Management of Ovarian Cancer: Bright New Future or False Dawn?

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The proportion of UK women surviving five years after diagnosis of ovarian cancer has improved by only 5% since 1995 [1], yet, there is great optimism as new treatment strategies emerge that may genuinely improve the outlook of patients.

Current management and recent advances

For the past 15 years, the standard initial management of ovarian cancer has been primary debulking surgery followed by six cycles of platinum (carboplatin or cisplatin) and paclitaxel chemotherapy. The superiority of regimes containing both platinum and taxane emerged in the mid-1990s [2]. This remains standard management for the minority of women presenting with early stage ovarian cancer (stages I and II),

A marked change in management of advanced disease has recently emerged, with debulking surgery deferred until after three cycles of primary/neoadjuvant chemotherapy. The hypothesis is that these three cycles should reduce the bulk of tumours and increase the likelihood of complete macroscopic resection. The EORTC55971 trial compared conventional management with primary chemotherapy and interval surgery in 670 women with advanced disease. Women undergoing primary chemotherapy were more likely to have no visible residual disease after debulking. However, this did not translate into a survival advantage [3], although surgical morbidity was significantly lower in the primary chemotherapy group. Thus, it was concluded at the recent 4th Ovarian Cancer Consensus Conference that the use of primary chemotherapy in advanced ovarian cancer is an appropriate international standard in clinical trials [4].

Another advance has been the use of dose-dense fractionated paclitaxel with carboplatin as first-line chemotherapy. The Japanese JGOG3016 trial randomised 637 women to receive either standard post-operative chemotherapy or the dose-dense regime. Initial results were extremely encouraging, with a highly significant increase in progression-free survival (PFS) in favour of the dose-dense arm (28 vs 17 months, hazard ratio 0.71; $p = 0.0015$) [5]. The data presented at ASCO 2012 also showed a significant improvement in overall survival.

The activity of bevacizumab in the first line treatment of ovarian cancer is attracting much attention. Two large randomised phase III trials, GOG218 [6] and ICON7 [7], showed improved PFS when bevacizumab was included with carboplatin and paclitaxel chemotherapy, and also when given as single agent maintenance for up to 15 months. The women who benefited most were those with the poorest prognosis (residual tumour following primary surgery and/or stage IV disease). In ICON7, the PFS curves showed non-proportional hazards, with most benefit at the end of bevacizumab maintenance treatment, but diminishing thereafter. With license approval in both the EU and USA, bevacizumab is the first new drug in initial ovarian cancer management for 15 years.

Bevacizumab can also improve PFS when added to chemotherapy in relapsed disease that is either platinum-sensitive [8] or platinum-resistant [9]. Some questions remain, however, regarding the most appropriate dose (7.5 or 15mg/kg), with potentially huge cost implications for the NHS. It is also unclear in which setting bevacizumab would be most appropriate (first-line, platinum-sensitive relapse or platinum-resistant relapse), whilst no reliable predictive biomarkers of benefit are available.

As a drug with undoubted activity in ovarian cancer, bevacizumab is the first of many targeted agents that may enter the oncologist's armamentarium over the next few years.

State of the scientific basis

It is now universally appreciated that the disease called 'ovarian cancer' for the past 40 years is, in fact, at least five different diseases linked only by a common anatomical location [10]. Thus, the maxim of 'one-treatment-regime-for-everyone' is increasingly untenable [11]. Oncologists must, therefore, strive towards customising treatment for each patient, perhaps with different treatments being used for the different subtypes.

High Grade Serous Type

The most common type of ovarian cancer is high grade serous, accounting for two thirds of all cases and disproportionately presenting at an advanced stage (up to 90% of stage IIIc/IV patients have high grade serous pathology). Women with inherited germline mutations in BRCA1 and BRCA2 also overwhelmingly develop high grade serous ovarian cancer compared to other subtypes.

The first key revelation is that high grade serous disease does not actually arise in the ovary, but in the distal fallopian tube [12]. The second is that a near-universal molecular abnormality has been identified - mutations in the tumour suppressor gene, TP53, are seen in >95% of all high grade serous cases [13]. This frequency was confirmed by the Cancer Genome Atlas (TCGA) consortium, which subjected 489 of these tumours to an array of genomic analyses [14].

Not unexpectedly, TCGA also uncovered further fascinating data. For many years, it was thought that inherited ovarian cancer resulting from BRCA1 and BRCA2 mutations was rare (<5% of cases). However, TCGA suggested that ~15% of cases arose in women with inherited BRCA1/2 mutations, a figure subsequently confirmed by others [15,16]. This has huge implications for women and their families – there may be many more women at genetic risk of ovarian cancer than previously thought, many of whom will have no obvious family history of breast or ovarian cancer.

Mutations in BRCA1/2 cause a defect in a cell's ability to repair DNA damage using the process of Homologous Recombination (HR). This has two

consequences: cells lacking BRCA1/2 function will acquire multiple unrepaired genetic abnormalities that might eventually produce cancer; however, the malignant cells that arise are exquisitely sensitive to DNA-damaging drugs. Thus, ovarian cancer caused by mutations in BRCA1 or 2 responds very well to platinum-based chemotherapy and overall survival is significantly better than sporadic ovarian cancers [17]. In addition, BRCA1/2-mutated cancers can also respond to a novel group of anti-cancer drugs, called PARP inhibitors, which induce irreparable DNA damage by blocking a separate repair pathway [18,19].

TCGA has also shown that abnormalities in other HR genes are common in high grade serous cancer: up to 50% of tumours have some form of HR pathway defect. The same frequency was observed in a separate study using a functional assay of HR activity in primary tumour cells [20]. The implication of these studies is that up to half of women with high grade serous ovarian cancer may benefit from PARP inhibitor treatment. Indeed, one large study has already demonstrated that women with relapsed disease show a dramatic increase in PFS when treated with a PARP inhibitor following platinum-based chemotherapy [21].

Overall, three great challenges in high grade serous ovarian cancer exist – first, to develop specific therapies for TP53-mutated cancers, which is the universal feature of this disease; second, to continue developing PARP inhibitor therapy, with a simple test to identify tumours with defective HR; third, and the most difficult, to identify the abnormalities underpinning the 50% of high grade serous tumours with normal HR – these cases respond less well to conventional chemotherapy and have a poor prognosis.

Other subtypes of ovarian cancer

Low grade serous cancer, despite its name, is very different from high grade. Mutations in TP53 are very rare and HR pathway genes are invariably intact. Low grade serous cancers can arise from borderline or low-malignant potential tumours, which are more frequent in younger women, and they tend not to respond to conventional platinum-based chemotherapy. Their pattern of growth could be described as slow but inexorable.

However, distinct and targetable abnormalities have now been identified. The most commonly mutated genes are B-Raf, KRas and NRas, which lie in a common pathway, with the kinase MEK acting as key effector. The potential for MEK inhibitors in the treatment of low grade serous tumours will be explored in the LOGS trial, run in both the UK and the USA, which will compare single agent MEK inhibitor with conventional chemotherapy in 250 women with relapsed disease. Most importantly, all women will have a biopsy of their relapsed cancer as they start treatment, so that correlations can be made between tumour biology and response to treatment. This idea of taking new biopsies is a vital new paradigm in modern clinical trials; only by having a sample of cancer that is contemporaneous with the treatment being given can researchers hope to understand the biology of the disease.

Another rarer type of ovarian cancer is Clear Cell Carcinoma (CCC). In European populations, it accounts for approximately 10% of tumours, although in Japan it is as high as 30%. CCC has a fearsome reputation because advanced disease is almost completely resistant to platinum-based chemotherapy. However, CCC is much more likely to present at very early stages and the survival of patients with stage I CCC is extremely good [22].

At a biological level, two key features have recently emerged. Many cases of CCC, as well as another type of ovarian cancer called endometrioid, arise on a background of endometriosis, and mutations in the gene ARID1A are highly frequent [23]. ARID1A encodes a protein called Baf250a, which is a key component of a complex remodelling chromatin that influences gene expression by regulating the gross 3-dimensional structure of DNA. Mutations in this complex are seen in other cancers [24], but novel ARID1A/Baf250a-specific therapies need to be developed.

A more targetable abnormality in CCC is increased activity of the inflammatory cytokine, interleukin-6 (IL-6), together with HIF1α, a gene that regulates cellular responses to low oxygen concentration [25]. Clinical trials of IL-6 inhibitors have already been undertaken in ovarian cancer [26], and a new trial of nintedanib, a drug that should inhibit the downstream effects of IL6-HIF1α activity in women with relapsed CCC, will start in the UK in 2013.

Summary

For many years, ovarian cancer has only had one active drug, based on platinum. However, the next decade should see significant improvements in the outlook for patients. Five key points need to be considered:

1. Ovarian cancer covers many diseases, the commonest of which probably does even not arise in the ovary.

2. We need specific treatments for the different subtypes, starting with subtype-specific clinical trials. The one-size-fits-all era both in treatment and clinical trials must end. Trials will have to be smaller, run rapidly and have rigorous clinical and scientific endpoints.

3. New targets for therapy are required. Although BRCA1 and IL-6 are exciting, there are multiple other abnormalities present that require elucidation and the possible uncovering of new therapeutic targets.

4. Tumours adapt and become resistant to therapy. High grade serous disease is particularly heterogeneous; intrinsically resistant clones of tumour may exist at diagnosis. It is essential that further samples of tissue are taken when tumours relapse to identify changes that have occurred during treatment and relapse.

5. Ovarian cancer is relatively rare and international effort is required to combat it. No individual research team can defeat this disease.

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