Ovarian Cancer in 2021 – Where are we?

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Epithelial ovarian cancer remains a lethal enigma. It is increasingly accepted that many serous carcinomas emanate from the fimbrial epithelium of the fallopian tube, however appropriately sensitive screening tests and early diagnosis remain elusive. Largescale multi-omic profiling of high grade serous ovarian cancer (HGSOC), the most common histological subtype, via The Cancer Genome Atlas (TCGA) has come to two significant conclusions. Firstly, approximately 50% of HGSOCs have defects in DNA damage response and secondly that this is a disease of genomic chaos, driven by copy number alterations with very few targetable mutations. The first conclusion has led to significant therapeutic advances with the development of PARP inhibitors (see below), the second highlights the difficulties in developing any targeted therapy for this disease.

As more than 70% of women still present with advanced (stage III/IV) disease, the cornerstone of ovarian cancer treatment remains aggressive cytoreductive surgery (CRS) and platinum-based systemic chemotherapy. Primary CRS, formerly known as "debulking" surgery can be performed in the upfront setting followed by 6 cycles of adjuvant carboplatin and paclitaxel. Primary CRS should only be offered if a multidisciplinary discussion suggests that a complete macroscopic resection (i.e no visible disease at the end of surgery) can be performed. If this not feasible then the patient should be offered neoadjuvant chemotherapy and considered for interval cytoreductive surgery after 3 or 4 cycles. A number of large trials and a recent meta-analysis by our group have all come to the conclusion that in women who are not fit for primary cytoreduction due to comorbidities or disease distribution, neoadjuvant chemotherapy reduces surgical morbidity without impacting on survival. Despite these findings, many experts continue to suggest that primary CRS is associated with improved survival and the results of the forthcoming TRUST trial are eagerly awaited and will hopefully finally answer this question.

One of the most exciting advances in ovarian cancer in the last five years has been the OVIHIPEC-1 trial, which demonstrated that the addition of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) in the form of cisplatin for 90 minutes at 40°C at the time of interval cytoreductive surgery increased overall survival by almost 12 months. Although the trial has received some justified criticism based on length of accrual and pre-operative randomization, the rationale for intra-peritoneal chemotherapy is based on a long history of clinical trials some of which were profoundly positive. We have been offering HIPEC to selected patients in the Mater Hospital for the last two years with some very promising results and no significant increased morbidity. We hope to open the OVIHIPEC-2 study in 2021 in the Mater Hospital, which will be a randomize patients after primary cytoreductive surgery.

It is important to highlight that HIPEC is only offered to patients who have a complete macroscopic resection. HIPEC does not replace inadequate surgery, it should be considered an adjunct to good surgery. It is abundantly clear from almost every clinical trial and population-based study published that residual disease at the end of surgery is the single most important prognostic factor in ovarian cancer. Cytoreductive surgery can involve a multi-visceral resections including posterior exenteration, subtotal or total colectomy, omentectomy, splenectomy and diaphragmatic peritonectomy. Less common sites affected included the porta-hepatis and coeliac plexus, however teams must be capable of resecting these areas safely if necessary. High volume centres have better outcomes and the need for surgical centralisation is clear. We recently published our experience of the implementation of a multidisciplinary surgical team including gynaecological oncologists, colorectal, hepato-biliary and upper-GI surgeons to increase complete macroscopic resection rates, without increasing morbidity.

The last two years have also seen the publication of a number of landmark studies demonstrating the efficacy of maintenance PARP inhibitors, particularly in women with a somatic or germline BRCA mutation. Germline BRCA mutations occur in 18-20% of non-mucinous ovarian cancers and it is imperative that all women are offered testing at diagnosis, a major deficit in Ireland at present. BRCA testing may allow stratification of patients into different treatment algorithms and also for cascade testing of family members who could be offered risk reducing surgery. ASCO recently recommended PARP inhibitors be offered to all women, however the cost-effectiveness of this approach is as yet unproven

The impact of PARP inhibitors on ovarian cancer cannot be underestimated and a small proportion of women may well be cured by these innovative medications. There have also been many failures – the highest profile being immunotherapy, a problem my own lab continues to study. As a result, most women follow a relapsing course and eventually develop platinum resistant disease. Therefore, the focus must be on treating ovarian cancer as a chronic disease, allow women to live with the disease and avoid any reference to a battle mentality. I often refer to HIV and the numbers of people living with HIV, patients find this analogy helpful and I believe over time we will find more and more ways to allow women to live long and fruitful lives with ovarian cancer and perhaps eventually they will die of other causes.