PARP inhibitors in ovarian cancer

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Background: Slow progress in improving the outcome of ovarian cancer with chemotherapy over the last decade has stimulated research into molecularly targeted therapy. Poly(ADP-ribose) polymerase (PARP) inhibitors target DNA repair and are specifically active in cells that have impaired repair of DNA by the homologous recombination (HR) pathway. Cells with mutated BRCA function have HR deficiency (HRD), which is also present in a significant proportion of non-BRCA-mutated ovarian cancer.

Design: In the last decade, olaparib, the first and most-investigated oral PARP inhibitor, has undergone phase I-III trials as a single agent, in comparison with and in addition to chemotherapy, and as a maintenance therapy following chemotherapy.

Results: The greatest benefit to-date has been in the maintenance setting, prolonging the progression-free survival of high-grade serous ovarian cancer with a BRCA1/2 mutation. In this group of patients, olaparib has received approval as maintenance following chemotherapy from the EMA, and accelerated approval as a single agent in women who have had three or more lines of therapy. Olaparib can be given for a prolonged period with few significant side-effects in most patients. Similar trials with other PARP inhibitors (rucaparib, niraparib and veliparib) are in progress and include non-BRCA-mutated ovarian cancer. Second-generation studies are exploring the combination of PARP inhibitors with anti-angiogenic drugs.

Conclusions: PARP inhibitors represent a step change in the management of ovarian cancer. BRCA mutations are the first genotypic predictive markers in ovarian cancer and can be used to select patients who will most likely benefit from PARP inhibitors. BRCA testing is now becoming a routine part of the evaluation of women with ovarian cancer, and tests for HRD are being used to evaluate PARP inhibitors in an extended population of non-BRCA-mutated ovarian cancer.

Key words: ovarian cancer, PARP inhibitors, BRCA mutation, olaparib, homologous recombination deficiency, maintenance therapy

introduction

The introduction of platinum-based drugs and paclitaxel were landmark developments in the treatment of ovarian cancer. However, there has been little progress in the results of first-line therapy for more than a decade, and long-term survival improvements seen during this time have been due to better treatment of recurrent disease. Progression-free survival (PFS) in ‘platinum-sensitive’ relapsed ovarian cancer treated with platinum-combination therapies has remained relatively unchanged [1], and ∼11 months, but women are being offered a greater number of lines of treatment. During this time, maintenance therapy to delay progression and re-treatment with chemotherapy has evolved as a new therapeutic approach. The inhibition of angiogenesis [2, 3] and DNA repair pathways are two strategies that have led this development. The second is exemplified by inhibitors of PARP (poly(ADP-ribose) polymerase), an important enzyme activated in response to single-strand damage of DNA. It was originally believed that PARP inhibitors could be used to potentiate chemotherapy [4], but the observation that the survival of cells with homozygous mutations of the BRCA1 or BRCA 2 genes is significantly impaired by PARP inhibitors [5, 6] has opened new treatment opportunities for ovarian cancer. Cells with defective BRCA proteins are deficient in the repair of double-stranded DNA breaks by homologous recombination (HR) and rely on other pathways to repair DNA damage, notably the PARP pathway that detects single DNA strand breaks and activates a number of effector proteins to initiate repair. The inhibition of PARP in the presence of HR deficiency (HRD) leads to cell death from gross genetic disarray due to a process called ‘synthetic lethality’ [7]. Several PARP inhibitors are being evaluated in ovarian cancer. Initial studies were in BRCA-deficient tumours but as knowledge of the molecular and genetic biology has increased, studies are being extended to include a larger group of ovarian tumours.

early clinical trials with PARP inhibitors

Olaparib (AZD2281) is a potent small-molecule oral PARP inhibitor and was the first to enter clinical trials in ovarian cancer
and show clinical activity in women with BRCA1 or BRCA2 mutations. Tumour responses were seen during the first dose-escalation studies and many of these patients who had previously been treated with several lines of therapy had durable responses. The key side-effects seen in some patients were fatigue (30%), nausea (32%) and anaemia (5%) [8]. In the 19 patients with a BRCA1/2 mutation (which included ovarian, breast and prostate cancer), 63% had a clinical benefit from olaparib treatment with radiological or tumour-marker responses, or disease stabilization for a period of 4 months or greater. In an expansion phase in ovarian cancer, there was a 40% response rate [9]. Response rates were associated with the platinum-free interval, with an overall clinical benefit rate of 69.2%, 45.8% and 23.1% in the ‘platinum-sensitive’ (defined as recurrence 6 or more months after prior platinum therapy), ‘platinum-resistant’ (defined as recurrence <6 months after prior platinum therapy) and ‘platinum-refractory’ groups, respectively. Although responses were seen at 100 mg twice daily, a multicentre phase II study was undertaken to assess the efficacy and safety of oral olaparib monotherapy at the maximum tolerated dose (400 mg twice daily). Two cohorts of heavily pre-treated patients with a median of three previous chemotherapy regimens (range 1–16) and BRCA1/2 mutations were enrolled. An objective response was observed in 33% of patients in the 400 mg twice daily regimen and 13% of the 100 mg twice daily group, with a median PFS of 5.8 months [95% confidence interval (CI) 2.8–10.6] and 1.9 months (95% CI 1.8–3.6), respectively [10].

strategies to develop olaparib in ovarian cancer

The initial development pathway compared the activity of olaparib with pegylated liposomal doxorubicin (PLD) in BRCA-mutated ovarian cancer. The first multicentre, open-label phase randomized II trial included both a 200 mg bd dose of olaparib and the later established phase II dose of 400 mg bd. In ‘study 12’, 97 patients with ovarian cancer that recurred within 12 months of prior platinum therapy and with a confirmed germline BRCA1 or BRCA2 mutation were randomized to one of two doses of olaparib given continuously, or intravenous PLD, 50 mg/m² every 28 days. The median PFS was 6.5 months (95% CI 5.5–10.1 months), 8.8 months (95% CI 5.4–9.2 months) and 7.1 months (95% CI 3.7–10.7 months) for the olaparib 200 mg, olaparib 400 mg and PLD groups, respectively, with no statistically significant difference in PFS [hazard ratio (HR), 0.88; 95% CI 0.51–1.56; P = 0.66] for the combined olaparib doses versus PLD [11]. The overall response rates by RECIST were also not significantly different (25%, 31% and 18% for olaparib 200 mg, olaparib 400 mg and PLD, respectively). While the activity of olaparib was as anticipated from the phase I/II trials, the response to PLD in patients with a BRCA1/2 mutation was greater than expected. Subsequent retrospective data have confirmed that patients with recurrent ovarian cancer and a BRCA1/2 mutation respond well to PLD [12], a drug that causes DNA damage that is less well repaired in tumours with HRD.

During this time, other phase II studies were carried out that included women with recurrent ovarian cancer without a BRCA mutation. Emerging data from the Cancer Genome Atlas study suggested that HRD could be more widespread in ovarian cancer, particularly in high-grade serous tumours that are sensitive to platinum treatments [13]. A phase II study in recurrent ovarian cancer confirmed this; 11 out of 46 patients (24%; 14–38) without a BRCA mutation responded to olaparib [14].

maintenance therapy

The concept of evaluating olaparib as a maintenance therapy to extend PFS in recurrent ovarian cancer arose from the aforementioned data. A randomized trial, ‘study 19’ was launched in 2008 to measure the PFS following the addition of olaparib or placebo maintenance therapy following the completion of platinum-based chemotherapy for ‘platinum-sensitive’ high grade serous relapsed ovarian, fallopian tube or peritoneal cancer. A minimum of two prior platinum containing regimens was required for study entry, and the median number of regimens received in both arms was 3. In the 265 randomized patients BRCA status was known in 38%. The primary end point was PFS, which was significantly increased by olaparib, 400 mg bd (HR 0.35; 95% CI 0.25–0.49; P < 0.0001), extending the median time to progression or death following chemotherapy by 3.6 months (from 4.8 to 8.4 months) [15]. An early evaluation of overall survival (at 38% maturity) showed no difference, and this led to a temporary cessation of the development of olaparib, as it was felt unlikely that it would be approved by regulatory authorities. However, in a pre-planned subgroup analysis, it appeared that there might be a survival benefit in the subgroup with a known BRCA mutation. As a consequence, a retrospective analysis of BRCA status in germline and/or tumour was carried out as consent had been obtained at the outset of the trial. The germline BRCA and tumour BRCA status became available in 96% of the patients and 136 (51.3%) had a BRCA mutation in either germline or tumour (BRCAm) and 118 were BRCA wild-type. Re-analysis showed that the effect of olaparib in BRCAm patients was even greater. The median PFS was extended by 6.9 months, from 4.3 to 11.2 months [HR = 0.18; 95% CI (0.10, 0.31); P < 0.00001] [16]. A smaller but significant benefit was also seen in BRCA wild-type patients [HR = 0.54; 95% CI (0.34, 0.85); P = 0.0075]. There was no significant difference in overall survival at the second interim analysis (58% maturity). For the whole group, the HR was 0.88 (95% CI 0.64–1.21; P = 0.44); similar findings were noted for patients with BRCAm [HR 0.73 (0.45–1.17); P = 0.19]. However, the detection of differences in survival is confounded by crossover to a PARP inhibitor at a later date in 23% of patients taking placebo. The study confirmed that olaparib is well tolerated by most patients with fatigue, nausea and anaemia accounting for the greatest differences in side-effects compared with placebo. Dose interruptions due to side-effects occurred in 36% of those taking olaparib compared with 16% of patients on placebo. Similarly, dose reductions were more common in women taking olaparib than placebo, 42% versus 22%, respectively. Nine patients taking olaparib discontinued treatment due to adverse events compared with two in the placebo group.

It is well known that even large differences in PFS do not often result in significant differences in OS due to the effect of post-progression therapies and crossover. Consequently, the European Medicines Agency (EMA) proposed that the time to
subsequent progression after next-line therapy (PFS2) could be accepted as a secondary supportive regulatory end point to PFS [17]. Measurement of PFS is an important scientific and regulatory end point, but its practical clinical value is open to question. For patients, it is not so much the time to progression, but rather the time to the next line of treatment that is clinically important. Patients may not necessarily start a new line of treatment merely because of RECIST progression. Such decisions in ovarian cancer are usually based on composite information of the radiological appearances of the tumour, symptoms and the CA-125 level. In study 19, unblinding of the treatment allocation did not occur on progression. Many patients did not immediately restart chemotherapy on progression and some continued trial treatment beyond RECIST progression until the start of the next line of treatment. An exploratory analysis of TFST (Time to First Subsequent Therapy) and TSST (Time to Second Subsequent Therapy), an approximation of PFS2, was carried out to evaluate these secondary end points. In the overall population, the time to initiation of further treatment was significantly longer in the olaparib group than with placebo (13.4 versus 6.7 months, HR 0.40; 95% CI 0.30–0.52) and in both the BRCAm population (15.6 versus 6.5 months, HR 0.33; 95% CI 0.22–0.50) and wild-type BRCA subgroups (12.9 versus 6.9 months, HR 0.45; 95% CI 0.30–0.67) [16]. Olaparib also extended the time to second subsequent therapy in both BRCA1/2 mutated and BRCA1/2 wild-type tumours, suggesting that olaparib treatment did not adversely affect a response to subsequent treatment.

The results of the BRCAm subgroup analysis were submitted to the EMA and approval for maintenance olaparib was granted in October 2014. A submission to the USA Food and Drug Administration (FDA) was rejected but in December 2014, accelerated approval to use olaparib as a single agent in patients with a germline BRCA mutation who have had at least three prior lines of therapy was granted by the FDA. This was based on composite data from several studies, but principally, ‘study 42’ a trial of olaparib monotherapy that included 193 patients with ovarian cancer with a BRCA1/2 mutation [18]. The data reviewed by the FDA were in 137 women who had received three or more previous lines of therapy. In this group, 34% of women had responded to olaparib for an average of 7.9 months. Thus, on two sides of the Atlantic, there are very different implications for this disease defined by a genetically predictive biomarker. The implications for this are far-reaching as testing for BRCA mutations needs to be incorporated into clinical practice. It is estimated that up to 20% of women with high-grade serous ovarian cancer have a germline or somatic BRCA mutation [19] and many of these women do not have a family history of cancer [20]. Strategies for introducing routine BRCA mutation testing are being incorporated by individual countries. Their implementation can be complex; the cost of testing, involvement of local genetics units and social implications of identifying germline mutations all need to be taken into consideration. Furthermore, testing only for germline BRCA mutations will miss somatic mutations that may be present in 5%–6% of these tumours [21, 22].

development strategies of PARP inhibitors in ovarian cancer

The promising results seen with the early studies using olaparib, and temporary cessation of the development of olaparib announced in December 2011 led other manufactures of PARP inhibitors to develop similar a maintenance programme (Table 1). Both niraparib and rucaparib have been shown to be active in patients with a BRCA1/2 mutation [23, 24]. Both maintenance studies are including patients without a BRCAm, to test the effect of PARP inhibitors in the BRCA wild-type population, incorporating a companion diagnostic test for HRD. The SOLO1 trial with olaparib tablets has a similar design to SOLO2 but is evaluating the role of olaparib maintenance in the first-line setting. There continues to be interest in combining PARP inhibitors in ovarian cancer with a germline BRCA mutation [19] and many of these women do not have a family history of cancer [20]. Strategies for introducing routine BRCA mutation testing are being incorporated by individual countries. Their implementation can be complex; the cost of testing, involvement of local genetics units and social implications of identifying germline mutations all need to be taken into consideration. Furthermore, testing only for germline BRCA mutations will miss somatic mutations that may be present in 5%–6% of these tumours [21, 22].

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**Table 1.** Multi-centre trials intended to expand the licensing of PARP inhibitors in ovarian cancer

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<th>PARP inhibitor</th>
<th>Company</th>
<th>Target</th>
<th>Summary</th>
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<tr>
<td>Olaparib (AZD2281)</td>
<td>AstraZeneca</td>
<td>PARP1/2/3</td>
<td>Phase III trials with tablet formulation 1. 1st line (SOLO-1; NCT01844986) in BRCAm patients 2. Relapsed ‘platinum-sensitive’ high-grade serous and endometrioid tumours in BRCAm patients (SOLO-2; NCT01874353)</td>
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<td>Rucaparib (AG-014699; CO-338)</td>
<td>Clovis Oncology</td>
<td>PARP1/2</td>
<td>Ongoing phase II studies in ‘platinum-sensitive’ disease in conjunction with a companion diagnostic test for HRD (ARIEL2; NCT0189344). Randomized maintenance study in ‘platinum-sensitive’ recurrent high-grade ovarian cancer in both BRCAm, BRCA wild-type patients (ARIEL3; NCT01968213)</td>
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<tr>
<td>Veliparib (ABT-888)</td>
<td>Abbvie</td>
<td>PARP1/2</td>
<td>First-line 3-arm phase III in combination with carboplatin and paclitaxel, and one arm continuing veliparib maintenance therapy (GOG 3005; NCT02470585)</td>
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<td>Niraparib (MK4827)</td>
<td>Tesaro</td>
<td>PARP1/2</td>
<td>Ongoing phase III (NOVA; NCT01847274) maintenance in BRCAm and BRCA wild-type; companion diagnostic for HRD being developed for wild-type patients</td>
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inhibitors with chemotherapy. Although olaparib combined with carboplatin and paclitaxel for platinum-sensitive recurrent disease increased PFS over chemotherapy alone, the results did not suggest an additive effect of olaparib and chemotherapy; the dose and schedule of both carboplatin and olaparib had to be altered to reduce toxicity [25]. However, veliparib in combination with carboplatin and paclitaxel is being evaluated in a three-arm trial (GOG 3005), comparing veliparib with chemotherapy, and also as maintenance in the first-line treatment of ovarian cancer. In 2015, rucaparib was given ‘breakthrough’ status by the FDA and it is likely that some if not all the other PARP inhibitors will be licensed in the future. While a choice of drug may exist, there are still many key unanswered questions, such as: when in the treatment pathway should PARP inhibitors be used? Are they best used as maintenance treatment after chemotherapy, or as monotherapy for active disease? What are the mechanisms responsible for resistance, and can patients be re-treated with the same or a different PARP inhibitor later in the treatment pathway?

‘second generation’ molecular combination therapy studies

It has been hypothesized that there may be synergy between PARP inhibitors and other signalling pathways inhibitors with little overlapping toxicity. Pre-clinical studies have demonstrated the additive effect of anti-angiogenesis and PARP inhibition as hypoxia leads to down-regulation of HR repair proteins and enhanced PARP inhibitor sensitivity [26, 27]. A phase I trial combining the oral VEGF receptor tyrosine kinase inhibitor, cediranib with olaparib demonstrated activity in recurrent ovarian cancer with an objective response rate of 44% [28] leading to a randomized phase II study that was recently reported. Liu et al. randomized patients with relapsed high-grade serous or endometrioid ovarian cancers to olaparib (400 mg capsules twice-daily, \(n = 46\)) monotherapy, or the combination of olaparib and cediranib (cediranib 30 mg daily and olaparib 200 mg twice daily, \(n = 44\)). BRCA1/2 mutations were present in 52% of patients in both treatment arms. The median PFS was significantly longer in the combination arm than for olaparib alone, 17.7 versus 9.0 months (HR 0.42; 95% CI 0.23–0.76; \(P = 0.005\)), and the objective response rate higher, 79.6% versus 47.8% (odds ratio 4.24, 95% CI 1.53–12.22; \(P = 0.002\)) [29]. An exploratory analysis was carried out in BRCA mutation and BRCA wild-type or unknown subsets which showed that the relative benefit appeared greater in patients in the BRCA1/2 wild-type/unknown group, median PFS 16.5 versus 5.7 months in the BRCA-mutated group (HR 0.32, 95% CI 0.14–0.74). This retrospective analysis should be interpreted with caution as the number of patients in each subset was small. These results suggest that the combination of olaparib and cediranib could be synergistic and the results have led to the launch of new studies combining olaparib with cediranib, or other anti-angiogenic agents, and trials with other PARP inhibitors and anti-angiogenic agents (Table 2).

summary

PARP inhibitors are a new group of drugs for the treatment of ovarian cancer. Olaparib is the first-in-class to be licensed for the treatment of recurrent ovarian cancer harbouring deleterious BRCA mutations. These constitute the first predictive markers for the treatment of ovarian cancer. Two different indications for use in the United States and Europe underline the complexity of clinical trial approvals, but also the versatility of this type of drug. Several other PARP inhibitors are undergoing clinical trials in the maintenance setting, in combination with chemotherapy, and with other molecular targeted therapies. Results are expected during the next 2–5 years and will most likely extend the opportunities for treatment of ovarian cancer. Testing for BRCA mutations now needs to be incorporated into everyday clinical practice, so that patients have the opportunity of benefiting from this new personalized therapy.

<table>
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<th>Table 2. Phase III clinical trials combining anti-angiogenic drugs with PARP inhibitors</th>
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<td>Niraparib</td>
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HGOG, high-grade serous or endometrioid.
disclosure

JAL is chief investigator on the AstraZeneca-sponsored ‘Study 19’ olaparib trial and has received funding for lectures on olaparib. He is the joint lead co-ordinating investigator for ARIEL 3 and has attended Advisory Boards for Clovis Oncology with funding to his institution.

references