RESEARCH PAPER

Ovarian Cancer: Advances in Diagnosis, Targeted Therapy, and Precision Medicine

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ABSTRACT

Ovarian cancer is a major gynaecological malignancy with a very high rate of late stage at presentation, high rates of recurrence and significant mortality. This review looks at the epidemiology, pathogenesis, the difficulties of diagnosis and the current and emerging therapeutic options. There are a number of molecular alterations involved in the disease (most notably in the BRCA1/BRCA2 genes) which impact on the disease and its response to treatment. The current management of the disease is cytoreductive surgery and platinum-based chemotherapy with a number of targeted agents now available including PARP inhibitors and anti-angiogenic agents.

The major problems still remain with diagnosis being delayed, with the development of drug resistance and disease relapse. There are a number of emerging therapies in the pipeline including immunotherapy, antibody-drug conjugates and precision medicine. The future lies in the identification of reliable early detection biomarkers, in the development of truly personalised treatment strategies and in a better understanding of the mechanisms of therapeutic resistance. The integration of molecular profiling with novel diagnostic and therapeutic approaches is likely to be key to improving survival and quality of life for patients with ovarian cancer.

Keywords: Ovarian cancer; Early diagnosis; Biomarkers; PARP inhibitors; Targeted therapy

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INTRODUCTION

Ovarian cancer is one of the most deadly gynaecological cancers and a major global public health problem due to its high mortality rate, its heterogeneous molecular profile and the fact that it is very often diagnosed at an advanced stage. It can arise from any of the ovarian cell types (epithelial, germ cell and sex cord stromal) with epithelial ovarian cancer being the most common. In 2022 alone there were an estimated 324,000 new cases and 207,000 deaths from ovarian cancer worldwide [1] making it a significant contributor to cancer burden in women globally. The burden of the disease varies by geography, reflecting differences in population structure, reproductive history, genetic predisposition and access to health care. From an epidemiological standpoint it's a disease that strikes predominantly in middle aged and older women with risk increasing with age. The key risk factors are inherited pathogenic variants in BRCA1 and BRCA2, Lynch syndrome, a family history of ovarian or breast cancer, endometriosis (for certain histologies), and a range of reproductive and hormonal factors. On the other hand oral contraceptive use, pregnancy, breastfeeding and tubal ligation are all associated with a reduced risk in some populations [2,3]. It's a disease which is notoriously difficult to detect early as the presenting symptoms (abdominal distension, pelvic pain, early satiety, urinary symptoms etc) are very non-specific. There is no effective population based screening strategy for asymptomatic women at average risk which means that it's going to be diagnosed at a relatively late stage and that leads to poor clinical

outcomes [2,4]. The aetiology of ovarian cancer is multifactorial and involves the stepwise accumulation of genetic and epigenetic alterations, dysregulated cell signalling, uncontrolled proliferation, resistance to apoptosis, angiogenesis and interaction with the tumour microenvironment. HGSC (high grade serous carcinoma) is by far the most common and aggressive of the epithelial subtypes and is very frequently TP53 mutated with a significant proportion of cases also being homologous recombination deficient (particularly those with BRCA1/2 alterations) [3,5]. There is now a growing body of evidence to suggest that the fallopian tube secretory epithelium is the likely site of origin for many HGSCs. The other histological subtypes (endometrioid, clear cell, mucinous and low grade serous) have very different molecular profiles and clinical features and thus ovarian cancer is far from being a single, biologically homogeneous disease [3,5]. Despite all the advances in surgery, chemotherapy and targeted therapy the management of ovarian cancer is still very difficult. The standard of care is generally cytoreductive surgery combined with platinum based chemotherapy (usually carboplatin and paclitaxel). Bevacizumab, the PARP inhibitors and a range of other biomarker directed therapies have all had a positive impact on the management of some patients. There are still a number of treatment limitations though: patients often present at an advanced stage, not all patients are amenable to complete cytoreduction, there is acquired platinum resistance, there is disease recurrence, there is treatment related toxicity and there is variation in response to therapy depending on the molecular subtype and biomarker profile of the tumour [4–6]. The PARP inhibitors have certainly changed the management of some patients but the benefit is highly context dependent and will vary with the individual patient and the biology of their tumour. Resistance to the agents is a major issue and there are also concerns around haematological toxicity and the very rare occurrence of secondary malignancies [6,7]. The absence of a sufficiently sensitive and specific early detection test and the lack of predictive biomarkers to guide treatment response are still major impediments to improved long term survival. These issues underscore the need for a thorough review that brings together the current understanding of the epidemiology of ovarian cancer, its molecular pathogenesis, the limitations of diagnosis and the state of the art in therapy. There have been a number of reviews and clinical guidelines looking at ovarian cancer and there remains a need for ongoing research into tumour heterogeneity, molecular biomarkers, drug resistance, the development of new targeted agents and novel therapeutic approaches [5,8]. This review therefore aims to provide an up to date overview of ovarian cancer, with a focus on the global burden of disease, the pathogenic mechanisms, the limitations of current therapy and the range of emerging therapeutic options. It will critically appraise the current evidence in order to identify areas of research that may lead to earlier diagnosis and more personalised treatment and ultimately improved outcomes.

METHODOLOGY

A narrative literature review was undertaken to provide an overview of the current state of the art in ovarian cancer, covering the epidemiology, pathogenesis, diagnosis and management of the disease. The literature search was performed using a range of electronic databases (PubMed, Scopus, Web of Science and Google Scholar). Papers on ovarian cancer biology, diagnostic biomarkers, conventional therapy, targeted therapy, immunotherapy and novel therapeutic approaches were included. Emphasis was placed on recent peer-reviewed publications, clinical trials, systematic reviews and relevant clinical guidelines. The literature was then critically appraised and synthesised to highlight the key issues, recent advances and areas for future research.

RESULTS

Global epidemiology and disease burden

Ovarian cancer is still a major global health problem due to its high mortality rate, the fact that it is very often diagnosed at an advanced stage and the high rate of recurrence. GLOBOCAN 2022 data shows that there were some 324,603 new cases and 206,956 deaths worldwide from the disease [9]. The burden of ovarian cancer varies by region of the world, by age structure, by reproductive history, by genetic susceptibility and by access to health care. There is epidemiological evidence of a change in the burden of epithelial ovarian cancer over time with different incidence trends in different countries and regions [10]. This all points to the need for prevention, early detection and treatment strategies to be tailored to the particular characteristics of the population and the health care system in that population.

Age is a major risk factor for epithelial ovarian cancer although the age distribution varies between the different histological subtypes. Germ cell tumours are more common in younger women whereas the epithelial malignancies are predominantly seen in the older population [11-13]. Hereditary risk is also a significant factor with pathogenic variants in BRCA1 and BRCA2 being associated with an increased risk of high grade serous ovarian cancer. Lynch syndrome and a family history of ovarian or other gynaecological cancers are other factors which can be used to indicate increased risk. Endometriosis is also associated with certain subtypes (clear cell and endometrioid carcinomas).

Reproductive and hormonal factors also play a part in ovarian cancer risk. There is an association with reduced risk of ovarian cancer in relation to the use of oral contraceptives and some of the reproductive

factors, though the strength of the association varies considerably between populations and between histological subtypes. This again reinforces the concept that ovarian cancer develops as the result of the interplay of genetic susceptibility, reproductive biology, hormonal factors and acquired molecular changes rather than being the result of a single cause. A key consequence of the epidemiological data is that the actual incidence of ovarian cancer is not necessarily reflective of the true burden of disease. The high rate of mortality is attributable to the fact that it is a disease with very non-specific symptoms, it is notoriously difficult to diagnose at an early stage and it is very prone to recurrence. The UK Collaborative Trial of Ovarian Cancer Screening showed that the various screening strategies that were assessed in the trial did not result in a significant reduction in ovarian cancer mortality, even though they did result in the detection of a number of additional cases [14]. Improved awareness, appropriate assessment of the symptomatic patient, genetic risk assessment and the development of validated early detection strategies all remain key priorities [15].

Molecular pathogenesis and tumour heterogeneity

Ovarian cancer is in fact a collection of several distinct malignancies with different histologies, different molecular profiles and different clinical behaviour. High grade serous ovarian carcinoma (HGSOC) is by far the most common and aggressive of the epithelial subtypes and is almost invariably associated with TP53 mutations, widespread genomic instability and defects in DNA repair. The importance of molecular alterations in HGSOC was established through integrated genomic analysis by the TCGA Research Network which also demonstrated the sheer complexity of the genomic landscape of this disease [16-17]. This has led to a much greater understanding of the biology of ovarian cancer and has in turn informed the development of more targeted treatment approaches. The old view that ovarian cancer arises solely from the ovarian surface epithelium has been considerably modified. It's now well established that a large proportion of high grade serous carcinomas (HGSOC) actually arise in the distal fallopian tube, from the precursor lesions known as serous tubal intraepithelial carcinomas [18-19]. This has major implications for our understanding of disease initiation and for the development of risk reduction strategies in women with hereditary susceptibility. The origin and evolution of ovarian cancers will vary according to histological subtype and so the findings in HGSOC cannot be simply extrapolated to clear cell, endometrioid, mucinous or low grade serous carcinomas.

Genetic instability and defective DNA damage repair are key mechanisms in the development of ovarian cancer. BRCA1 and BRCA2 are genes which code for proteins that are involved in homologous recombination, the high fidelity pathway for repair of DNA double strand breaks. Mutations in these genes can lead to defective DNA repair, genomic instability and malignant transformation. They also create a therapeutic vulnerability which can be exploited by PARP inhibitors in certain patients [20]. This is a classic example of how a better understanding of the pathogenesis of a disease can have a direct impact on clinical management.

Beyond the DNA repair defects, dysregulation of the PI3K/AKT/mTOR and RAS/RAF/MAPK pathways can have an impact on cell proliferation, survival, metabolism and response to stress. These pathways interact with the cell cycle regulators, the apoptotic machinery and a range of other processes which are important in the development of the tumour. The extent of their contribution is different in the various subtypes of ovarian cancer and so it is highly unlikely that there will be a single molecular target that will be effective in all cases. Molecular heterogeneity is therefore a fundamental consideration in the choice of experimental model, in the interpretation of biomarker data and in the design of targeted therapies.

The tumour microenvironment also plays a major role in ovarian cancer progression with interactions between the tumour cells themselves, immune cells, cancer associated fibroblasts, the extracellular matrix and various soluble mediators all able to contribute to angiogenesis, immune evasion and metastatic spread [6,10,12]. Ovarian cancer is a disease that tends to spread extensively within the peritoneal cavity with malignant cells able to survive in the ascitic fluid, form multicellular aggregates and then go on to establish secondary tumour deposits. This is an important consideration in terms of disease management as the behaviour of the tumour is not simply dictated by the genetics of the malignant cells but is also heavily influenced by the nature of the microenvironment in which they exist.

Overall the evidence points to ovarian cancer research incorporating histopathological classification, genomic profiling and assessment of the tumour microenvironment. This could lead to the identification of more clinically meaningful molecular subgroups and provide an explanation for the differing responses to treatment that can be seen in patients with apparently identical disease stages. It also provides a basis for the development of combination therapies that target different mechanisms rather than just one pathway [21-22].

Diagnostic challenges and limitations of early detection

Early detection is still a huge unmet need in the management of ovarian cancer. The symptoms (abdominal bloating, pelvic pain, early satiety, increased abdominal girth, urinary symptoms) are all very non-specific and so often go uninvestigated.

As a result a large number of patients are diagnosed with disease that has already spread beyond the ovaries. Earlier diagnosis could lead to better treatment options but it has been extremely difficult to develop an effective screening strategy given the low prevalence of the disease in the general population and the limitations of the available tests.

Serum CA-125 and transvaginal ultrasound are both useful in the clinical assessment of women, but have significant limitations if used as a screening tool for asymptomatic women at average risk. CA-125 can be raised in a number of benign gynaecological conditions as well as other diseases and indeed some ovarian cancers will not have a substantial rise in CA-125 at all (especially at an early stage). Transvaginal ultrasound can identify adnexal pathology but is not capable of reliably differentiating all malignant from benign lesions. The findings from the UKCTOCS trial showed that screening using CA-125 algorithms and ultrasound did not result in a significant reduction in ovarian cancer mortality.

These limitations underscore the importance of making the distinction between screening, diagnosis, prognosis and treatment response monitoring. A biomarker that is useful for monitoring an established malignancy may well be entirely unsuitable for the detection of early disease. Future work should look at combinations of circulating biomarkers, molecular signatures, imaging findings and clinical risk factors rather than simply positing that one biomarker will be the answer.

Emerging approaches using CTCS, extracellular vesicles and other molecular markers may offer further insights into tumour biology. The extent to which they may be of clinical value will be determined by analytical validity, sensitivity at an early stage, specificity in the presence of benign disease and confirmation in large prospective studies. Until a screening strategy has been shown to have an overall favourable balance of benefits and harms, population screening of asymptomatic women at average risk should not be regarded as a proven preventative strategy [3–5].

Conventional treatment and the problem of recurrence

Epithelial ovarian cancer is generally treated with cytoreductive surgery and platinum-based chemotherapy. The most common first line regimen is carboplatin and paclitaxel. The choice of and timing of surgery will depend on the distribution of the disease, the extent to which complete cytoreduction is feasible and the patient's own clinical condition. In the advanced disease setting treatment may be either primary cytoreduction followed by chemotherapy or neoadjuvant chemotherapy followed by interval surgery, the latter being selected on the basis of clinical assessment and in accordance with established guideline recommendations [23-25].

Although a large number of patients will initially respond to platinum based chemotherapy, disease relapse remains a significant problem. The residual malignant cells may have the capacity to survive chemotherapy in a number of ways including altered drug accumulation, enhanced DNA repair, altered apoptotic signalling and adaptive responses to cellular stress. The resultant selection of a population of treatment resistant cells can have a negative impact on the efficacy of subsequent therapy and on long term disease control.

Platinum resistance is of particular importance as it is associated with a limited number of effective treatment options and with worse clinical outcomes. Resistance is not due to a single mechanism but may be the result of a number of interacting genetic, epigenetic, metabolic and microenvironmental changes [26-29]. This is one of the reasons why simply escalating the intensity of conventional chemotherapy may not be sufficient to overcome resistance and may in fact lead to an increase in treatment related toxicity.

Clinical trials have shown the value of adding treatments in certain treatment settings. GOG-0218 looked at bevacizumab as part of the initial treatment of ovarian cancer and AURELIA looked at bevacizumab in combination with chemotherapy in the setting of platinum resistant recurrent disease. These have been the studies that have really established the clinical utility of anti-angiogenic therapy in particular patient populations. The benefit of treatment is of course highly dependent on the disease setting, the patient population and the treatment regimen and the risk of toxicity must always be borne in mind.

The evidence that is available supports the development of strategies that look at both tumour reduction and the mechanisms of recurrence. A better understanding of the resistant tumour population, in conjunction with biomarker driven treatment selection, may allow us to identify those patients who are most likely to benefit from alternative or combination therapies [20-21].

Targeted therapy and the role of molecular biomarkers

The advent of targeted therapies has had a huge impact on the management of ovarian cancer, especially in the setting of tumours with specific molecular vulnerabilities. PARP inhibitors are a prime example of targeted therapy and work via the principle of synthetic lethality. In cells with a defect in homologous recombination (DNA repair), PARP inhibition leads to an increase in DNA damage and ultimately cell death [11,21–26].

The clinical utility of PARP inhibition has been established in a number of randomised trials. SOLO1 showed that olaparib as maintenance therapy improved progression free survival in

patients with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation who had responded to platinum chemotherapy . PAOLA-1 looked at the use of olaparib in combination with bevacizumab as maintenance therapy and PRIMA assessed the use of niraparib in the setting of newly diagnosed advanced ovarian cancer. ARIEL3 and SOLO2 both looked at the use of rucaparib and olaparib respectively as maintenance therapy in the recurrent setting following response to platinum chemotherapy . NOVA looked at the use of niraparib as maintenance therapy in patients with platinum sensitive recurrent ovarian cancer [30].

Together these trials demonstrate the significance of molecular characteristics and treatment setting in the evaluation of the benefit of targeted therapy. They should not be read as evidence that all patients with ovarian cancer will derive equal benefit from PARP inhibition. The choice of therapy is dependent on a number of factors including biomarker status, prior therapies, disease setting, regulatory guidance and individual clinical circumstances .

PARP inhibitors have a number of important drawbacks despite their clinical benefit. Acquired resistance can occur via restoration of homologous recombination, alterations in DNA replication fork protection and a number of other cellular adaptations which result in reduced sensitivity to DNA damage [19,20]. There are also treatment related adverse effects (anaemia, thrombocytopenia, neutropenia, fatigue and, very rarely, serious haematological toxicities) which need to be carefully monitored. The long term value of PARP inhibitors will therefore depend on patient selection, the balance of efficacy and toxicity and the development of strategies to delay or overcome resistance [31-32].

Antiangiogenic therapy is another form of targeted therapy. Bevacizumab works by inhibiting VEGF-mediated angiogenesis and thus may limit the vascularisation of the tumour. There is clinical evidence from the GOG-0218 and AURELIA trials for its use in selected first line and recurrent disease situations [17,18]. Angiogenesis is of course just one facet of tumour progression and the effect of antiangiogenic therapy will vary according to the clinical situation and the individual patient. It may be of value in some instances to combine antiangiogenic therapy with other therapies but the potential benefits and risks in any such situation would have to be evaluated on the basis of appropriate clinical evidence.

Overall the literature supports the use of molecular testing in the management of disease. The most effective application of precision medicine goes beyond simply identifying a molecular alteration and requires evidence that the alteration is a predictive biomarker for a clinically meaningful benefit from a given therapy. Future studies should therefore focus on validated predictive biomarkers, robust methods of monitoring for resistance and therapeutic strategies that take into account the dynamic molecular evolution of the recurrent tumour [33-34].

Immunotherapy and emerging therapeutic strategies

Immunotherapy has been of considerable interest as immune responses can impact tumour progression and treatment outcomes. Immune checkpoint inhibitors (e.g. antibodies against the programmed cell death protein 1 (PD-1) pathway) are designed to restore anti-tumour immune activity by blocking the inhibitory signals. Clinical studies have demonstrated that the efficacy of checkpoint inhibition varies considerably between patients with recurrent ovarian cancer, suggesting that the therapy is not effective in all patients .

The phase II nivolumab study by Hamanishi et al looking at anti-PD-1 in patients with platinum resistant ovarian cancer provided early clinical evidence of anti-tumour activity in a subset of patients. The subsequent KEYNOTE-100 study looked at pembrolizumab in advanced/recurrent ovarian cancer and found that responses were seen in only a minority of patients . So immunotherapy may be of relevance in a subset of patients, but clearly we need better predictive markers and better combination therapies.

Differences in tumour antigenicity, immune cell infiltration, immune suppression and the tumour microenvironment are all likely to play a part in the variable responses to immunotherapy . Research is ongoing into combinations of immune checkpoint inhibitors with chemotherapy, anti-angiogenics and other targeted agents. These combinations may have complementary mechanisms of action but can also be associated with increased toxicity and should not be regarded as standard of care without appropriate clinical data.

Other emerging strategies are antibody based therapies, inhibitors of specific signalling pathways and approaches that are designed to exploit DNA repair deficiencies. The potential value of these is in targeting biological mechanisms which are not adequately addressed by conventional chemotherapy or by the currently available targeted agents. Indeed promising mechanistic data or early clinical activity in no way establishes superiority over existing therapy. Each approach will require proper assessment of efficacy, safety, patient selection and durability of response.[35-37]

Natural products and their derivatives are also a potential source of compounds for anticancer drug discovery. The structural diversity of these compounds may provide us with chemical scaffolds which in principle could modulate apoptosis, oxidative stress, inflammatory signalling, cell cycle progression and other processes pertinent to cancer biology. Any evidence from computational predictions, isolated cell work or animal studies should be viewed as very preliminary. Confirmation

of the molecular target(s), selectivity, pharmacokinetics, bioavailability, toxicity and therapeutic efficacy is absolutely required before any inference as to clinical benefit can be made.

CRITICAL SYNTHESIS AND FUTURE RESEARCH DIRECTIONS

The totality of the evidence points to a number of interrelated problems which continue to impede progress in the management of ovarian cancer. There is a huge burden of disease and no effective population based screening strategy for asymptomatic women at average risk, thus the need for a more effective early detection strategy is clear [1–5]. The disease is also highly molecularly and histologically heterogeneous which makes it very difficult to identify a therapy that will be effective for all patients [6–12]. Finally, recurrence and acquired resistance remain the major impediment to the long term efficacy of both conventional chemotherapy and targeted therapies.

Despite the advances that precision medicine has made in terms of treatment selection for certain patient groups there are still significant gaps in our ability to predict treatment response, to identify resistance prior to clinical progression and to select an appropriate treatment when faced with treatment failure following prior therapy. Many promising findings from the laboratory do not go on to translate into clinical benefit due to the differences between the experimental models and human tumours, the lack of adequate drug exposure, treatment toxicity and biological adaptation [38].

Future work should be focused on the integration of genomic profiling, functional studies, biomarker validation and clinical outcomes. A better understanding of the interplay between DNA repair, apoptosis, cell cycle control, immune response and the tumour microenvironment may allow us to identify combinations that can target multiple mechanisms of disease progression. Longitudinal studies of recurrent tumours may also help us to understand how treatment alters tumour biology and reveal the vulnerabilities that arise during resistance.

In addition early detection research should make a clear distinction between biomarkers intended for screening and those intended for diagnosis or monitoring. Therapeutic research should likewise make a clear distinction between mechanistic evidence, preclinical efficacy, preliminary clinical activity and established clinical benefit. These distinctions are absolutely critical if we are to draw reliable conclusions and avoid over-interpreting the emerging data.

CONCLUSION

Ovarian cancer is still a huge global health problem due to its late diagnosis, its molecular heterogeneity, the high rate of recurrence and the development of resistance to treatment. There have been significant advances in our understanding of the disease through molecular profiling and in the application of precision medicine, with the availability of PARP inhibitors, anti-angiogenic agents and a number of novel immunotherapies. The problems of early detection, treatment response and long-term disease control are still very much with us. The future lies in the development of robust early detection biomarkers, in the delivery of truly personalised therapy and in the development of effective strategies to overcome resistance. The integration of genomic insights with novel diagnostics and a truly multidisciplinary approach to care will be key to improving survival, reducing recurrence and improving quality of life for patients with ovarian cancer.

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