/2* mutants. Indeed, olaparib, rucaparib, and niraparib have been approved by the Food and Drug Administration (FDA) and/or European Medicines Agency (EMA) for the treatment of EOC, while veliparib and talazoparib are in the late stage of clinical development (6,7). Combination of PARP inhibitors with chemotherapy has been recommended with the rationale of disrupting base excision repair via PARP inhibition (8).

In addition, encouraging preliminary results support the therapeutic combination of PARP and immune checkpoint inhibitors (ICI). The input of immunotherapy in ovarian cancer is based on the observation that immunosuppressive microenvironments can affect tumour growth, metastasis, and even treatment resistance (8). Results from ongoing trials demonstrated better outcome of the combined strategy as compared to ICI monotherapy. The definition of optimal predictive biomarkers is essential to optimally identify treatment's candidates.

The standard therapeutic strategy of advanced ovarian cancer is cytoreductive surgery (CRS), followed by systemic chemotherapy. However, neoadjuvant chemotherapy prior to interval debulking surgery could represent an equally effective and even better tolerated alternative. Complete cytoreduction represents the most important clinical endpoint of patients undergoing debulking surgery (9). Unresectability is based on clinical, imaging, and biomarker criteria and guide therapeutic decisions (10). Furthermore, intestinal involvement, extra-pelvic disease, hormone levels and patient's profile are additionally proposed prognostic factors that should be taken into consideration prior to surgical decision (11,12).

Hyperthermic intraperitoneal chemotherapy (HIPEC) becomes nowadays an additional therapeutic strategy for candidate patients (13). The efficacy of HIPEC in combination with CRS is based on the fact that hyperthermia enhances tumor penetration and the cytotoxic effects of chemotherapy. It seems that HIPEC does not increase the mortality and morbidity compared to CRS alone. The latest National Comprehensive Cancer Network (NCCN) guidelines recommend HIPEC at interval cytoreduction (14). HIPEC has been better investigated in the recurrent setting, resulted in improved survival (15). Overall, HIPEC should be offered by highly experienced teams in appropriately selected patients.

Serous primary peritoneal carcinoma (SPPC) differ from the primary EOC. It is mostly multifocal, characterized by diffuse micronodular spread, resulting in high tumor burden in upper abdomen and diaphragm. The involvement of separate genetic events at different peritoneal loci, differentiates SPPC from EOC with the unifocal nature (16). Immunohistochemically, it is typically positive for CK7, CD15, S-100, P53, WT-1, ER, and PAX-8 and negative for calretinin. Furthermore, SPPC is distinguished from peritoneal mesotheliomas, which are negative for Ber-EP4 and MOC-31 and positive for calretinin and D2-40 (17). The treatment strategy of CRS-HIPEC in patients with primary or recurrent SPPC is still under investigation. The rationale for the HIPEC is the effective regional control of peritoneal carcinomatosis (18).

Treatment with metformin *in vitro* and *in vivo* has resulted in decreased angiogenesis in metastatic tissues, probably driven by blockage of the mammalian target of rapamycin (mTOR) signaling pathway (19). Furthermore, metformin targets ALDH+ EOC stem cell populations *in vitro*, resulting in suppressed angiogenesis, invasion and migration capabilities of EOC cells (20). Regardless the preclinical evidence, results of studies are inconclusive for the association between metformin treatment and survival in EOC patients with type 2 diabetes (21,22).

Patients with endometriosis have an increased risk of EOC, specifically ovarian clear cell carcinoma (OCCC) and endometrioid ovarian carcinoma EnOC (23). Genetic studies provide possible mechanistic link between endometriosis and ovarian cancer. *ARID1A* mutations coincide with loss of *ARID1A* protein expression in OCCC (46–57%) and EnOC (30%) (24,25). Moreover, conditional homozygous knockout of phosphatase and tensin homolog (PTEN) may drive EnOC. There is also evidence of differential expression of miRNAs in endometriosis and ovarian cancer, mainly linked with epithelial–mesenchymal transition (26). Histone deacetyltransferase (HDAC) inhibitors increase the level of acetylated histones, resulting in reactivation of silenced tumor suppressor genes. FDA has already approved the HDAC inhibitors vorinostat, romidepsin, and panobinostat (27).

Non-epithelial ovarian cancers are histologically and clinically distinct uncommon tumors with more favorable prognosis than EOC. The most frequently diagnosed subtypes are the non-epithelial malignant ovarian germ cell tumors (MOGCTs) and the sex cord-stromal cell tumors, subdivided into several histological types (28). Ovarian small cell cancers and sarcomas are rare and biologically aggressive cancers (1,29). MOGCTs typically occur in children and young women, whilst diagnostic challenges in postmenopausal women result in delayed or suboptimal treatment (28,30). Surgical staging remains the cornerstone in the management of MOGCTs, and approximately 60–70% of MOGCTs are diagnosed at stage I.

In this special series, we tried to review the state of the art of the diagnosis and treatment and share future challenges in ovarian cancer, although several areas warrant further research. We would like to express our sincere gratitude to the authors for their efforts, diligence and commitment.

Acknowledgments

Funding: The authors acknowledge support from the Research and Innovation department of Medway NHS Foundation Trust.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine* for the series “Ovarian Cancer: State of the Art and Perspectives of Clinical Research”. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-2020-oc-14>). The series “Ovarian Cancer: State of the Art and Perspectives of Clinical Research” was commissioned by the editorial office without any funding or sponsorship. SB and NP served as the unpaid Guest Editors of the series. SB serves as an unpaid editorial board member of *Annals of Translational Medicine* from Nov 2019 to Oct 2021. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Submitted Jul 20, 2020. Accepted for publication Aug 05, 2020.

doi: [10.21037/atm-2020-oc-14](https://doi.org/10.21037/atm-2020-oc-14)

View this article at: <http://dx.doi.org/10.21037/atm-2020-oc-14>

Cite this article as: Boussios S, Pavlidis N. Ovarian cancer: state of the art and perspectives of clinical research. *Ann Transl Med* 2020;8(24):1702. doi: [10.21037/atm-2020-oc-14](https://doi.org/10.21037/atm-2020-oc-14)