Update on PARP inhibitor therapy for solid tumors

Abstract

Poly (ADP-ribose) polymerases (PARPs) play an important role in DNA damage repair. They are primarily involved in base excision repair in single strand breaks. So far, the clinical trial results are very promising in breast and ovarian cancer with deleterious germline BRCA1 and BRCA2 mutations, and their use is expanding to include other solid tumors with homologous recombination (HR) repair defect. Studies suggest a correlation between tumor sensitivity to platins and response to PARP inhibitors (PARPi) in women with ovarian cancer. The hypothesis is that by interfering with DNA repair, PARPi sensitize cells to DNA-damaging chemotherapies and radiation therapy. This article provides an overview of clinical trial results obtained with PARPi in the treatment of breast, ovarian, prostate, gastric, pancreatic, and lung cancers. In addition, we review resistance mechanisms to PARPi, toxicities of PARPi, and potential treatment combinations with PARPi.

Keywords: BRCA1, BRCA2, breast cancer, ovarian cancer, niraparib, olaparib, PARP inhibitor,rucaparib, talazoparib, veliparib

Abbreviations: SSB, single-strand break; HR, homologous recombination; NHEJ, non-homologous end joining; PARPi, PARP inhibitors; PFS, progression-free survival; CT, care chemotherapy; CI, confidence interval; TNBC, triple-negative breast cancer; FDA, food and drug administration; G-CSF, granulocyte colony stimulating factors

Introduction

PARP function in DNA damage repair

There are different types of DNA defects caused by chemicals and environmental factors which include single-strand break (SSB), mismatch repair (MMR), and double-strand break (DSB). Polyadenosine diphosphate [ADP] ribose polymerase-1 (PARP1) and -2 (PARP2) enzymes are responsible for repair of most of the SSB. When those proteins are recruited to the damaged site, the PARP-DNA interaction becomes unstable so that DNA repair can proceed. If the SSB are not repaired, they are converted to DSB. In that situation, another repair mechanism called homologous recombination (HR) will play a role. This mechanism is well represented in PARP1 knockout mice that SSB could not be repaired, but HR repair and non-homologous end joining (NHEJ) pathways were able to repair the formed DSB (Figure 1). HR is slower than NHEJ, but it is more accurate.

![Figure 1 PARP function and mechanism](Adapted by Rimar et al, Cancer, 2017).
In homologous recombination and synthetic lethality

As explained above, BRCA1 and BRCA2 proteins play an important role in the HR repair pathway. If they are dysfunctional, DSB can’t be repaired. If both PARP and BRCA repair enzymes are insufficient, then DNA damage may become irreversible and result in apoptosis. Therefore, inhibition of PARPi leads to very selective toxicity in BRCA1/2-deficient cells, but sparing the BRCA proficient cells, the so-called synthetic lethality (Figure 2). The other example of synthetic lethality is seen with the platinum agents, where, interstrand cross linking caused by platinum agents is not adequately repaired by homologous recombination deficient cells leading to cell death through mitotic catastrophe or apoptosis.

PARPi inhibitors (PARPi) mechanism of action

When PARPi are given to a patient, unrepaired DSBs will cause apoptosis and cell death. Another mechanism which has been attributed to PARPi were shown by Murai et al. in which PARPi creates an irreversible bond between PARPi and DNA damaged site, known as “PARP-trapping” (Figure 1). This irreversible complex also will result in cell death. Recently, PARPi has also been shown to induce mitophagy (degradation of mitochondria by autophagy) and cell apoptosis.

There are currently several PARPi in clinical development, including olaparib, veliparib, niraparib, rucaparib, and talazoparib all of which bind to both PARPi1 and PARPi2, but they have different potency in PARPi trapping. Talazoparib is known as the most potent PARPi, thus requiring lower concentrations of talazoparib is enough to fully inhibit PARPi-1 and -2. Rucaparib is another PARPi which is shown to inhibit tankyrase 1 and 2 as well as PARPi -4, -12, -15, and -16.

PARPi monotherapy in metastatic breast cancer (MBC)

Olaparib: The first clinical trial conducted to assess the efficacy, safety, and tolerability of olaparib monotherapy in BRCA1 or BRCA2 mutation positive women with MBC who had received three or more lines of chemotherapy previously. Overall response rates (ORR) ranged from 22% to 41% with favorable toxicity profile. However, a phase II study evaluating olaparib monotherapy 400 mg twice a day among patients with MBC (n=26, 81% TNBC) did not show any responses in neither germline BRCA1/2 (gBRCA1/2) mutation positive (n=10) nor negative (n=16) cases, even though the target lesions were reduced in size by >30% in 50% patients with positive gBRCA1/2 mutations. Following these discouraging results, finally came positive results from the phase III OlympiAD trial. In this trial, patients with gBRCA-mutated HER2-negative MBC who had received ≤2 prior therapies were enrolled and olaparib monotherapy (300-mg PO BID) was compared to standard of care chemotherapy (CT) (vinorelbine, capecitabine or eribulin). After a median follow-up of 14.5 months, progression-free survival (PFS) was significantly longer with olaparib versus CT (7.0 vs 4.2 months; hazard ratio [HR], 0.58; 95% confidence interval (CI), 0.43–0.8; P<0.001); ORR in the olaparib group was also higher (59.9% vs 28.8%). On the other hand, the overall survival (OS) outcomes was not different (19.3 months in olaparib arm vs 19.6 months in CT arm; HR 0.90, 95% CI: 0.63–1.29, p=0.57). The greatest benefit from olaparib were seen in group of patients who were platinum-naive and also in patients with triple-negative breast cancer (TNBC). In this trial, patients who had olaparib had fewer grade 3/4 toxicities compared to CT (16.1% vs 4.4%). After these encouraging results, Based on these results, Food and Drug Administration (FDA) approved olaparib in January 2018.
for gBRCA1/2-mutated HER2-negative MBC setting after 1 prior line of chemotherapy, or endocrine therapy if they have ER-positive MBC.

**Talazoparib:** The EMBRACA study is a recently reported phase III clinical trial comparing talazoparib, 1 mg orally daily to CT (eribulin, vinorelbine, capetitabine, or gemcitabine) in patients with gBRCA-mutated MBC who had ≤3 lines of chemotherapy in the advanced setting. Median PFS was significantly prolonged with talazoparib versus CT (8.6 vs 5.6 months; HR, 0.54; P<0.0001), and the ORR was superior (62% vs 27%; HR, 5.0; P<0.0001). The HR for death was 0.76 (95% CI, 0.55 to 1.06; P=0.11). Any hematologic grade ≥3 adverse events were more common in PARPi group vs chemotherapy group (55% vs 38%), including grade 3 or 4 anemia (39.2% vs 4.8%) and thrombocytopenia (15% vs 2%); only neutropenia was less common with talazoparib (21% vs 35%). In contrast to OlympiAD trial, all subsets of patients benefited from talazoparib, ER-positive vs TNBC, platinum-naïve vs not, presence or absence of brain metastases, or BRCA mutation status. In October 2018, The FDA approved talazoparib for ≥1st line monotherapy for gBRCA-mutated HER2-negative MBC.

**Niraparib and Rucaparib:** Niraparib has been tested in two phase III clinical trials, one of which is looking at single-agent niraparib therapy versus CT for gBRCA-mutated HER2-negative MBC patients who had ≥2 lines of CT in metastatic setting (BRAVO trial) (Table 1). At the present time, rucaparib is in early phases of development. Rucaparib is undergoing single arm phase II trial NCT02505048 (RUBY) as a monotherapy in HER2-negative MBC patients who had ≥1 lines of CT in the metastatic setting, and who carry a BRCA1ess tumor profile which was defined as “high tumor genomic LOH” score and/or a somatic BRCA mutation, but no BRCA1/2 germine mutations.

### Table 1 selected phase III trials in breast cancer

#### Advanced/metastatic setting

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>OlympiAD</td>
<td>Olaparib vs PCT</td>
<td>gBRCA, ≤2 prior lines</td>
</tr>
<tr>
<td>LUCY</td>
<td>Single arm olaparib</td>
<td>gBRCA, ≤1 prior lines containing taxane or anthracycline</td>
<td>Active and recruiting</td>
</tr>
<tr>
<td>Veliparib</td>
<td>BROCADE 3</td>
<td>C+P+V→maintenance V vs C+P+placebo</td>
<td>gBRCA, ≤2 lines of therapy</td>
</tr>
<tr>
<td>Talazoparib</td>
<td>EMBRACA</td>
<td>Talazoparib vs PCT</td>
<td>gBRCA, ≤3 prior lines</td>
</tr>
<tr>
<td>Niraparib</td>
<td>BRAVO</td>
<td>Niraparib vs PCT</td>
<td>gBRCA, ≤2 prior lines</td>
</tr>
</tbody>
</table>

#### Neoadjuvant setting

| Veliparib | BrighTNess | C+P+V (CPV)→AC vs C+P+placebo (CPP)→AC | TNBC | pCR: CPV: 53% vs CPP: 57% (p=NS) |
| Olaparib | PARTNER | Olaparib+weekly P+C vs Placebo+P→AC | TNBC or gBRCA, stage III, HER2(-), BRCA1-like breast cancer patients | Active and recruiting |
| SUBITO | ddAC→C+P→olaparib maintenance vs ddAC→CTC | |

#### Adjuvant setting

| Olaparib | OlympiA | Olaparib vs Placebo | gBRCA, post-completion SOC neo/adjuvant therapy | Active, not recruiting |

**Abbreviations:** AC, doxorubicin+cyclophosphamide; C, carboplatin; V, veliparib; gBRCA, germline BRCA mutated; P, paclitaxel; PCT, physician’s choice of chemotherapy; SOC, standard of care; TNBC, triple-negative breast cancer; CTC, cyclophosphamide 3000mg/m² day 1 mesna 500 mg (push) + 2000 mg in 24 hours day 1 carboplatin (400 mg/m²; days 1,2 thiopeta 250 mg/m² day 2; NS, non-significant

PARPi monotherapy in early stage breast cancer

Olaparib: Olympia A (NCT02032823) is a phase III trial evaluating olaparib at 300mg PO BID for 1 year in patients with high-risk stage 2/3 gBRCA1/2 mutated breast cancer. The Olympia A trial has now completed enrollment and results are awaited.

Talazoparib: A neoadjuvant setting, talazoparib was given for 2 months to 13 patients with early-stage gBRCA1/2 associated breast cancer. Overall response rate was almost 100%. This study is now evaluating extended neoadjuvant talazoparib therapy.

Combining PARPi with chemotherapy in breast cancer

Myelosuppression is the primary dose-limiting toxicity for PARPi, which has made combination of PARPi with cytotoxic chemotherapies difficult. Veliparib has been considered the most suitable PARPi to combine with cytotoxic agents because of its modest hematotoxicity. Different strategies have been employed to mitigate the myelosuppressive effects of PARPi: PARPi dose reduction, intermittent dosing schedules, and support with granulocyte colony stimulating factors (G-CSF). It is not currently clear which one is a more viable therapeutic option, but the results of the phase III BrighTness trial (discussed later) suggests that using subtherapeutic doses of PARPi in combination with standard dosages of cytotoxic chemotherapeutic agents does not significantly improve clinical outcomes.

Veliparib plus chemotherapy: The results of the 3-arm, randomized, placebo-controlled phase III BrighTness trial which evaluated carboplatin/taxol plus veliparib versus carboplatin/taxol versus taxol alone followed by 4 cycles of doxorubicin and cytoxan chemotherapy given neoadjuvantly to patients with TNBC. This trial did not show any benefit addition of veliparib (PCR rates were 53% vs 57%, respectively). It should be noted that paclitaxel, 80 mg/m², and carboplatin AUC6 were standard full doses, but the veliparib dose is 1/8 of the monotherapy dose of veliparib, 400 mg twice daily.

In phase II BROCADE study, Han et al. evaluated the safety and efficacy of addition of veliparib to either temozolomide (VT) or carboplatin/paclitaxel (VCP) versus carboplatin/paclitaxel alone (PCP) in gBRCA1-mutated MBC patients. In contrast to BrighTness trial, ORR was much better after the addition of veliparib (77.8% vs 61.3%; P=0.02). However, survival outcomes were not different. An ongoing phase III BROCADE trial is testing VCP vs PCP, followed by maintenance veliparib in this patient population. The veliparib dose is 120 mg PO BID and is only given on days 1–7 of every 4 week cycle. We eagerly await results from this trial.

Olaparib plus chemotherapy: The placebo-controlled PARTNER trial (NCT03150576) is a phase III trial testing the combination of olaparib and weekly taxol and carboplatin AUC 5 in neoadjuvant setting among patients with TNBC and/or gBRCA mutated breast cancer. Stage 1 accrual is complete and stage 2 began in August 2017.

The phase II NCT01074970 trial is evaluating 2-year DFS among patients with gBRCA-mutated TNBC treated with single agent cisplatin versus cisplatin plus rucaparib following neoadjuvant systemic therapy. SUBITO is a randomized, (ne)adjuvant phase III trial in stage III, HER2-negative, germline BRCA1 or BRCA 2 mutated or BRCA1-like breast cancer patients, comparing standard of care chemotherapy followed by one year of adjuvant olaparib and high dose chemotherapy. Table 1 shows the most important randomized phase III trials investigating the use of PARPi, either as a single agent versus combined with chemotherapy in different settings.

Combining PARPi with immunotherapy in breast cancer

Combining immunotherapy with PARPi is a promising approach because BRCA mutated cancers are more genomically unstable due to the defect in HR, and therefore may be more immunogenic. The expected cross-toxicity is also limited.

Olaparib plus immunotherapy: Olaparib plus durvalumab in patients with advanced solid tumors who had prior therapy with antracycline/taxane/platinum-containing chemotherapy regimens was tested in MEDIOLA trial is a phase II/II trial. Patients received olaparib, 300mg orally twice daily for 4 weeks which was followed by olaparib plus durvalumab combined therapy. Of 25 patients enrolled, the ORR was 67% in patients who had this regimen as a first line therapy. Median PFS has not been reached at the time of presentation. Phase II DORA (NCT03167619) is studying olaparib in combination with durvalumab in platinum-treated metastatic TNBC.

Other PARPi plus immunotherapy: Additional PARPi and PARPi combination studies are also in development. Niraparib plus pembrolizumab is being studied in a phase I/II study among TNBC and ovarian cancer patients (TOPACIO/Keynote-162/NCT02657889). Phase II NCT02849496 will evaluate veliparib plus atezolizumab in gBRCA1/2+ TNBC patients. Phase IIb/JA VELIN PARP MEDLEY (NCT03330405) will enroll patients with gBRCA1/2+ or ATM-mutation associated breast cancer for evaluation of talazoparib plusavelumab.

PARP inhibition in ovarian cancer

Approximately 41-50% of ovarian carcinomas are estimated to exhibit homologous recombination defect (HRD). However, the frequency of HRD varies among ovarian cancers associated with germline mutations versus somatic mutations, and according to the histological subtype. Pennington et al. found that defective HR genes (germline or somatic) are found in 31% of ovarian carcinomas. Elvin et al. evaluated the presence of BRCA mutations or loss of heterozygosity (LOH) in different histological subtypes. The serous subtype was associated with a higher prevalence of HRD, with 43.8% of the patients presenting BRCA mutations (gBRCAmut, 18.7%) or BRCA wild-type/LOH-high (BRCAwt/LOH-high, 25.1%). In relation to high-grade versus low-grade serous carcinoma, Norquist et al. found a vital difference in germline and somatic mutation rates of HR genes, which were 10.9% for low-grade versus 27% for high-grade serous ovarian carcinoma (HGSOC) (HR, 0.33; 95% CI, 0.1-0.8; p=0.02).

Olaparib: Kaufman et al. evaluated efficacy of olaparib in 137 gBRCA-mutated recurrent ovarian cancer patients who had received ≥ 3 lines of chemotherapy. The results were impressive in this heavily treated population. The reported ORR, PFS and OS were 34%, 7.9 months and 16.6 months, respectively. Most toxicities were manageable. On the basis of these data, FDA approved olaparib as a single agent in patients with advanced gBRCA-mutated ovarian cancer who had ≥ 3 or more lines of chemotherapy.

In the SOLO 1 phase 3 trial, patients with newly diagnosed or platinum-sensitive stage III or IV high-grade serous or endometrioid ovarian cancer (HGSOC and HGEOC), primary peritoneal cancer, or fallopian-tube cancer with a germline or somatic BRCA1/2 mutations were given olaparib maintenance therapy. After a median follow-up of 41 months, HR for risk of death was 0.30 in olaparib arm compared
Update on PARP inhibitor therapy for solid tumors

Results

Population

Olaparib 300 mg BID
Median PFS: 19.1 vs 5.5 mo (p<0.0001)

Design

Table 2

Selected phase II/III trials in ovarian cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>SOLO 1</td>
<td>Olaparib 300 mg BID maintenance vs placebo</td>
<td>Platinum sensitive HGSOC after first line platinum based CT, germline or somatic BRCA mutation</td>
</tr>
<tr>
<td></td>
<td>SOLO 2</td>
<td>Olaparib 300 mg BID maintenance vs placebo</td>
<td>Platinum sensitive recurrent HGSOC or HGEOC, primary peritoneal or fallopian tube cancer, gBRCA mutant</td>
</tr>
</tbody>
</table>

**Table 3** Selected phase III trials in pancreatic and prostate cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLO 3</td>
<td>Olaparib 300 mg BID vs PCT(NCT02282020)</td>
<td>Platinum sensitive recurrent HGSOC or HGEOC, primary peritoneal or fallopian tube cancer, germline or somatic BRCAmut</td>
<td>ORR: 72.2% for olaparib vs 51.4% PCT (p=0.002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS: 13.4 vs 9.2 mo (p=0.013)</td>
</tr>
<tr>
<td>Study 19</td>
<td>Olaparib 400 mg BID maintenance vs placebo</td>
<td>Platinum sensitive recurrent HGSOC or HGEOC, primary peritoneal or fallopian tube cancer, germline or somatic BRCAmut</td>
<td>PFS: 8.4 vs 4.8 mo (p=0.0001) OS: 29.8 vs 27.8 mo (HR, 0.73)</td>
</tr>
<tr>
<td>PAOLA-1</td>
<td>Olaparib vs Placebo plus Carboplatin/ Paclitaxel/ Bevacizumab as primary treatment and maintenance</td>
<td>Advanced FIGO stage IIIb - IV HGSOC or HGEOC, fallopian tube, or peritoneal cancer</td>
<td>ongoing</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>ARIEL 2 PART 1 Rucaparib 600mg BID</td>
<td>Platinum sensitive recurrent HGSOC or HGEOC, primary peritoneal or fallopian tube cancer</td>
<td>Median PFS: BRCAmut: 12.8 mo (p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCAwt LOH high: 5.7 mo (p=0.011) BRCAwt LOH low: 5.2 mo (p=0.011)</td>
</tr>
<tr>
<td>ARIEL 3</td>
<td>Rucaparib 600 mg BID maintenance vs placebo</td>
<td>Platinum sensitive recurrent HGSOC or HGEOC, primary peritoneal or fallopian tube cancer</td>
<td>Median PFS: BRCAmut:16.6 vs 5.4 mo (p&lt;0.0001) HRD+: 13.6 vs 5.4 mo (p&lt;0.0001) ITTP: 10.8 vs 5.4 mo (p&lt;0.0001)</td>
</tr>
<tr>
<td>ARIEL 4</td>
<td>Rucaparib 600 mg BID vs PCT</td>
<td>Platinum sensitive or resistant recurrent HGSOC or HGEOC, primary peritoneal or fallopian tube cancer</td>
<td>ongoing</td>
</tr>
<tr>
<td>NCT01968213</td>
<td>Switch Maintenance Monotherapy</td>
<td>HGSOC or HGEOC, primary peritoneal or fallopian tube cancer</td>
<td>ongoing</td>
</tr>
<tr>
<td>Niraparib</td>
<td>NOVA Niraparib 300 mg maintenance vs placebo</td>
<td>Platinum sensitive recurrent HGSOC, primary peritoneal or fallopian-tube cancer</td>
<td>Median PFS: gBRCAmut: 21 vs 5.5 mo (p=0.001) BRCA wt HRD+: 12.9 vs 3.8 mo (p=0.001) Overall non-gBRCA: 9.3 vs 3.9 mo (p&lt;0.001)</td>
</tr>
<tr>
<td>Veliparib</td>
<td>NCT02470585 Velparib with Carboplatin and Paclitaxel as continuation maintenance therapy</td>
<td>Newly diagnosed FIGO stage IIIb - IV HGSOC or HGEOC, fallopian tube, or peritoneal cancer</td>
<td>ongoing</td>
</tr>
</tbody>
</table>

**Abbreviations:** PTS, patients; HGSOC, high grade serous ovarian cancer; OC, ovarian cancer; HGEOC, high-grade endometrioid cancer; BRCA mut, BRCA mutated; CT, chemotherapy; HRD+, homologous recombination deficiency positive; PFS, progression free survival; ORR, objective response rate; DCR, disease control rate; MDR, median duration of response; gBRCA, germline BRCA mutated; BRCA wt, BRCA wild type; LOH, loss of heterozygosity; ITTP, Intention to treat population; NR, not reached; PCT, physician's choice of chemotherapy

DOI: 10.15406/jcpcr.2019.10.00400
PARP inhibition in prostate cancer

Germline BRCA2 carriers have a 5 to 9 times more risk of developing prostate carcinoma.10 BRCA-associated prostate cancers are more aggressive than non-BRCA associated prostate cancers.39 Among all prostate cancers, 8-14% of them are associated with BRCA deleterious mutations.60,61 Additionally, 20% of all prostate cancers have deficient PTEN expression which can result in HR repair defects and make the tumor more susceptible to PARPi.62

PARPi olaparib was tested in 19 patients with advanced prostate cancer in the TOPARP-A trial (Trial of Olaparib in Patients with Advanced Castrate Resistant Prostate Cancer).44 This trial shed light into the subgroup of patients who may benefit from PARPi. According to this trial, 88% of patients who had a germline or somatic deletions mutations in BRCA1/BRCA2, ATM serine/threonine kinase (ATM), Checkpoint kinase 2 (CHEK2), or Fanconi anemia gene had a positive response to olaparib compared to only 6% of patients who did not have any alteration in any of those genes.44 After these results are published, FDA approved the use of olaparib in metastatic castration-resistant prostate cancer (CRPC) patients with BRCA1/2 or ATM alterations who have progressed on chemotherapy and at least one hormonal agent (abiraterone or enzalutamide). The phase 3 PROFOUND study was designed after these encouraging results are reported. This trial will include patients who had failed at least one hormonal agent and patients will be screened for somatic HR deficiency mutations and will then be randomized to either another AR-targeted therapy or olaparib.

The phase II trial TRITON2 (NCT02952534) is studying rucaparib 600mg twice daily in CRPC patients with a germline or somatic alteration in BRCA1/2 or HR deficiency who progressed on ≥1 lines of AR–targeted therapy and 1 line of chemotherapy.48 According to the preliminary results presented at ESMO, 48% and 45% of BRCA carriers had a PSA response and radiological response, respectively. Now the continuation trial, the phase III TRITON3, will be evaluating rucaparib efficacy compared to physician’s choice of abiraterone, enzalutamide, or docetaxel.

Molecular studies suggest that PARP1 may also be involved in regulation of AR activity at later stages of androgen-independent action. PARP1 activity is significantly increased in CRPC cells compared to hormone sensitive prostate cancer cells, and PARP1 causes depletion of both the AR and PARP1 on chromatin in CRPC cells.46 Mathew et al.47 are testing the combination of PARPi with AR-targeted therapy to increase the cancer cells sensitivity to PARPi, and another group is testing PARPi plus radiation due to their synergistic impact on cell death.48,49

PARPi leading to absence of DNA repair and cell death, will increase the antigenicity as there will be increased DSB and this enhanced antigenicity may increase the efficacy of immune check point inhibitors. Therefore, studies are going on regarding combination therapy of olaparib with durvalumab (PD-L1 inhibitor) in prostate cancer (NCT02484404). At 2017 Annual meeting of American Society of Clinical Oncology, preliminary results were presented, which showed >50 reduction in PSA in 43% patients who got treatment for 2 months.50

PARP inhibition in GI malignancies

Gastric cancer: There is a low prevalence of BRCA mutations in gastric cancer. Low ataxia telangiectasia mutated (ATM) levels have been shown to be associated with olaparib sensitivity in gastric cancer cell lines.51 Thirteen percent to 22% of tumors from patients with gastric cancer have low or undetectable ATM expression,52 so may be an attractive target for PARP inhibition.

A phase II trial evaluated the efficacy of olaparib combined with paclitaxel as second-line therapy in Asian patients with advanced gastric cancer.53 One hundred and twenty-four patients were randomly assigned to paclitaxel with olaparib vs. paclitaxel with placebo. Forty-four percent of patients had ATM low gastric tumors. Olaparib did not lead to a significant improvement in PFS; however, it significantly improved OS vs. placebo in both the overall population (13.1 vs. 8.3 months, P=0.005) and the ATM low population (not reached vs. 8.2 months, P=0.002). On the other hand, in the phase III GOLD trial, olaparib/paclitaxel did not meet its primary endpoint of improvement in OS.54 The study randomized 525 Asian patients with advanced gastric cancer to olaparib plus weekly paclitaxel or paclitaxel alone. Median OS was 8.6 months in the olaparib arm and 6.9 months in the placebo arm (HR =0.79, P=0.0262). In ATM protein-negative patients (n=94), OS was 12.0 vs. 10.0 months, respectively (HR =0.73, P=0.2458). The lack of benefit was seen in both the entire study population and in patients selected for ATM protein negativity.

Pancreatic cancer: Familial pancreas cancer is associated with BRCA1 and BRCA2 mutations.55 Among patients with FPC, 3.7%–5.6% carry BRCA2 mutations, and 1.2% carry BRCA1 mutations.55 Hu et al.56 reported even higher prevalence (14%) of mutations in 4 selected genes (BRCA1, BRCA2, ATM, and MSH6). The optimal chemotherapy regimen is not known for these patients and currently they are treated with the same regimens we use for patients with no mutations. There are reports showing that they may be more susceptible to platinum-containing chemotherapy regimens.

Several clinical trials of PARP inhibitors are underway testing PARPi maintenance therapy after platinum-based induction regimen. The results of the RUBRACA trial were recently reported in AACR 2019 meeting which showed PFS of 9.1 months, and median overall survival has not been reached yet. RUCAPANC trial reported 32% ORR among patients with APC harboring BRCA1/BRA2 mutation.57 Veliparib on the other hand has not shown any benefit among this patient population.58,59

Phase III POLO trial60 APC patients with germline BRCA1/BRCA2 mutated APC were treated with olaparib 300 mg twice daily or placebo after ≥16 weeks of platinum-based regimen. PFS were improved in olaparib arm versus placebo arm (7.4 months versus 3.8 months, HR=0.56, P=0.004). On the other hand, OS was not different (18.9 months versus 18.1 months, HR=0.91, P=0.68).

Veliparib plus GEM/CDDP was studied in patients with untreated germline BRCA1/BRA2 mutated APC. The ORR was 78% with median OS of 23 months in BRCA-mutated cases.61 A randomized phase II trial of GEM/CDDP with or without veliparib is being performed for APC patients both harboring BRCA mutation as well as PALB2 mutation (NCT01585805).

PARP inhibition in small cell lung cancer (SCLC)

PARP protein levels are upregulated in SCLC relative to other lung cancers.62 In particular, PARP1 has been found to be highly expressed at both the mRNA and protein levels in SCLC samples. In a phase I study of extensive stage SCLC, patients were treated with talazoparib monotherapy; ORR was 9% and the clinical benefit rate at ≥16 weeks was 26%.63 Clinical trials of a number of PARPi, in a range of different treatment settings, are ongoing in patients with SCLC.
BRCA1/2 mutations are notably rare in primary human SCLCs, occurring in ~2% of cases, and HRD-assay scores do not seem to correlate with sensitivity to PARPi in SCLC cell lines. A distinct mechanism, high expression levels of schlafen family member 11 (SLFN11), has been identified as a critical determinant of PARPi sensitivity in SCLC cell lines and patient-derived xenografts. In a randomized phase II clinical trial, SCLC patients treated with temozolomide and veliparib who had favorable ORR, PFS, and OS had high levels of SLFN11 expression. The utility of SLFN11 expression as a predictive biomarker for PARPi therapy in SCLC will require validation in prospective trials.

Toxicities

Each of the three different PARPi inhibitors has its own specific indications and individual toxicity profiles. With olaparib, the most commonly reported AE include nausea (59–78%), fatigue (41–65%), vomiting (34–50%), and anemia (12–32%). The olaparib-related MDS/AML is rare, occurring in 1% of patients treated with this agent which can happen from 6 months to 2 years’ after therapy. It is only seen in gBRCA-mutation carriers.

The dose-limiting toxicity (DLT) profile of veliparib is different from that of olaparib which include more nausea/vomiting and seizures. The reported AEs for veliparib in phase II trials are generally low grade and include fatigue (6%), nausea (4%), and leukopenia (2%). The most common side effects of niraparib are fatigue, pneumonitis, and thrombocytopenia in the phase I trial. Talazoparib has a toxicity profile very similar to that of chemotherapy.

CYP3A inhibitors and/or inducers should not be used with olaparib, as olaparib is primarily metabolized by the CYP3A enzymes. Furthermore, since thrombocytopenia is common with niraparib and talazoparib, antiplatelet and anticoagulation drugs should be avoided.

Mechanisms of resistance

15% of ovarian cancer patients with BRCA-deficient tumors remain disease free for more than 5 years from the beginning of the olaparib therapy, so many patients develop resistance. Several mechanisms have been postulated including new shifting mutations in BRCA1/2 genes, using ATM-dependent HR repair pathway, and increased expression of BRCA1, RAD54L, and RMI2 proteins.

Conclusion

Compelling clinical data, particularly in ovarian cancer, led to reevaluation of these agents in various cancers. The approval of these agents in metastatic gBRCA mutated breast cancer and in first line (germline or somatic BRCA mutated), second line maintenance (with or without BRCA mutation) and palliative settings in gBRCA mutated ovarian cancer and promising results in other solid cancers has created enormous enthusiasm in practicing clinicians to incorporate this drug in their therapeutic armamentarium. Although to date, there is no data demonstrating an OS benefit for PARPi inhibitors in breast cancer patients, none of the studies have been powered to detect OS. The ongoing phase III trial OlympiA is powered to assess OS in patients with HER2-negative breast cancer with gBRCA1/2 mutations treated with olaparib in the adjuvant setting; data are expected in 2020. Further accumulation of evidence may yield OS benefit through the studies incorporating OS as the primary end point.

Future perspectives

Future studies are required to better define which patients to treat with PARPi and whether the target population can be extended beyond those with gBRCA mutations. It will also be important to assess when to treat these patients; how to sequence these drugs with currently established therapies, particularly platinum agents; how to combine PARPi with other novel therapies; and how to overcome resistance. The data so far suggests that platinum sensitivity predicts response to PARP inhibitors, PARP inhibitors may be useful radiosensitizers and chemosensitizers, and that intermittent dosing and G-CSF support are feasible tactics to mitigate myelosuppressive toxicities of PARP inhibitors when combined with cytotoxic chemotherapies.

Acknowledgments

None.

Conflicts of interest

The authors declare there is no conflict of interest.

References

Update on PARP inhibitor therapy for solid tumors


Update on PARP inhibitor therapy for solid tumors


