PARP Inhibitors for Recurrent Ovarian Carcinoma: Current Treatment Options and Future Perspectives

PARP-Inhibitoren beim rezidivierenden Ovarialkarzinom, aktuelle Therapieoptionen und zukünftige Entwicklungen

Abstract

More than simply a promising management option, PARP inhibitors can be regarded as a milestone in the development of personalised treatment of recurrent ovarian carcinoma. Their mechanism of action, known as “synthetic lethality”, is dependent on functional differences of the DNA repair mechanisms of healthy cells and tumour cells; cells that repair DNA damage less efficiently are particularly sensitive to PARP inhibitors. Olaparib, licensed for use this year, is the best studied PARP inhibitor used for treatment of high-grade serous ovarian carcinoma (HGSC). The efficacy ofPARP inhibitors appears to be increased when used in combination with other treatments.

Introduction

Ovarian carcinoma is the 5th most common cause of cancer related death in German women and has the highest mortality of all gynaecological cancers [1]. Treatment options have continued to improve in recent years due to both better operative techniques and systemic therapies, however a relative 5-year survival rate of 42% [1] is still disappointing; most patients have disease recurrence despite radical surgery and platinum/taxane-based chemotherapy [2]. Ovarian carcinoma is usually sporadic with 5 to 10% being hereditary, mostly with mutations of the BRCA1 and/or BRCA2 genes. Women with a BRCA1 mutation have a 40–55% lifetime risk of ovarian carcinoma before the age of 70; for carriers of BRCA2 mutations the risk is 11–17% [3]. The clinical course of ovarian carcinoma in the presence of BRCA mutations differs significantly from that with intact BRCA. Overall survival is significantly better for carriers of BRCA1 and BRCA2 mutations (for BRCA1: hazard ratio (HR), 0.73; 95% CI, 0.64–0.84; p < 0.001; for BRCA2: HR, 0.49; 95% CI, 0.39–0.61; p < 0.001) [4]. There is evidence that BRCA associated tumours are particularly sensitive to DNA alkylators and intercalating agents such as the platinum derivatives. Studies of tumour tissue from the TCGA project (the Cancer Genome Atlas http://cancergenome.nih.gov) have shown that mutations of genes involved with DNA repair mechanisms (HRR, homologous recombination repair) are present in about 50% of high-grade (G2–3) serous ovarian carcinomas (HGSC) [5].

The introduction of PARP inhibitors as a new, targeted intervention has shown clinical benefit in numerous studies of recurrent platinum-sensitive ovarian carcinoma, the greatest benefits ap...
Poly (ADP-ribose) polymerases (PARP) are a family of numerous individual enzymes of which at least 2 (PARP-1 and PARP-2) are involved in repairing damaged DNA [7,9]. DNA repair mechanisms play an important role in the maintenance of genomic integrity and consequently in cell survival. Numerous factors, e.g. metabolic byproducts such as reactive oxygen species, can damage DNA through causing single-strand breaks. Repair of these single-strand breaks usually occurs through base excision repair (BER), a mechanism in which members of the PARP family of enzymes are involved. If repair does not occur or is incomplete, double-strand breaks arise during the next DNA replication. In healthy cells these are repaired by homologous recombination (HRR) and the error-prone non-homologous end joining (NHEJ) mechanism resulting in the accumulation of DNA damage that can restrict the cell’s ability to repair DNA damage efficiently. Repair is then carried out more often by the error-prone NHEJ mechanism resulting in the accumulation of DNA damage that leads to cell death. In addition to inhibiting the BER pathway PARP inhibitors stimulate the NHEJ pathway promoting cell death of HRR deficient cells [10]. The mechanism of action of PARP inhibitors is known as “synthetic lethality”; schematic representation in Fig. 1.

BRCA and “BRCAness”

The PARP inhibitors block the enzymatic activity of PARP by attaching to the enzyme’s active centre and competing with its natural substrate. In addition to their pure enzyme blocking action some PARP inhibitors appear to induce the formation of a PARP-DNA complex that further impairs DNA repair [11].

BRCA1 and BRCA2 are classified as tumour suppressor genes. Their gene products are involved in homologous recombination (HR) mediated DNA repair. Patients with BRCA1/2 mutations are at increased risk of various forms of cancer; for ovarian carcinoma the risk is 10–55%. The term “BRCAness” describes characteristics of a sporadic tumour that are usually found in tumours among BRCA1/2 germ line mutation carriers; genetic or epigenetic errors are usually present leading to loss of HR associated DNA repair. Tumour cells that do not have efficient DNA repair mechanisms are particularly sensitive to DNA damaging drugs such as platinum-based chemotherapies. PARP inhibitors are promising for tumour treatment not only in the presence of BRCA mutations but possibly also where there is “BRCAness”.

Clinical Studies in Recurrent Ovarian Carcinoma

The PARP inhibitors available for tumour treatment today have high potency and specificity. Their efficacy and tolerability in patients with ovarian carcinoma, most often with BRCA1 and/or BRCA2 gene mutations, have been studied in numerous clinical trials. Data from the clinical development of the most promising of the PARP inhibitors will now be detailed. Since its antitumour action is no longer ascribed to PARP inhibition [12], niraparib will not be considered further here.

Olaparib

Olaparib is currently the best-studied oral PARP inhibitor (PARP-1 and PARP-2 blockade) for use in ovarian carcinoma. Numerous phase I and phase II trials have shown its efficacy for BRCA asso-
ciated ovarian carcinoma and recurrent somatic mutation high-grade serous ovarian carcinoma (data summarised in Table 1) [6,13–16]. In a phase I trial, Fong et al. [13] showed that the clinical benefits of olaparib (200 mg twice daily) for BRCA associated malignant epithelial tumours of the ovary, salpinges (fallopian tubes) and peritoneum was significantly greater in platinum-sensitive disease (clinical benefit rate [CBR] 69.2%) compared to platinum-resistant and refractory disease (CBR 45.6% and 23.1% respectively). A course of olaparib (400 mg twice daily) [17] increased progression-free survival (PFS) in platinum-sensitive recurrent HGSC measurably. This effect was particularly impressive among women with BRCA-mutation associated tumours (PFS in olaparib group 11.2 months vs. 4.3 months in placebo group) [6]. With data collection still incomplete (58% of events) a statistical difference in overall survival has not yet been shown for olaparib, though a numeric effect is already evident (total study duration: HR 0.73 [95% CI 0.45–1.17]) [6].

Olaparib (Lynparza®) is now available on the market as the first officially licensed PARP inhibitor. After its fast-track licensing by the FDA (1/2015) it was subsequently licensed by the EMA (4/2015) as monotherapy for maintenance treatment of platinum-sensitive recurrent BRCA-mutation (germ line and/or somatic) high-grade serous epithelial ovarian carcinoma, carcinoma of the salpinges or primary peritoneal carcinoma with clinical response to platinum-based chemotherapy.

**Veliparib**

Veliparib (ABT-888) was initially researched in numerous pre-clinical and pharmacokinetic trials. A pharmacokinetic trial of diverse tumour entities showed an inhibitory effect (veliparib dose 25 mg and 50 mg) on PARP in tumour tissue and blood samples [19]. Since then numerous phase I trials of veliparib as a drug combination partner for various tumour entities have been conducted (cyclophosphamide [20]; temolozomide [21]; topotecan [22]). Published in March 2014, the provisional findings of a phase II trial involving 52 patients with recurrent or persistent BRCA-associated ovarian carcinoma suggest veliparib is potentially effective used as monotherapy [23]. At a veliparib dose of 400 mg twice daily the overall response rate was 26% with a better response rate for platinum-sensitive disease than platinum-resistant disease (35 vs. 20%). Toxicity of veliparib monotherapy was described as acceptable. Side effects included gastrointestinal symptoms, fatigue and haematotoxicity with a need for dose reduction because of toxicity in 48% of patients. The efficacy of veliparib for recurrent ovarian carcinoma is currently being tested in numerous phase II trials. Most current phase III trials are focused on combination strategies using veliparib and other chemotherapeutic agents for various solid tumours (breast carcinoma, non-small cell bronchial carcinoma, glioblastoma).

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**Table 1** Pivotal trials on the efficacy olaparib monotherapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Requirements (inclusion criteria) with respect to previous treatment</th>
<th>BRCA status and patient number in olaparib group</th>
<th>Dose</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I [13]</td>
<td>No requirement, categorisation according to platinum resistance or sensitivity</td>
<td>BRCAm*: n = 50</td>
<td>40 mg daily up to max. 600 mg BID Dose escalation</td>
<td>CBR Plat-sens: 69% Plat-res: 45% Plat-refr: 23%</td>
</tr>
<tr>
<td>Phase II [14]</td>
<td>At least one previous unsuccessful chemotherapy</td>
<td>BRCAm*: n = 33</td>
<td>400 mg BID</td>
<td>ORR 33%</td>
</tr>
<tr>
<td>Phase II [15]</td>
<td>No requirement</td>
<td>BRCAm*: n = 24</td>
<td>100 mg BID</td>
<td>ORR 13%</td>
</tr>
<tr>
<td>Phase II [16]</td>
<td>Recurrence/progression within 12 months of previous platinum-based therapy</td>
<td>BRCAm*: n = 17, BRCAwt: n = 46</td>
<td>400 mg BID</td>
<td>ORR: 31%</td>
</tr>
<tr>
<td>Phase II [6]</td>
<td>At least 2 previous platinum-based agents, platinum sensitivity</td>
<td>BRCAm*: n = 74, BRCAwt: n = 57</td>
<td>400 mg BID</td>
<td>ORR: 25%</td>
</tr>
</tbody>
</table>

BID: twice daily; BRCAm*: Mutation in BRCA1/BRCA2; BRCAwt: BRCA Wildtype; CBR: Clinical Benefit Rate; ORR: Overall Response Rate; PFS: Progression-free Survival; RD: Response Duration

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shown in an animal model on artificial use of niraparib have not yet been published. Results of phase II and phase III trials on the clinical carcinoma are currently being tested in an international phase III trial (NOVA). niraparib plus topotecan. The efficacy and tolerability of oral niraparib monotherapy have been tested in clinical studies. In addition to good tolerability [27], antitumour effect has been shown among patients with ovarian and peritoneal carcinoma both in platinum-sensitive and platinum-resistant disease (total tumour follow-up rate 86%) with doses between 40 to 500 mg rucaparib daily and 240 mg rucaparib twice daily respectively [28]. There is also published data on rucaparib in combination with cytostatic drugs. The efficacy of rucaparib as maintenance therapy for platinum-sensitive recurrent ovarian carcinoma is the focus of two current international trials (ARIEL2 und ARIEL3).

### Niraparib

Niraparib (MK4827) is a selective PARP1 and PARP2 inhibitor whose antiproliferative effect was first shown in in-vitro trials on BRCA1 and BRCA2 deficient cancer cells. Its efficacy was also shown in an animal model on artificial BRCA1-deficient tumours [24]. A phase I dose-finding trial found a maximum tolerable dose of 300 mg daily. Toxic effects such as gastrointestinal symptoms, fatigue, anaemia, thrombocytopenia and neutropenia occurred frequently but severity was mostly low. Of patients with BRCA-associated ovarian carcinoma 40% (8 out of 20) showed partial response (RECIST) [25]. The efficacy and tolerability of niraparib monotherapy for platinum-sensitive recurrent ovarian carcinoma are currently being tested in an international phase III trial (NOVA). Results of phase II and phase III trials on the clinical use of niraparib have not yet been published.

### Rucaparib

Ihnen et al. [26] studied the effect of the PARP inhibitor rucaparib (CO-338, AG014699, PF-01367338) on 39 different ovarian carcinoma cell lines in-vitro. The antitumour action of rucaparib was not limited to BRCA-mutated cells alone but also shown in cells with low-level expression of HRR-associated genes. The most obvious synergistic effects were shown for the combination of rucaparib plus topotecan. The efficacy and tolerability of oral rucaparib monotherapy have been tested in clinical studies. In addition to good tolerability [27], antitumour effect has been shown among patients with ovarian and peritoneal carcinoma both in platinum-sensitive and platinum-resistant disease (total tumour follow-up rate 86%) with doses between 40 to 500 mg rucaparib daily and 240 mg rucaparib twice daily respectively [28]. There is also published data on rucaparib in combination with cytostatic drugs. The efficacy of rucaparib as maintenance therapy for platinum-sensitive recurrent ovarian carcinoma is the focus of two current international trials (ARIEL2 und ARIEL3).

### Combination Strategies

In addition to use as monotherapy, PARP inhibitors have shown promise when used in combination with other treatments. The following is a selection of possible therapeutic approaches:

- **In combination with chemotherapy:** The DNA repair blocking effects of PARP inhibitors cause cells to be more sensitive to DNA damaging substances and can also delay the development of resistance to chemotherapy. [31]. Oza et al. [32] studied the combination of olaparib with carboplatin/paclitaxel followed by olaparib maintenance therapy in patients with platinum-sensitive recurrent serous ovarian carcinoma. The addition of olaparib to carboplatin/paclitaxel chemotherapy and as maintenance thereafter resulted in a significant increase in progression-free interval from 9.6 (arm B) to 12.2 months (arm A) (arm A: olaparib 2 × 200 mg daily, day 1–10 with paclitaxel 175 mg/m² and carboplatin AUC6 on day 1, for 6 cycles at intervals of 21 days followed by olaparib maintenance therapy.

### Table 2: Pivotal trials on the safety of olaparib monotherapy in ovarian carcinoma.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dose/Patient number</th>
<th>Toxicity</th>
<th>Grade 1–2</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II [14]</td>
<td>400 mg BID n = 33</td>
<td>nausea 42%, fatigue 30%, anaemia 15%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Phase II [15]</td>
<td>100 mg BID n = 24</td>
<td>nausea 29%, fatigue 38%</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Phase II [16]</td>
<td>400 mg BID n = 32</td>
<td>nausea 72%, fatigue 56%, abdominal pain 25%</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Phase II [17]</td>
<td>200 mg BID n = 32</td>
<td>nausea 56%, fatigue 38%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Phase II [17]</td>
<td>400 mg BID n = 136</td>
<td>nausea 66%, fatigue 42%, vomiting 29%</td>
<td>2%</td>
<td>7%</td>
</tr>
</tbody>
</table>

BID: twice daily; OvCa: ovarian carcinoma; BCa: breast carcinoma
In combination with PI3-kinase inhibitors: The PI3K/PI3K/AKT/mTOR signal pathway is critical for many cell functions such as growth, metabolism, and the initiation of DNA translation. The inhibition of PI3-kinase with PI3K inhibitors is a particularly interesting potential treatment strategy for ovarian carcinoma, since up to 70% of these tumours show overactivity of this pathway. Promising preclinical data have been published for the combination of PARP inhibitors with PI3K inhibitors [33]. The combination of olaparib and the PI3K inhibitor BKM120 for triple negative breast carcinoma and high-grade serous ovarian carcinoma (NCT01623349) is the subject of a current phase I trial that is still in the recruiting phase.

In combination with angiogenesis inhibitors: Preclinical trials have provided evidence of hypoxia-mediated, reduced expression of proteins involved in DNA repair via the HRR pathway. A hypoxic environment is also known to increase the sensitivity of cells to PARP inhibitors [34–36]. Combinations of olaparib with bevacizumab [37] and cediranib [38] have been studied in clinical trials. In a phase II trial Liu et al. [39] showed that the “chemotherapy-free” combination of olaparib with cediranib clearly improved progression-free survival rate in platinum-sensitive recurrent ovarian carcinoma compared to olaparib monotherapy (PFS 17.7 months vs. 9.0 months respectively), although from the outset patients in both groups received no chemotherapy during recurrence. A phase III trial of the same combination strategy is planned [40].

Future Prospects

The treatment of recurrent ovarian carcinoma remains a major challenge to clinicians. Since the disease in this form is incurable treatment is aimed at achieving a compromise between antitumour effect and a reasonable degree of reduced bodily reserves and quality of life. The fundamental treatment strategies target the platinum-free interval and are governed by differing tumour sensitivities to previous platinum-based chemotherapy. Results of all trials to date allow the conclusion that the various members of the PARP inhibitor drug class have clinically meaningful antitumour effects especially in high-grade serous platinum-sensitive ovarian carcinoma. With its licensing for treatment of platinum-sensitive BRCA-mutated ovarian carcinoma, olaparib is the first PARP inhibitor to become part of the gynaecological-oncological treatment spectrum. This innovative treatment approach is a further step towards improved individualisation and the establishment of personalised, goal-directed therapy in clinical practice. This is conditional on a new level of clinical understanding of tumour complexity as well as molecular genetic evidence of disturbed DNA repair caused by BRCA mutations, both somatic and germ line. An exact genetic characterisation of tumours should thus be performed early on in tumour management. To achieve this prompt analysis of somatic and germ line mutations in patients with ovarian carcinoma the promotion of efficient organisational structures is necessary.

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Conflict of interest

Jalid Sehouli received honoraria for the participation in the following Advisory Boards: AstraZeneca, Pfizer, MSD, PharmaMar. The other authors declare no conflict of interest.

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