The molecular genetics of hereditary and sporadic ovarian cancer: implications for the future

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Accepted 14 October 2014

Abstract

Introduction: Epithelial ovarian cancer (EOC) is a heterogeneous condition with poor survival outcomes. The genetics of hereditary and sporadic ovarian cancers will be covered and its implications to management and future research are discussed.

Sources of data: Key recent published literature.

Areas of agreement: Both genetic and environmental factors play a role in the development of EOC. Most EOCs develop sporadically and are divided into low-grade/genetically stable type I tumours and high-grade/genetically unstable type II tumours. The commonest hereditary syndromes are hereditary breast ovarian cancer syndrome (HBOC—BRCA mutations) and Lynch syndrome (DNA mismatch repair mutations).

Areas of controversy: The different histological types of EOC may not solely originate from the ovary but from the fallopian tube and endometriosis deposits; there is increasing evidence to support this.

Growing points: Our understanding of the genetics and frequencies of mutations in ovarian cancer is expanding. The proportion of heritable EOC is larger than previously estimated and not all patients have a clear family history for this. Mutations in genes involving the downstream BRCA signalling pathway have recently been implicated in HBOC. TP53 mutations are the single most commonly identified mutations in aggressive sporadic high-grade serous carcinomas, affecting essentially 100% of such tumours. Furthermore, there is increasing recognition that the different histological sub-types need to be treated as separate entities.
Areas for timely research: Given how heterogeneous ‘ovarian’ cancer is, trials into new drugs should report responses for the different histo-/geno-types rather than simply using staging. Although the effect of new drugs such as poly (ADP-ribose) polymerase inhibitors are being investigated in ovarian cancer, there is still a need to develop targeted therapies—especially to tackle mutations in PI3 K pathway, RAS pathway and TP53.

Key words: ovarian cancer, origins, genetics, hereditary, sporadic, management

Introduction

Ovarian cancer has the highest mortality rate of all gynaecological malignancies. In fact, it is the fifth commonest cancer and the fourth commonest cause of malignancy-related deaths in women living in the UK. Despite the improvement in five-year survival figures over the past three decades, prognosis is still poor with an estimated five-year survival of 41% compared with 21% in the 1970s. This is thought to relate to delayed diagnosis and the presence of disseminated advanced-stage disease with large volume heterogeneous tumour at presentation; despite high initial response rates, therapy results in the selection of resistant disease in most patients. This has been a major reason for the limited progress in effective therapeutic options in this disease.

Primary ovarian tumours can be classified into three major categories: epithelial ovarian tumours (include benign, borderline and malignant tumours), germ cell tumours and sex cord-stromal tumours. Malignant epithelial ovarian tumours, also known as epithelial ovarian cancer (EOC), are the most prevalent and will be the focus of this article. EOCs can be further classified histologically into serous, clear cell, endometrioid, mucinous, and undifferentiated tumours. Emerging evidence suggests that a significant proportion may have an extra-ovarian origin: high-grade serous carcinomas from the fallopian tube epithelium particularly the fimbrial end that is part of the tubo-ovarian complex; clear cell/endometrioid carcinomas from the endometrial tissue or the ovarian surface, and mucinous carcinomas from the gastrointestinal (GI) tract or more rarely from the ovarian surface epithelium. The general consensus is that both genetic and environmental factors play a role in the development of EOC (Table 1). The most significant of these risk factors are age, family history of ovarian cancer and presence of certain heritable and somatic genetic mutations. The hope is that our expanding knowledge of the genetics of ovarian cancer will allow us to develop genetically tailored therapeutic options and better survival outcomes.

This review will cover the genetics of both hereditary and sporadic ovarian cancer and will discuss the implications of understanding the genetics on screening, prophylaxis and treatment of ovarian cancer.

Hereditary ovarian cancer

The two main syndromes associated with familial ovarian cancer are hereditary breast ovarian cancer syndrome (HBOC) and Lynch syndrome (also known as heritable non-polyposis colorectal cancer syndrome, HNPCC). Other much rarer syndromes associated with hereditary ovarian cancer include Li-Fraumani, Cowden and Peutz-Jeghers syndromes. Heritable cancers form a small, yet larger than previously estimated, proportion of EOCs. It is now thought that up to 25% of all EOCs have a heritable component. It is important to actively consider this possibility because of the implications for the patients and their families in terms of screening, prevention and management. Features that point towards a hereditary origin include a young age at presentation, multiple primaries (i.e. bilateral tumours or different cancer primaries) and/or a family history of malignancy that is inherited in an autosomal dominant pattern.
HBOC syndrome

As the syndrome name would suggest, families with HBOC often have a history of breast and/or ovarian cancer that is passed down the generations in an autosomal dominant manner. It accounts for $\sim 80\%$ of the hereditary ovarian cancers and is typically associated with mutations in the breast cancer susceptibility ($BRCA$) genes. However, more recently, mutations of different genes have been implicated in the pathogenesis of HBOC.

**BRCA1/2**

$BRCA1$ and $BRCA2$ encode proteins that are involved in DNA repair; specifically, they are involved in homologous recombination—a highly accurate mechanism of double-stranded DNA break repair. $BRCA1$ also has the added function of regulating cell cycle checkpoint activation and may even play a role in different DNA repair mechanisms such as single-strand annealing and non-homologous end-joining. Once there is loss of the wild-type allele in a carrier, poor DNA repair mechanisms result in the development of breast/ovarian cancer.

Although these inherited mutations are rare, with the UK prevalence estimated at 0.07–0.09% for $BRCA1$ mutations and 0.14–0.22% for $BRCA2$ mutations, the lifetime risk for development of ovarian cancer for mutations in these genes is 20–45

### Table 1 Risk factors and protective factors for ovarian cancer

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<thead>
<tr>
<th>Risk factors</th>
<th>Protective factors</th>
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<tr>
<td>Older age</td>
<td>Use of the oral contraceptive pill (OCP) relative risk of developing EOC with OCP use for:</td>
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<tr>
<td></td>
<td>2–4 years is 0.78 (95% CI 0.73–0.83),</td>
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<td>5–9 years is 0.64 (95% CI 0.59–0.69),</td>
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<td>10–14 years is 0.56 (95% CI 0.50–0.62),</td>
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<td></td>
<td>More than 15 years is 0.42 (95% CI 0.36–0.49)</td>
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<tr>
<td>Personal history of breast cancer</td>
<td>Single term pregnancy is associated with significant reduction in ovarian cancer risk; OR</td>
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<td></td>
<td>0.47 (95% CI 0.4–0.56). This is further improved with multiple pregnancies; OR</td>
</tr>
<tr>
<td></td>
<td>0.29 (95% CI 0.20–0.42)</td>
</tr>
<tr>
<td>Family history of ovarian cancer</td>
<td>34% reduction; OR 0.66 (95% CI 0.50–0.86)</td>
</tr>
<tr>
<td>Presence of $BRCA1/BRCA2$ mutations</td>
<td>34% reduction in risk of developing EOC (RR = 0.66, 95% CI 0.60–0.73)</td>
</tr>
<tr>
<td>Presence of DNA mismatch repair</td>
<td>Risk of invasive ovarian cancer reduced by aspirin use; RR 0.88 (95% CI 0.79–0.98)</td>
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<tr>
<td>Nulliparity</td>
<td>Hysterectomy with ovarian conservation</td>
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<tr>
<td>Endometriosis</td>
<td>Tubal ligation</td>
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<tr>
<td>Obesity</td>
<td>Aspirin ingestion</td>
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<tr>
<td>Use of talc on perineum</td>
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and 10–20%, respectively. This contrasts with the general population lifetime risk of only 1.4%. It is important to note that certain ethnicities, including Ashkenazi Jewish, have an even higher prevalence of BRCA1/BRCA2 mutations. Several studies have estimated that ~13–15% of patients with ovarian cancer carry germ-line mutations in BRCA1 or BRCA2, with this frequency reaching 17% in patients with high-grade serous adenocarcinoma. Family history of breast or ovarian cancer is not always elicited—estimates suggest that only 65–75% of patients have a significant family history.

Carriers of BRCA1 and BRCA2 mutations have a very similar phenotype. Those with BRCA2 mutations tend to be diagnosed with ovarian cancer at a slightly older age than BRCA1 carriers (55–58 years and 49–53 years, respectively). The tumours of BRCA1/BRCA2 carriers are almost always of high-grade serous histology, but can also present as endometrioid and more rarely, clear cell histology. Zhang et al. tested a series of 1342 patients with invasive ovarian cancer and found that 18.1% of serous, 9.1% of endometrioid and 2.2% of clear cell tumours were from patients with germ-line BRCA1 or BRCA2 mutations. Interestingly, out of the 112 cases of mucinous ovarian cancer identified, none carried germ-line BRCA1/BRCA2 mutations. Despite the aggressiveness and late presentation of their disease (in common with all ovarian cancers), the tumours respond well to DNA-damaging platinum-based chemotherapy, have long disease-free periods between relapses and have a better prognosis than non-BRCA1/BRCA2-related ovarian cancers, particularly when complete tumour removal has been undertaken by debulking surgery.

BRCA2 mutations have been also found to be associated with an increased risk of developing pancreatic and prostate cancer. However, given that BRCA1/BRCA2 mutations affect DNA repair, it is unclear why these mutations are predominantly associated with breast and ovarian cancers. Because these tissues share the property of being hormonally regulated, some researchers have speculated that there may be an interaction between hormones and BRCA1/BRCA2 signalling; while others speculate that hormonal signalling may increase oxidative stress on DNA therefore increasing the susceptibility to mutations. Further research to understand the mechanisms behind this predilection is needed. Indeed, it is interesting to note that use of the oral contraceptive pill (OCP) is a protective factor for ovarian cancer in patients with BRCA1/BRCA2 mutations.

Ovulation creates a pro-inflammatory state at the ovarian surface epithelium and distal fallopian tube through the release of cytokines, reactive oxygen species and steroids (part of the major ‘incessant ovulation’ hypothesis of Fathalla); repeated ovulation may therefore increase risk of damage to DNA in these areas. Weaknesses of this theory include increased risk of ovarian cancer in women with polycystic ovarian syndrome (who ovulate less frequently) and reduced risk of EOC in progesterone-only contraception despite lack of inhibition of ovulation. Some speculate that explanation for the above observations can be unified by lower gonadotropin hormone levels in these patient groups (the ‘gonadotropin hypothesis’), but more work into this is needed.

**Other genes in HBOC syndrome**

There is a subset of families who are truly BRCA1/BRCA2 mutation negative, yet exhibit the HBOC syndrome phenotype. Genetic analysis demonstrated that many of these patients possess mutations in genes along the BRCA signalling cascade—also known as the Fanconi anaemia/BRCA signalling pathway. It was discovered just over a decade ago that the FANCD1 gene implicated in Fanconi’s anaemia—a rare condition of chromosomal instability, aplastic anaemia and increased risk of malignancy—was actually the BRCA2 gene. Examples of genes along this pathway that have been implicated in ovarian cancer include RAD51C, RAD51D, BRIP1, PALB2, BARD1, NBN and MRE11A. Germ-line RAD51C and RAD51D mutations have been found in 2.9 and 0.9% of highly penetrant breast/ovarian cancer families, respectively. The clinical implication of carrying a defect in these genes is not well understood; data are limited, but expanding. A better understanding of the risks of developing cancer as well as tumour behaviour is needed to help guide prophylaxis and treatment measures in this subset of patients.
Lynch syndrome/HNPCC

Lynch syndrome is the second commonest cause of hereditary ovarian cancer, accounting for 10–15% of such familial presentations.\(^25\) It is an autosomal dominant condition that is characterized by the presence of synchronous or metachronous colorectal tumours. It is also associated with an increased frequency of extra-colonic tumours including endometrial, ovarian, urogenital, brain, renal, gastric and biliary cancers. In fact, the risk of developing endometrial cancer in women with Lynch syndrome is higher than that of colonic cancer.\(^25\) Patients who satisfy the Amsterdam II criteria/Revised Bethesda Guidelines for Lynch syndrome or who have a tumour that is suspicious of Lynch syndrome subsequently undergo appropriate testing to confirm this diagnosis.

Several genes encoding DNA mismatch repair (MMR) proteins have been implicated in Lynch syndrome: \(MLH1\), \(MSH2\), \(MSH6\) and \(PMS2\).\(^26\) MMR proteins recognize and correct short insertions and deletions as well as single base mismatches. When these genes are faulty or silenced, areas of small sequence repeats, known as DNA microsatellites, can change in size causing frameshift mutations and DNA instability. This microsatellite instability (MSI) affects genes with important cell functions such as apoptosis, cell signalling and DNA repair, increasing the risk of tumorigenesis.\(^27\) It is estimated that the majority of Lynch syndrome cases are a result of mutations affecting \(MLH1\) and \(MSH2\) (32 and 38%, respectively), with the remainder due to \(PMS2\) and \(MSH6\) mutations (15 and 14%, respectively).\(^28\) More recently, an epimutation (a mutation causing abnormal activation or repression of a gene) has been discovered to cause heritable Lynch syndrome in a subset of patients. These patients have normal \(MSH2\)-encoding genes, but no expression of the protein on a cellular level. They were found possess a deletion in the 3′ segment of the epithelial cell adhesion molecule (\(EPCAM\)) gene, resulting in read-through and downstream hypermethylation of the \(MSH2\) promoter region and subsequent silencing of \(MSH2\).\(^29\)

The overall lifetime risk of ovarian cancer in Lynch syndrome is estimated at 8–12%.\(^18,26\) Recent data suggest that the risk of developing ovarian cancer becomes significant after the age of forty and is different for the different DNA MMR genes—the ERISCAM study estimated the cumulative risk by the age of seventy to be 20, 24 and 1% for \(MLH1\), \(MSH2\) and \(MSH6\), respectively.\(^30\) Patients tend to present at a mean age of 42.7 years.\(^10,26\) The tumours are often moderately or well differentiated\(^10\) and can be of any histology, but a meta-analysis of MMR-mutation associated ovarian cancers found an over-representation of non-serous, and particularly endometrioid cancers (29% of cases vs. the estimated 7–14% in the general population).\(^31\) This is of particular interest when considering the association of Lynch syndrome with endometrial cancer and the controversy around the origins of EOC—genetic analysis of low-grade endometrioid and clear cell cancer suggests that the origins of these cancers are endometriomas/endometriosis.\(^32,33\) A European multicentre retrospective study of 144 MMR carriers with ovarian cancer estimated the 30-year ovarian cancer survival to be 71.5%—better than \(BRCA1/BRCA2\) mutation carriers and the general population.\(^34\)

Sporadic ovarian cancer genetics

The majority of patients diagnosed with ovarian cancer are considered to have a ‘sporadic’ form of this malignancy; in other words, there is no known familial preponderance to their ovarian cancer.

The genetics of this group of ovarian cancer patients is very diverse and involves multiple cellular pathways. Kurman and Shih have suggested a dualistic model for the pathogenesis of ovarian cancer that takes into account the histology, precursor cell types, genetic mutations, tumour behaviour and prognosis for those affected.\(^32\) They divide sporadic ovarian cancer into two main groups: type 1 and type 2 tumours. Type 1 tumours are low-grade/low-stage tumours that develop from well-defined precursors such as endometriosis and borderline tumours, as well as the ovarian surface epithelium.\(^32\) They are genetically stable and develop in a step-wise manner similar to that of colorectal adenocarcinomas. They are generally indolent tumours with low mortality and include the histological types of low-grade serous, endometrioid, clear cell and mucinous.\(^32\) The somatic mutations associated with type 1 tumours include \(K\)RAS, \(BRAF\), \(ERBB2\), \(PIK3CA\), \(ARID1A\),
CTNNB1 and PTEN mutations. KRAS, BRAF and ERBB2 mutations affect the mitogen-activated protein kinase (MAPK) pathway stimulating cell growth, division and tumorigenesis. PIK3CA and PTEN affect the phosphatidylinositol 3'-kinase/akt (PI3K/MTOR/AKT) pathway that has an active role in protein synthesis, cell motility, proliferation and apoptosis and mutations/dysregulation in the PI3K pathway occur in both type I and type II tumours (see below). ARID1A encodes the protein BAF250 that plays an important role in the remodelling of chromatin and regulation of DNA repair, cell differentiation and proliferation. Mutations in β-catenin encoded by CTNNB1 affect cell motility, differentiation and growth through the Wnt pathway, as well as affecting intercellular signalling and cell adhesion (Table 2).

On the other hand, type 2 tumours tend to be high-grade, aggressive cancers with poor prognosis. It includes high-grade serous, high-grade endometrioid and undifferentiated malignancies and characterizes familial as well as sporadic tumours of this type. The commonest mutation is that of TP53 followed by somatic inactivation of BRCA1/BRCA2. TP53 encodes p53—a transcription factor protein that is involved in DNA repair, cell cycle regulation and apoptosis. TP53 mutations are found in more than 95% of high-grade serous EOCs; no other mutation has been consistently found in this type of sporadic tumour. BRCA1/BRCA2 have been shown to be inactivated in 40–50% of sporadic high-grade serous carcinomas. This inactivation is frequently a result of hypermethylation and sometimes from somatic mutations to the gene itself. Thus, both TP53 and BRCA1/2 play an important role in genetic stability, and mutations in these genes result in tumours that are chromosomally chaotic and heterogeneous. It is estimated that type 2 tumours account 90% of ovarian cancer deaths.

### Screening, prevention and management of ovarian cancer

#### Screening and prevention

There is currently no evidence to support the use of population-wide screening tools for the detection of ovarian cancer. Results from the Prostate, Lung, Colorectal and Ovarian (PLCO) trial suggest imaging and blood tests are not sensitive enough to justify screening of the general population, and as such it is not recommended. However, results from another population screening trial—the UK collaborative Trial of Ovarian Cancer Screening trial are still pending. Preliminary data from this trial suggest that monitoring CA125 and using the Risk of Ovarian Cancer Algorithm (ROCA) together can detect low volume malignancy; however, whether this will also detect early-stage malignancy and demonstrate a mortality reduction in the screened population is a more challenging proposition.

As for women with known heritable risk of ovarian cancer, such as familial BRCA mutation, the evidence strongly supports the use of risk-reducing bilateral salpingo-oophorectomy (BSO) with or without hysterectomy to reduce the risk of developing cancer. A meta-analysis assessing the benefits of this surgery in

<table>
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<th>Table 2 Dualistic model of ovarian cancer pathogenesis</th>
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<td><strong>Type 1 tumours</strong></td>
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<tr>
<td>Low-grade serous</td>
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<tr>
<td>Low-grade endometrioid</td>
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<tr>
<td>Clear cell</td>
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<td>Mucinous</td>
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Summary of the histology and associated genetic mutations of type 1 and type 2 tumours.
BRCA1/BRCA2 mutation carriers indicated a 79% reduction in risk of development of ovarian/fallopian tube/primary peritoneal malignancy. Risks of developing ovarian and uterine cancer are also significantly reduced with risk-reducing surgery in Lynch syndrome, where removal of the uterus in addition to BSO would be important. As such, surgery should be offered to women by the age of 40, or once child-bearing is complete. The best approach for women who decline surgery is unclear; but research to assess whether there is any benefit from active monitoring with yearly ultrasounds and CA-125 level monitoring is still ongoing. Initial results from the UK Familial Ovarian Cancer Screen Study suggest that patients who were not screened in the year prior to diagnosis were more likely to have a high-stage malignancy compared with those who were screened in the previous year. False-positive rates are also low at 1.5%, and there was a trend, although not significant, towards improvement in optimal cytoreduction and better overall survival (OS); however, this has to be set against the large effects seen from prophylactic BSO. Oral contraceptive use has also been shown to be associated with lower risk of developing ovarian cancer. A meta-analysis looking at OCP use in BRCA1/BRCA2 mutation carriers demonstrated significant risk reduction (OR 0.57; 95% CI 0.47–0.70); this effect was more notable with longer duration of OCP use. Indeed, similar trends were seen in recent a meta-analysis of OCP use for the general population (OR 0.73; 95% CI 0.66–0.81), with a reduction in incidence of ovarian cancer of more than 50% with ten or more years of use. Studies to quantify the benefits of oral contraceptive or progestin use in Lynch syndrome are still needed. Despite the available data, the use of the OCP is associated with some risk (e.g. thrombosis among others) and there are no published guidelines recommending the widespread use of OCPs for the modification of ovarian cancer risk.

Management of patients with ovarian cancer

A patient who presents with a newly diagnosed ovarian cancer will undergo a diagnostic work-up that includes the performance status, a thorough family history, a staging CT scan of the chest, abdomen and pelvis, assessment of kidney function, routine blood tests and a baseline CA-125 tumour marker level. Following such baseline investigations, patients are optimally managed by primary debulking surgery that results in total macroscopic clearance of all visible ovarian cancer. A histological review of the diagnosis of the malignancy is required prior to commencing adjuvant therapy. Decisions around patient care are undertaken within the context of a multidisciplinary team (MDT) involving oncologists, surgeons, radiologists, histopathologists and nurses.

Despite the clear differences in the genetic mutation profile and phenotypic behaviour of the various EOC histology types, the current National Institute for Health and Care Excellence (NICE) guidelines for the management of ovarian cancer are based mainly on tumour staging. The FIGO (International Federation of Obstetrics and Gynaecologists) staging classification for ovarian cancer is as follows:

Stage I—confined to the ovaries.
Stage II—tumour involving one or both ovaries has extended into the pelvis.
Stage III—tumour involving one or both ovaries has microscopic peritoneal metastases outside the pelvis or lymph node metastases.
Stage IV—development of metastases beyond the peritoneal cavity and/or liver or other organ parenchymal metastasis.

Approximately 60% of ovarian cancer patients in the UK are diagnosed at the advanced stages III and IV. Survival drops drastically with more advanced disease, with 5-year figures for stages I, II, III and IV being 92, 55, 22 and 5.6%, respectively.

Primary disease
Surgery. Primary debulking surgery involves a total abdominal hysterectomy, bilateral salpingo-oophorectomy (BSO), infracolic omentectomy, peritoneal deposit resection, assessment and sampling of retroperitoneal lymph nodes and taking random biopsies of the peritoneum. The aims of the surgery are to provide a histological sample for analysis, allow accurate surgical staging and to remove as much of the tumour as possible; the residual volume of tumour has prognostic implications. An exploratory
analysis of three prospective randomized phase 3 multicentre trials demonstrated that the median survival times for patients with no visual residual disease, 1–10 mm residual tumour and >10 mm residual were 99.1 months (95% CI 83.5–11), 36.2 months (95% CI 34.6–39.4) and 29.6 months (95% CI 27–32.2), respectively. Multivariate analysis, taking into account factors such as age, staging, histology, grade and presence of ascites, found that lower residual tumour volume is independently associated with better OS and progression-free survival (PFS). It is hard to say if this association is causal or relates to the disease being intrinsically less aggressive where optimal debulking surgery has been possible.

Patients can sometimes present with disease that is not amenable to complete debulking surgery at diagnosis. In these situations, tumour sampling would take place by other means such as CT-guided biopsy. The patients would subsequently be offered neoadjuvant (i.e. preoperative) chemotherapy for three to six cycles before reconsideration for surgery. A Cochrane review comparing primary debulking surgery/adjuvant chemotherapy to neoadjuvant chemotherapy/interval debulking in Stage IIIc/IV found no significant difference in PFS and OS. A subsequent meta-analysis which also compared PFS/OS in Stage IIIc/V also found no significant difference in these outcomes. However, the optimal debulking surgical rates for the two large randomized control trials in this meta-analysis was lower than anticipated, casting some doubt over the validity of these results. As such, a third randomized trial with stricter monitoring of optimal debulking rates is underway to add to this body of information.

Avoiding extensive debulking surgery is a possibility for young women with unilateral Stage I disease wishing to preserve their fertility. This conservative surgery involves unilateral salpingo-oophorectomy in addition to peritoneal sampling, retro-peritoneal lymph node sampling and omentectomy for accurate staging of disease. Relapse is estimated at 9–29%, with 5-year survival ranging from 83 to 100%. Outcomes are better in lower-stage and lower-grade tumours. Patients considering this option need to be referred to tertiary centres for comprehensive discussions around fertility outcomes and treatment options, including use of adjuvant chemotherapy, thus allowing them to make informed decisions.

Chemotherapy. For early-stage disease, a Cochrane review into the use of adjuvant platinum-based chemotherapy is found that its use improved overall survival (HR 0.71; 95% CI 0.53–0.93) and PFS (HR 0.67; CI 0.53–0.84) compared with surgery alone. Sub-group analysis of patients deemed to have inadequate surgical staging also had improved OS with adjuvant chemotherapy (HR for OS 0.63; 95% CI 0.46–0.85); but not in those with adequate staging. However, adjuvant chemotherapy in low-risk (Ia grade 1) and medium-risk patients (Ia grade 2, Ib, Ic grade1) did not confer any benefit in OS at 10 years (HR 0.95; 95% CI 0.54–1.66). Current NICE guidelines for early-stage disease are consistent with the above findings, recommending adjuvant chemotherapy for higher risk patients, and not for lower risk disease; while also recommending discussions with patients about the risks and benefits of chemotherapy in cases of sub-optimal surgical staging.

As for more advanced disease (FIGO III and IV), the standard first-line chemotherapy recommended by NICE is either a single platinum agent or combination of a platinum and a taxane, usually carboplatin with paclitaxel given in three weekly cycles. More recently, a Japanese study found that an increased dose density of paclitaxel (in combination with carboplatin) conferred better OS (100.5 vs 62.2 months; HR 0.79; 95% CI 0.63–0.99) and PFS (28.2 vs 17.5 months, HR 0.76; 95% CI 0.62–0.91, respectively) compared with the standard 3 weekly regimen. The long-term adverse effects were not investigated in this study. The results from two further trials, ICON8 and GOG 262, also looking at the impact of increasing the dose density of paclitaxel are awaited.

The impact of delivering chemotherapy intra-peritoneally has also been explored. The rationale behind this is that it allows the delivery of high-dose chemotherapy directly to the affected area/area of most likely recurrence. It should be ideally be used in patients with no gross residual disease post-surgery.
as the chemotherapy can only penetrate a depth of 2–2.5 mm.53 A Cochrane review, which pooled the results from 2119 women receiving primary intraperitoneal chemotherapy, found significantly improved PFS (HR 0.78; 95% CI 0.70–0.86), and reduced mortality (HR 0.81; 95% CI 0.72–0.90).54 However, it was associated with more serious toxicities including fever (RR 1.64; 95% CI 1.13–2.38), fatigue (RR 2.32; 95% CI 1.06–5.07), GI effects (RR 1.70; 95% CI 1.28–2.26), infection (RR 3.34; 95% CI 2.06–5.43), metabolic adverse effects (RR 4.45; 95% CI 2.72–7.26) and pain (RR 7.47; 95% CI 4.41–12.67).54 Therefore, intra-peritoneal chemotherapy is not routinely recommended on NICE, unless it is part of a clinical trial.44

Newer agents that may soon alter first-line treatment choices include poly(ADP-ribose) polymerase (PARP) inhibitors, and anti-angiogenic agents such as anti-vascular endothelial growth factor (VEGF) monoclonal antibody.

PARP proteins are important in DNA repair, and their inhibition results in persistence of single-strand DNA breaks. During DNA replication, these breaks become double stranded.55 As described earlier, BRCA genes are important in the homologous repair of these double-stranded breaks. Cells with BRCA1/BRCA2 mutations are unable to repair the DNA damaged by PARP inhibition, leading to cell death. This concept of inhibiting two pathways to cause cell death is known as synthetic lethality.56 PARP inhibitors therefore provide an opportunity for targeted/personalized therapy in patients with BRCA1/BRCA2 mutations. Examples of PARP inhibitors include Olaparib, Niraparib and Rucaparib. Results have been promising, with improved outcomes in BRCA mutation carriers. In an interim analysis on the use of olaparib as maintenance therapy, Ledermann et al. demonstrated that the use of this drug in patients with BRCA1/BRCA2 mutations is associated with a significantly improved PFS compared with placebo (11.2 vs 4.3 months; HR 0.18; 95% CI 0.10–0.31).57 Improvement in PFS with olaparib use was also seen in patients with wild-type BRCA compared with placebo; although the difference was not as great (7.4 vs 5.5 months; HR 0.54; 95% CI 0.34–0.85).57 This may relate to mutations in other genes involved in homologous repair of DNA or epigenetic silencing of the BRCA1/BRCA2 genes. There has been no significant difference in overall survival figures in the olaparib group compared with placebo; although longer-term follow-up is ongoing.57 Nevertheless, the delay in disease progression, and time to subsequent treatment has been impressive; and supports personalization of ovarian cancer treatment.

Angiogenesis is a vital process in tumour growth; and inhibiting it has yielded promising results. Bevacizumab, a monoclonal antibody that binds Vascular Endothelial Growth Factor A to prevent its interaction with VEGF receptors, has been the most investigated of these anti-angiogenic agents. The use of bevacizumab alongside standard chemotherapy has been shown to be associated with significantly improved PFS (HR 0.82; 95% CI 0.75–0.89) and OS (HR 0.87; 95% CI 0.77–0.99); but with increased incidence of serious toxicities of GI perforation, bleeding and hypertension.58 It has not been recommended as first-line therapy by NICE because of cost-effectiveness. A number of other anti-angiogenic have also been investigated, such as pazopanib and trebananib, and are still under phase III development.59

**Recurrent disease**

Overall treatment response is assessed by monitoring the patients’ symptoms, CA-125 levels and tracking changes on interval CT scans. The patterns of response to treatment are classified according to duration of time to relapse from completing platinum therapy.44

1. Fully platinum-sensitive recurrent ovarian cancer: responds to treatment but relapses 12 months or more after completion of platinum therapy.
2. Partially platinum-sensitive recurrent ovarian cancer: responds to treatment but relapses between 6 and 12 months after completion of platinum therapy.
3. Platinum-resistant recurrent ovarian cancer: relapses within 6 months of completion of platinum therapy.
4. Platinum refractory progressive ovarian cancer: did not respond to platinum therapy and grows inexorably, with very poor prognosis.

Unfortunately, it is estimated that 70–75% of EOC patients will relapse and ultimately die of their
disease. Of these 75% of cases, 50% will be sensitive to and 25% will be resistant or refractory to platinum agents. The choice of chemotherapy used in recurrent disease predominantly depends on the duration of time elapsed until recurrence; in other words, platinum sensitivity. The longer the duration to relapse, the more likely that the cancer would respond to platinum agents.

In platinumsensitive disease, combination of paclitaxel with a platinum agent is associated with improved OS (HR 0.80; 95% CI 0.64–1.00; \( P = 0.05 \)) and PFS (HR 0.68; 95% CI 0.57–0.81; \( P < 0.001 \)) compared with platinum alone. It is the current first-line treatment recommended by NICE. In fact, the OS and PFS for platinum agents in combination with other drugs such as pegylated liposomal doxorubicin hydrochloride (affects DNA intercalation) and gemcitabine (a nucleoside analog) are also better than platinum alone. A recent trial investigating the role of anti-angiogenic agents in platinum-sensitive relapsed disease (Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease) demonstrated that the addition of bevacizumab to the platinum/gemcitabine combination resulted in improvement in PFS (HR 0.484; 95% CI 0.388–0.605) but not OS compared with platinum/gemcitabine alone. This correlated to a 4-month improvement in PFS. As for platinum-resistant or refractory disease, NICE currently recommends the use of single agents such as paclitaxel, doxorubicin and topotecan (a topoisomerase inhibitor).

**Personalising therapy in ovarian cancer**

Our understanding of the pathogenesis of ovarian cancer has expanded significantly over the past couple of decades; from the origins, to the genetic mutations (Fig. 1), and the roles immunology and angiogenesis play in disease progression. It is clear that the umbrella term ‘EOC’ actually encompasses multiple distinct disease entities.

Because of this, having a treatment strategy that is based primarily on tumour staging is not adequate. For example, clear cell and mucinous histo-types do not respond well to platinum agents, because type 1 tumours are likely to have preserved homologous repair systems. Therefore, reported trial results for ‘EOC’ would mask the lack of response in this group of patients. Indeed, many trials now make the histological diagnosis investigated and associated outcomes clear.

Although there are markers that prognosticate patient outcomes (such as tumour staging and extent of residual disease post-surgery), there is still a need to identify clinically validated biomarkers that predict potential responses to specific therapeutic agents. BRCA1/2 mutations have been shown to predict response to PARP inhibitors. Studies looking at mRNA expression profiles in HGSC have identified four disease sub-types with potentially actionable targets: immune modulation, angiogenesis, PARP inhibition and stromal targeted agents. Micro-RNAs are nucleotides, which play a role in post-transcriptional control of translation and may potentially be used diagnostically, or as a biomarker/means of monitoring effectiveness of treatment. For example, miR-214 expression is associated with cell survival and resistance to cisplatin. Biomarkers could also be incorporated into trial design, as done in the biomarker-integrated approaches of targeted therapy for lung cancer elimination (BATTLE) trial —in which ‘adaptive randomization’ was used to
treat patients based on knowledge of genetic mutations from biopsied tumour samples. It demonstrated that patients with non-small cell lung cancer and known KRAS mutations responded better to KRAS-targeting sorafenib than other treatments, and those with known EGFR mutations responded better to erlotinib. Taking this type of trial design forward in ovarian cancer, in conjunction with serial biopsies of tumours would allow us to validate biomarkers, explore the use of targeted therapy and better understand tumour resistance.

Finally, the repertoire of chemotherapeutic agents available to treat EOC is limited—with the mainstay being platinum and taxol-based agents. New targeted therapies are needed; we are just beginning to understand who would benefit from agents targeting angiogenesis and PARP inhibition. Given that virtually all high-grade serous tumours possess TP53 mutations, targeting this pathway may well result in pronounced effects on survival outcomes. There are also no agents that are currently directed at type I tumour mutation pathways, such as RAS which is estimated to affect up to 70% of low-grade serous tumours.33

Conclusion

Unfortunately, the majority of patients are treated for EOC relapse63 and eventually develop chemotherapy-resistant disease.33 Despite the challenges and unmet needs of ovarian cancer, there have been improvements in driving this disease away from certain short-term lethality to a more chronic disease course; with most of the recent gains in survival coming from life extension after the diagnosis of incurable recurrent disease. This drive to change ovarian cancer to a chronic disease state is a process that integrates multidisciplinary care with research and is currently being pursued in many centres of excellence around the world.

References


