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Progress in the treatment of ovarian cancer—lessons from homologous recombination deficiency—the first 10 years

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For several years, a major obstacle in the systemic treatment of ovarian cancer has been the lack of a therapeutic strategy tailored to specific biomarkers present in the individual patient's tumour. However, considerable progress has been made recently through the development of drugs targeting cells deficient in the key mechanism of double-strand DNA repair, known as homologous recombination (HRD). These drugs, inhibitors of the enzyme poly (ADP) ribose polymerase (PARP), selectively kill HRD cells through a process known as tumour-selective synthetic lethality. Olaparib is the first such agent, now approved for the treatment of ovarian cancer associated with mutations in the BRCA 1/2 genes, since these are characterised by cells with HRD. Importantly, another group of patients with tumours bearing a similar repair deficiency but without BRCA mutations may also be susceptible to PARP inhibition and efforts to develop an HRD assay are therefore a priority so that these patients can be identified as PARPi candidates. In addition, combination strategies are an area of intense research; these include combinations with antiangiogenic agents and with inhibitors of the P13K/AKT pathway and others are likely to merit assessment since resistance to PARP inhibitors will certainly emerge as the next challenge. While olaparib is the first PARP inhibitor to receive approval for ovarian cancer treatment, others including rucaparib and niraparib are clearly effective in this disease and, within the next year or two, the results of ongoing randomised trials will clarify their respective roles. PARP inhibitors are generally well tolerated; regulatory approval at present supports their use as a maintenance therapy (in Europe) and as treatment for advanced recurrent disease (in the United States), but it is likely that these indications will extend as the results of ongoing trials become available. Ten years have elapsed between the first pre-clinical publications and the regulatory approval of PARP inhibitors and the next 10 years promise to be even more productive.

Key words: poly(ADP)ribase polymerase, homologous recombination deficiency

In April 2005, two papers appeared in the journal *Nature*, describing the exquisite *in vitro* sensitivity of BRCA-mutated cells to treatment with a selective inhibitor of the enzyme poly (ADP) ribose polymerase (PARP) [1, 2]. The concept of tumour-selective synthetic lethality was born, and this heralded the beginning of an eventful decade, culminating in the approval by regulatory authorities both in Europe and in the United States of the first oral PARP inhibitor—olaparib—for the treatment (in two different clinical scenarios) of BRCA-mutated (BRCAm) ovarian cancer patients. Since BRCA mutations are a regular feature of high-grade serous ovarian cancer (~20% considering both germline and somatic mutations), the impact of this development in treatment is likely to be considerable. In reviewing the events of the past 10 years, it will be important to identify some lessons to be learnt and also to point to key issues for the future of this exciting aspect of ovarian cancer therapy.

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Within 2 months of that initial dual publication, the first clinical trial of the oral PARP inhibitor KU59436 (subsequently acquired by AstraZeneca and renamed olaparib) was initiated. PARP inhibitors had been subject to clinical trials in oncology previously but the initial focus had been as a combination partner for chemotherapy, aimed at circumventing drug resistance [3]. The first clinical trial with olaparib as a single agent was reported in 2009 [4] with the data from the expansion cohort published in 2010 [5]. These demonstrated that the drug was well tolerated, safe and active in patients with BRCAm ovarian cancer, particularly but not exclusively in those with platinum-sensitive disease. The overall response rate was 46% (23 of 50 patients) with a median response duration of 8 months and activity was later confirmed in a separate international phase II trial conducted at 2 dose levels (400 mg b.i.d. and 100 mg b.i.d.) [6], with the higher dose level appearing to be more active.

In a subsequent randomised phase II study, the higher dose of 400 mg b.i.d. again appeared to be more active (than 200 mg b.i.d.), although this small three-armed trial (in patients with BRCAm-relapsed ovarian cancer with a 0- to 12-month platinum-free

interval) was powered primarily to compare olaparib (pooled data from the two dose levels) with the control arm of conventional chemotherapy—pegylated liposomal doxorubicin (PLD) [7]. For the first time, it became clear in this study that, in patients with BRCAm ovarian cancer, PLD had a higher level of efficacy than in unselected cases, and this was supported by data from other studies [8]. To an extent, this led to a misinterpretation of the trial results. At the higher dose of 400 mg b.i.d. olaparib, the response rate and progression-free survival (PFS) were numerically superior to PLD, but the differences were not significant for the reasons stated. Some observers considered this to demonstrate a failure of olaparib to meet expectations, despite having a response rate of 59% and median PFS of 8.5 months, in BRCAm patients with advanced recurrent disease. Indeed, 4 years then elapsed before the drug was eventually approved by FDA for this specific indication [9] (without the need for further randomised trial data, but with the support of further data from a separate study in 193 patients with platinum-resistant BRCAm ovarian cancer, treated with single-agent olaparib and showing a 31% response rate and median PFS of 7 months) [10]. At present, and in contrast to the United States, olaparib is not approved in Europe for the treatment of advanced recurrent disease.

In the meantime, two lines of clinical development were actively pursued. The first examined the concept that PARP inhibition in ovarian cancer might have utility extending beyond those cases associated with BRCA mutations. The key property predicting efficacy is homologous recombination deficiency (HRD), and in 2011, Levine's work within the Cancer Genomic Atlas framework indicated that up to 50% of cases of high-grade serous ovarian cancer might be candidates for PARP inhibition, based on a range of genetic defects in addition to BRCA 1/2 germline and somatic mutations [11]. The clinical relevance of the observations was assessed in a clinical trial published in 2011, which demonstrated efficacy of olaparib in a series of patients with sporadic, BRCA wild-type ovarian cancer, albeit at a slightly lower level (24%) and confined mainly to patients with platinum-sensitive disease [12].

The second line of investigation, which led directly to the approval of olaparib by regulatory authorities in Europe, examined the use of the drug as a form of maintenance therapy and approval is specifically for that indication. The key randomised trial involved patients with platinum-sensitive relapsed disease ($n = 265$) who received single-agent olaparib or placebo following platinum-based treatment. The median PFS increased from 4.8 to 8.4 months [hazard ratio (HR) = 0.35] and overall treatment was well tolerated. The trial had not selected for patients with BRCA mutations, and mutation status was initially unknown in the majority of cases (64%) [13]. However, retrospective analysis (of both germline and somatic BRCA mutation status) indicated that 136 patients (51%) were positive for BRCA 1 or 2, and the treatment benefit in this subgroup was even more marked [median PFS increasing to 11.2 months (HR = 0.17)] [14]. Other notable features in this retrospective analysis included the positive benefit in patients with BRCA wild-type disease and in those with somatic BRCA mutations and both these observations will be taken forward in subsequent trials involving olaparib as well as two other PARP inhibitors (niraparib and rucaparib, both of which have shown comparable levels of efficacy and tolerability to olaparib in BRCA germline mutation-positive and wild-type patients) [15, 16].

Looking forward, a number of key issues regarding the clinical utility of PARP inhibitors come to mind. As the use of this treatment expands, further relapse and resistance to PARP inhibitors will become increasingly recognised. Current data indicate that resistance is likely to be multi-factorial; mechanisms including the development of secondary BRCA mutation, enhanced drug efflux relating to P-glycoprotein and changes in other repair proteins such as 53BP1 may all be involved [17]. The collection of tumour tissue in relapsing patients should be extremely informative in this context, with tumour heterogeneity likely to emerge as a key issue. Importantly, the clinical data suggest that cross-resistance between PARP inhibitors and platinum-based treatment is likely to be only partial [18]. Indeed, one of the main differences between these forms of therapy is the evidence that some patients (even with platinum-resistant disease) can enjoy a prolonged disease-remission with a PARP inhibitor. For example, in our own practice, we have a patient with platinum-resistant disease who has been receiving olaparib for over 8 years and remains on treatment.

Returning to the issue of potential PARPi efficacy in BRCA—wild-type cancer, other future developments are likely to include the establishment of a laboratory assay which accurately assesses HRD in ovarian cancer samples. A number of lines of investigation have pursued this, including functional and immunochemical assays, but the most promising appear to be two genomic DNA-based assays both based on loss of heterozygosity (LOH), which may reflect HRD and predict PARPi sensitivity irrespective of its cause.

These have been shown to correlate with pre-clinical (niraparib) [19] and clinical (rucaparib) [20] response to PARP inhibitors, and are both being assessed in ongoing randomised trials of maintenance therapy.

Finally, combination strategies involving PARP inhibitors are likely to receive increasing attention in the coming months and years. The utility of PARP inhibitors combined with cytotoxic chemotherapy is of doubtful value, because of enhanced toxicity of this combination, and because of data from a randomised trial indicating that the main benefit (of olaparib) was as maintenance treatment as a single agent rather than in combination concurrently with chemotherapy (carboplatin/paclitaxel) [21]. More promising strategies include the use of PARP inhibitors together with antiangiogenic agents, or with inhibitors of the P13K/AKT pathway. Both take advantage of pre-clinical observations indicating that it is possible to increase PARPi sensitivity with a concurrent targeting agent [22, 23], and clinical studies are already underway. The relevance of this, particularly in respect of antiangiogenic agents is particularly clear when one considers the potential treatment options for a patient with BRCA mutation-positive platinum-sensitive relapsed ovarian cancer. Bevacizumab presents one such option, based on the clear evidence of benefit in the OCEANS trial [24], while olaparib presents another—as described above. The intriguing notion is that the combination of the two approaches would be more successful than either alone, and combinations of olaparib together with the VEGFR TKI cediranib and with bevacizumab are being taken forward with this in mind [25, 26].

In summary, the first 10 years of the HRD story has been extraordinarily productive and a new treatment for patients with BRCA mutation-positive ovarian cancer (and hopefully others) has emerged. But this is the beginning not the end of the story, and careful clinical development taking account of lessons learnt in the past 10 years is likely to lead to further major improvements in the management of this disease in the next decade.

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