Maturitas xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

PARP inhibitors: A new era of targeted therapy

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ARTICLE INFO

Article history:
Received 15 January 2015
Received in revised form 26 January 2015
Accepted 28 January 2015
Available online xxx

Keywords:
PARP inhibitors
Lynparza
Olaparib
BMN-673
Personalized medicine

ABSTRACT

Personalized medicine seeks to utilize targeted therapies with increased selectivity and efficacy in pre-selected patient cohorts. One such molecularly targeted therapy is enabled by inhibiting the enzyme poly(ADP-ribose) polymerase (PARP) by small molecule inhibitors in tumors which have a defect in the homologous DNA recombination pathway, most characteristically due to BRCA mutations. Olaparib, a highly potent PARP inhibitor, has recently been the approved for ovarian cancer therapy by the FDA and European commission in patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer with BRCA1 or BRCA2 mutations. Currently, clinical trials with several PARP inhibitors are being conducted to assess the toxicities, the efficacies and the benefit of the drugs as monotherapies or combined with radiation or other chemotherapeutic agents, in ovarian, breast, prostate, rectal, lung, pancreatic, peritoneal, head and neck, brain, squamous cell carcinomas and sarcomas, to list a few. In this review, our focus is to outline the emerging molecular mechanisms, preclinical evidence and clinical applications of PARP inhibitors especially in nonBRCA cancers, and review the combination strategies compatible with PARP inhibitor therapy.

Contents

Poly(ADP-ribose) polymerase (PARP) is an abundant nuclear enzyme, which is recruited to repair DNA damage in cells, and also plays a role in cell proliferation, differentiation and transformation [1]. Although the existence of PARP was first reported nearly 40 years ago [2], the elucidation of the structure and the functions of this important enzyme had to wait for modern molecular biology cloning techniques, which subsequently led to the screening of many potent small molecule PARP inhibitors (PARPi).

Currently several PARP inhibitors are in phase 1 and 2 clinical trials as mono- or combination therapies to assess their safety and efficacy (www.clinicaltrials.gov). These are olaparib (Lynparza™, Astrazeneca), BSI-201 (Iniparib, BiPar/Sanofi), Rucaparib (Pfizer), Niraparib (Tesaro), BMN-673 (BioMarin) and ABT-888 (Veliparib, Abbott). The combination of therapeutic efficacy with minimal toxicity has ultimately led to the approval of olaparib by the US food and drug administration and European commission for the treatment of advanced ovarian cancer in patients with BRCA mutations.

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http://dx.doi.org/10.1016/j.maturitas.2015.01.015
0378-5122/

The events leading to the approval of olaparib are summarized in recent reviews [3]. The approval of a targeted therapy with its companion genetic diagnostic represents a major step in personalized medicine for cancer.

An extensive body of work has now revealed the applicability of PARP inhibitors in cancer therapy beyond the presence of BRCA mutations, often referred to as "BRCAness". The pre-clinical evidence and clinical trials in non-BRCA tumors are discussed here.

1. Mechanism of action

DNA damage in cells manifests mainly as single-strand breaks (SSB's), double strand breaks (DSB's) or replication fork stalling. In these instances the PARP-1 enzymes are recruited to regulate the process of autoPARylation. The PAR polymers thus synthesized rapidly bind to DNA strand breaks to reseal or repair the damage. Because of the high negative charge of PAR polymers, they eventually dissociate from the DNA–PARP repair complexes at the site signifying the completion of the repair process. Some small molecule PARP inhibitors, like BMN-673, enable the trapping of PARP-1 at sites of DNA damage, which prevents the accessibility of the repair site to other repair proteins, and has thus been attributed for PARP inhibition action [4]. PARP-1 also plays a critical role in the base excision repair (BER) pathway, and is a regulator of homologous recombination (HR) and non-homologous end-joining (NHEJ) processes [5,6]. Several studies have demonstrated that HR-deficient cells (e.g. those with BRCA mutations) are extremely sensitive to pharmacological inhibition of PARP, which results in stalled and collapsed replication forks. Furthermore activation of the NHEJ pathway, which selectively induces error-prone repair in HR-deficient cells, also leads to PARP inhibition sensitivity in cancer cells [5,6].

2. Expanding the PARP inhibitor applicability

PARP inhibitor therapy made its way into clinical trials after the discovery of the synthetic lethality of PARP inhibition in the presence of BRCA 1/2 mutations, which led to selective cell death, particularly in ovarian and breast cancers. Preliminary clinical evidence with BRCA mutant patients showed significant clinical efficacy upon chronic treatment with olaparib [5,7]. Recent studies have also indicated the pivotal role of BRCA1, BRCA2 dysfunctional pathology in prostate cancers in BRCA mutated men, suggesting the expanding application of PARP inhibitors in prostate cancer therapies [8–10]. Olaparib as a monotherapy is generally well tolerated; the most-common adverse events after treatment include mild-to-moderate nausea, fatigue, vomiting, and anemia [11].

Studies have also shown that the PARP inhibition has a significant lethal effect selectively on tumor cells with TMPRSS2:ERG gene fusions which are detected in more than 50% of prostate cancer tumors [12], especially in androgen independent metastatic prostate tumors [13]. Similar sensitization to PARP inhibitors was also found in EWSR1:FLI1 translocations in Ewing's sarcoma, and several studies suggested that there is direct mechanistic connection between PARP inhibition by olaparib and the *EWS–FLI* translocation. The proposed mechanisms include a positive-feedback loop involving EWS:FLI1 fusion protein and PARP-1 making it an attractive target for PARP inhibitory therapy in Ewings sarcoma [14]. These findings have led to clinical trials for PARP inhibitor therapy for prostate cancer and Ewing's sarcoma in patient cohorts who manifest these translocations. Another compelling study suggests that the PTEN (phosphatase and tensin homolog) tumor suppressor gene has a role in maintaining genomic stability and thus is a target for PARP inhibitor sensitization [15].

It was also shown that depletion or inhibition of cyclin dependent kinases (cdk1) compromises the cellular capacity to repair DNA by HR. Detailed PARP inhibition studies on these mouse models of patient derived lung adenocarcinoma resulted in delayed human tumor xenograft growth and tumor regression with prolonged survival [16]. Other genetic modulators of PARP inhibition that have been identified are *ATM*, *ATR*, *MRE11A* and *NBS1*, and could potentially lead to future clinical trials with patient cohorts harboring mutations in these pathways [17]. Studies have also shown that olaparib and veliparib are also promising chemopreventive candidates, since chronic treatment with these drugs delayed the tumor development in BRCA1 deficient mice, thus opening up avenues for new application for PARP inhibitors [18].

3. Interplay of PARP inhibitors with signaling pathways

In addition to the DNA damage repair functions, PARP-1 also regulates both tumor growth and progression through transcriptional regulatory functions. The transcriptional involvement of PARP-1 in androgen regulation has been observed to suppress critical signaling pathways, specifically for prostate cancer cell survival and progression. PARP-1 thus appears to be involved in the Androgen Receptor (AR) sensitive cancers where it is enzymatically linked to AR activity and progression of cancer [6].

4. Combination therapy with chemotherapeutics and radiation

A number of preclinical studies have demonstrated that PARP inhibitors can be potentially viable as chemopotentiators or chemo- and radiation sensitizers. These studies have led to clinical trials of PARP inhibitors in combination with chemotherapeutics that lead to DNA damage (Table 1), with the PARP inhibitor blocking the subsequent DNA repair mechanisms selectively in cancer cells. Some of the drugs being used with PARP inhibitors include platinum based DNA damaging agents such as cisplatin, carboplatin, oxaliplatin; alkylating agents like Temozolomide (TMZ) and topoisomerase inhibitors such as Camptothecin (CPT) and its derivatives (irinotecan and topotecan) [19–25]. TMZ therapy, when combined with radiation induces single stranded breaks (SSBs) and hence is the direct target of PARP inhibitors. PARP inhibitors also intervene with the recruitment of X-ray repair cross-complementing 1 (XRCC1), a scaffold protein recruiting other DNA polymerases and DNA ligases for the repair [20]. Given the complementary mechanism of actions of these drugs, the combination treatment strategy involving PARP inhibitors and TMZ has initiated several clinical trials in different anatomical malignancies, including Glioblastoma Multiforme where the median survival is 12–24 months [20,21,26].

Similarly, human topoisomerase-I is an enzyme of significant oncological interest and is the target for CPT derivatives. Topotecan is currently used for the treatment of metastatic ovarian cancer and small cell lung cancer after failure of first-line chemotherapy. The DNA damage resulting from the topoisomerase poisoning is counteracted by PARs. Hence PARP inhibitors can be used to antagonize the effect of PARs on the repair mechanisms, thus increasing the maintenance of persistent DNA breaks [23–25]. Other chemotherapeutics and biologics being used in combination with PARPi include taxane (paclitaxel), bevacizumab, gefitinib, cediranib, cetuximab, gemcitabine, capecitabine, lapatinib, dinaciclib, mitomycin and bortezomib (www.clinical.trial.gov).

The plethora of data available on PARP inhibitors had preclinically established them as radiosensitizers which may again be attributed to impaired DNA damage responses [14] and the cell-replication dependency [22]. One proposed mechanism for the

Please cite this article in press as: Tangutoori S, et al. PARP inhibitors: A new era of targeted therapy. Maturitas (2015), http://dx.doi.org/10.1016/j.maturitas.2015.01.015

Table 1
Active clinical trials (recruiting and non recruiting) with PARP inhibitors in combination with chemotherapy, in nonBRCA cancers.

Clinical trial.gov identifier	Disease	PARP inhibitor	Combination therapy	Clinical trial
NCT02116777	Adult solid neoplasm Childhood solid neoplasm Recurrent adult acute lymphoblastic leukemia Recurrent childhood acute lymphoblastic leukemia Recurrent Ewing sarcoma/peripheral primitive Neuroectodermal tumor	BMN-673	Temozolomide	Phase 1/2
NCT02044120	Recurrent Ewing sarcoma	Niraparib/olaparib	Temozolamide	Phase 1
NCT01017640	Adult solid neoplasm	Veliparib	Mitomycin C	Phase 1
NCT01085422	Prostate cancer	ABT-888	Temozolomide	Phase 1
NCT02049593	Metastatic cancer	BMN-673	Irinotecan hydrochloride	Phase 1
NCT02305758	Untreated metastatic colorectal cancer	Veliparib	FOLFIRI ± bevacizumab	Phase 2
NCT01123876	Gastric cancer	Veliparib	FOLFIRI	Phase 1
NCT00576654	Malignant neoplasm	Veliparib	Irinotecan hydrochloride	Phase 1
NCT00687765	Glioblastoma	BSI-201	Temozolomide	Phase1/2
NCT00535119	Advanced solid tumors	Veliparib	Carboplatin ± Paclitaxel	Phase 1
NCT02264990	Non small cell lung cancer	Veliparib	Carboplatin Paclitaxel Cisplatin Pemetrexed	Phase 2
NCT02289690	Small cell lung cancer	Veliparib	Carboplatin Etoposide	Phase 1
NCT01296763	Pancreatic cancer	Olaparib	ICM	Phase 1

ICM—irinotecan hydrochloride, cisplatin, methotrexate FOLFIRI regimen—irinotecan 180 mg/m^2 d1, leucovorin 400 mg/m^2 d1, 5-fluorouracil 400 mg/m^2 iv, 2.4 g/m^2 civ 46 h, repeated every 2 weeks.

increased response in combination with radiation is the inability of PARPi treated cells to repair radiation induced single strand breaks. It was also demonstrated that the combination of ABT-888 and radiation lead to delayed tumor growth in non-small cell lung cancer models [19]. These promising results have initiated several radiotherapy based clinical trials for malignant glioma, head and neck, and breast cancers (Table 2). Although highly desirable, these combination strategies are limited by the challenges with the optimization of treatment schedules for combined therapies and the validation of biomarkers in specific patients that will ascertain the benefit from PARP inhibitors in combination with either chemo- or radiotherapy [22,27] (Table 3). Q5

Table 2
Active clinical trials (recruiting and non recruiting) with PARP inhibitors in combination with Radiation, in nonBRCA cancers.

Clinicaltrial.gov identifier	Disease	PARP inhibitor	Combination therapy	Clinical trial
NCT01589419	Locally advanced rectal cancer	Veliparib	Capecitabine + radiation	Phase 1
NCT01477489	Breast cancer	Veliparib, olaparib	Radiation	Phase 1
NCT02229656 NCT02308072	Head and neck cancer	Olaparib	Radiation Radiation + cetuximab Radiaition + cisplatin	Phase 1
NCT01460888	Carcinoma of the esophagus	Olaparib	Radiation (radical external beam radiotherapy)	Phase 1
NCT01562210	Non small cell lung cancer	Olaparib	Cisplatin ± radiation	Phase 1
NCT01908478	Pancreatic cancer	Veliparib	Gemcitabine ± intensity modulated radiation therapy	Phase 1
NCT01551680	Brain metastases	Iniparib	Radiation	Phase 1
NCT01711541	Human papillomavirus infection Salivary gland squamous cell carcinoma Stage IV nasopharyngeal keratinizing squamous cell carcinoma Stage IVA laryngeal squamous cell carcinoma Stage IVA laryngeal verrucous carcinoma Stage IVA lip and oral cavity squamous cell carcinoma Stage IVA major salivary gland carcinoma Stage IVA nasal cavity and paranasal sinus squamous cell carcinoma Stage IVA oral cavity verrucous carcinoma Stage IVA oropharyngeal squamous cell carcinoma Stage IVB laryngeal squamous cell carcinoma Stage IVB laryngeal verrucous carcinoma Stage IVB lip and oral cavity squamous cell carcinoma Stage IVB major salivary gland carcinoma Stage IVB nasal cavity and paranasal sinus squamous cell carcinoma Stage IVB oral cavity verrucous carcinoma Stage IVB oropharyngeal squamous cell carcinoma tongue carcinoma	Veliparib	Placebo Cisplatin Fluorouracil **Radiation** Therapy Hydroxyurea Paclitaxel Carboplatin	Phase 1/2

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Table 3
Acronyms in the text and the relevancy to the PARP inhibitors.

Abbreviations in the text		Relevancy with PARP inhibitors
PARP	Poly(ADP-ribose) polymerase	DNA repair enzyme
FDA	Food and Drug Administration	Drug regulatory Govt. body in USA
BRCA	Breast cancer susceptibility gene	Mutations in this gene leads to synthetic lethality with PARP inhibitors
PARPi	PARP inhibitors	Class of small molecule inhibitors to abrogate the DNA repair in tumors
SSB	Single strand break	Type of DNA damage mechanism
DSB	Double strand break	Type of DNA damage mechanism
BER	Base excision repair	Type of DNA damage mechanism
HR	Homologous recombination	Reliable DNA repair pathway
NHEJ	Non-homologous end-joining	Error-prone DNA repair pathway
PTEN	Phosphatase and tensin homolog	Tumor suppressor. PARP has crosstalk with this pathway
ATM	Ataxia-telangiectasia mutated gene	Participate in DNA repair pathway
ATR	Serine/threonine-specific protein kinase	Participate in DNA repair pathway
MRE11A	Protein in double-strand break repair complex	Repairs DSB's in DNA
NSB1	Protein in double-strand break repair complex	Repairs DSB's in DNA
TMPRSS2:ERG	Fusion of two genes during transcription	Gene fusion found in 50% of prostate cancers.
ORF	Open Reading Frame	The part of gene which has the potential to code for proteins
XRCC1	X-ray repair cross-complementing 1	DNA repair protein
PAR	Poly(ADP-ribose)	Polymer produced in the presence of PARP. PAR is used to repair the DNA damage
PgP	Permeability glycoprotein	Transmembrane proteins to monitor the entry of xenobiotics into the cell

5. Resistance to PARP inhibitors

Three mechanisms of resistance to PARPi therapy have been identified thus far: (1) Upregulation of PgP transporter, (2) loss of PARP1 expression, (3) restoration of the HR pathway in BRCA targeted tumors [17,28]. Upregulation of PgP pumps is a common pharmacological effect that reduces the efficacy of a number of drugs including PARP inhibitors by effluxing the drugs out of the cell and thus reducing the intracellular concentration of the drug available for the therapy. Since PARP inhibitors are also known to stabilize the cytotoxic PARP–DNA complexes, a loss-of-function of PARP1 can potentially lead to 100 fold resistance due to lowered cytotoxicity of PARP–DNA complexes and impaired catalytic inhibition of the PARP protein [17]. Another resistance mechanism to PARPi therapy that has been noted clinically is via restoration of the HR pathway and is specific to BRCA targeted tumors. BRCA2 mutant patients have shown resistance to PARP inhibitors by way of a secondary mutation in the BRCA2 gene that restores the open reading frame (ORF). Restoration of the ORF results in translation of a functional BRCA2 protein [17]. More studies are warranted to establish whether the resistance to PARPi therapy in BRCA mutant cancers is solely due to the restoration of the HR pathway or if the other concomitant mechanisms would play an equal role.

6. Challenges of PARP inhibitor therapies

The predominant challenge with PARPi therapy is the suboptimal availability and accumulation of the drug at the intended anatomical tumor site owing to the pharmacokinetic properties of the poorly water soluble oral inhibitors. Another challenge especially with the combination therapies, are the concomitant and induced toxicities and pharmacological drug-drug interactions. Hence, the optimization of dosage regimen becomes key factor for a successful clinical trial with the combination treatment strategies. A significant step to improve the tumor accumulation has been made by developing nanoformulations of olaparib and BMN-673 which are showing improved performance in pre-clinical prostate and ovarian cancer models, and which may also minimize the synergistic toxicities in combination therapies [29]. It is also imperative to develop appropriate companion diagnostic tests to enable patient selection and identify reliable biomarkers for accurate prognosis of the PARP inhibitor therapies.

In summary, the approval of the PARP inhibitor Lynparza with its companion diagnostic for clinical use in BRCA positive ovarian cancer tumors is a major milestone in personalized cancer therapy. On the near horizon are combination therapies of PARP inhibitors with other chemotherapeutics and radiation. These developments also open the door for the use of other molecular inhibitors targeting specific pathways for cancer therapy. The use of these new therapies brings new challenges including the presence of resistance mechanisms, the complexities in optimizing the dose regimens, developing suitable biomarkers and the careful selection of patient cohorts for a successful clinical trial.

Contributors

Shifalika Tangutoori: Concept proposal, outline of the paper, literature study, writing, editing, table preparation.

Paige Baldwin: Contributed to sections on PARP resistance and mechanism of action, reviewed the tables and the paper in general.

Sridhar Srinivas: Initiated the review, approved the concept, and writing, coordination, editing, reviewing tables and the manuscript.

Competing interests

No potential conflict of interest to disclose.

Funding

This work was supported by Army—W81XWH-14-1-0092, the David Mazzone and Prostate Cancer Research Foundations, and NSF-DGE—0965843.

Provenance and peer review

Commissioned; externally peer reviewed.

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