Poly(ADP-ribose) polymerase inhibitors in Ewing sarcoma

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Purpose of review
In 2012, two publications revealed a particular sensitivity of Ewing sarcoma cells to the inhibition of poly(ADP-ribose) polymerase (PARP). This review updates the reader on PARP function, the development of PARP inhibitors (PARPi) and the evidence for targeting PARP in Ewing sarcoma. It concludes with a description of ongoing/emerging PARPi clinical trials in patients with Ewing sarcoma.

Recent findings
PARP has a major role in DNA repair, and is a transcription regulator. The oncoprotein in Ewing sarcoma, EWS-FLI1, is proposed to interact with PARP-1, driving PARP-1 expression, which further promotes transcriptional activation by EWS-FLI1. Thus, there are two rationales for PARPi in the treatment of Ewing sarcoma: to disrupt the interaction between EWS-FLI1 and PARP, and for chemo-potentiation or radio-potentiation. The first clinical trial with a single agent PARPi failed to show significant responses, but preclinical evidence for combinations of PARPi with chemotherapy or radiotherapy is very promising.

Summary
Despite initial excitement for the potential of PARPi as single agent therapy in Ewing sarcoma, the emerging preclinical data now strongly support testing PARPi in combination with chemo/radiotherapy clinically.

Keywords
chemosensitization, Ewing sarcoma, PARP inhibitors, radiosensitization

INTRODUCTION

Although for most childhood cancers, improved chemotherapy regimens have led to substantially increased response and survival rates, the improvement in the survival of patients with primary metastatic or relapsed Ewing sarcoma remains obstinately poor. Recent developments in the preclinical setting suggest that poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) may be particularly useful to treat Ewing sarcoma. This review aims to give some background to Ewing sarcoma as a disease, the current treatments and response to therapy. The function of PARP and the effects of PARPi will be described and the evidence for a role of PARP in Ewing sarcoma will be discussed. The review will conclude with a description of the most recent clinical studies of PARPi in patients with Ewing sarcoma.

EWING SARCOMA AND CURRENT THERAPY

Ewing sarcoma is the second most common primary bone cancer occurring most frequently in the second decade of life. It occurs predominantly in the long bones (femur, tibia, humerus) or pelvis, but can principally arise from any bone of the skeleton, and with increasing frequency in older adults also in extraskeletal sites (soft tissue, kidney, uterus). Pain in the affected site is usually the first symptom, followed by swelling and a palpable mass, but pathologic fractures also occur at presentation. About 25% of patients present with metastatic disease at diagnosis, most commonly to lungs, followed by bone or bone marrow involvement.

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KEY POINTS

- PARP inhibitors in Ewing sarcoma disrupt the interaction of EWS-FLI1 with PARP-1 and potentiate the DNA damage caused by certain chemotherapy (temozolomide, topoisomerase I poisons) or radiotherapy.

- PARP inhibitors used as single agents in Ewing sarcoma have shown promising activity *in vitro*, but none to only modest activity in xenograft models, and they had no effect in a phase II clinical trial with continuous high-dose olaparib.

- PARP inhibitors used in combination with either temozolomide, irinotecan or radiotherapy have shown excellent results *in vitro* and in xenograft tumour models, and clinical trials results using combination strategies are eagerly awaited.

First-line treatment is standardized and usually delivered within phase III clinical trials (e.g. EURO-E.W.I.N.G.99, subsequent EWING 2012). The multimodal treatment strategy consists of neo-adjuvant and adjuvant chemotherapy, local disease control through surgery, radiotherapy or a combination of both, and for certain subsets of patients, high-dose chemotherapy (e.g. busulfan-melphalan) with autologous stem cell support. These regimes are currently achieving survival rates of around 70% for local disease, but for primary metastatic disease, their predecessor trials achieved only 14–34% [1] or 8–29% [2].

Second-line treatment after relapse or for refractory disease is currently not standardized, although there is a proposed study comparing the most commonly used regimes (rEEcur study). Chemotherapeutic agents most commonly include combinations of cyclophosphamide/topotecan or temozolomide/irinotecan. Surgery and/or radiotherapy may be used to attempt local disease control or for metastatic sites. The overall outcome for patients with relapsed disease (5 year overall survival of 13%) [3] has remained unfavourable over the past decades and urgently requires the development of novel therapeutic approaches.

EWING SARCOMA AND ITS LINK TO POLY(ADP-RIBOSE) POLYMERASE

Ewing sarcoma is a unique cancer, as it is defined on a molecular level by a balanced tumour-specific translocation. In approximately 85% of all tumours, the *EWSR1* gene on chromosome 22 is fused to a member of the ETS family of transcription factors, the *FLI1* gene on chromosome 11. In the remaining 15% of tumours, the *EWS* gene is fused to other members of the ETS transcription factor family, most commonly the *ERG* gene on chromosome 21 [4]. The resulting oncoproteins, which serve as molecular signatures and are viewed as pathognomonic for Ewing sarcoma, function as aberrant oncogenic transcription factors.

Recently, the ETS transcription factors were shown to interact with PARP-1 in immunoprecipitation experiments published by Brenner *et al.* [5▪▪], who were first to report that Ewing sarcoma cell lines were highly sensitive to PARP inhibition. This publication was shortly followed by a widely perceived publication by Garnett *et al.* [6▪▪] from the Cancer Genome Project, who identified the EWS-FLI1 translocation as a biomarker for PARPi sensitivity.

POLY(ADP-RIBOSE) POLYMERASE AND THE THERAPEUTIC UTILITY OF ITS INHIBITORS

There is a superfamily of 17 PARP enzymes of which PARP-1 is the founding member and most abundant [7]. The best characterized role for PARP-1 is not only in the repair of DNA breaks but also the regulation of transcription by, for example, modulating chromatin structure, changing DNA methylation patterns and as a co-regulator of transcription factors [8]. PARP-2 has a somewhat overlapping role in DNA single-strand break repair and PARP-3 co-operates with PARP-1 in the repair of DNA double-strand breaks [9]. PARP-1 is activated by binding to DNA breaks to catalyze the formation of long homopolymers of ADP ribose (PAR) from NAD^+ that recruit the repair machinery and loosen chromatin to facilitate repair. PARPi were developed for cancer therapy based on the simple premise that cancer therapy damages DNA, and DNA repair compromises the therapeutic efficacy; therefore, inhibiting DNA repair should increase the efficacy. Inhibitor development started with academic groups in the late 1970s and early 1980s and for a long time, 3-aminobenzamide (3AB) was the only compound available. A decade later, inhibitors more than $100\times$ more potent than 3AB were developed. Because of the similarity of the catalytic domain, most PARPi are at least as active against PARP-2 as PARP-1. These second-generation inhibitors confirmed data obtained using 3AB, that PARPi inhibit the repair of DNA damage and enhance the cytotoxicity of DNA methylating agents (e.g. temozolomide), topoisomerase I poisons (e.g., topotecan) and ionizing radiation with some cell-specific potentiation of cisplatin [10]. Subsequent expansion of the investigations by academic and industrial groups identified ever more potent inhibitors that, as well as being

highly potent ($\geq 1000\times$ more potent than 3AB), had improved pharmacological properties that allowed studies in mice bearing a variety of xenografted tumours. These xenograft studies, which were largely representative of not only adult human tumours, particularly colon carcinoma [11], brain tumours and melanomas [12], but also for paediatric tumours, such as medulloblastoma [13] and neuroblastoma [14], confirmed the efficacy with temozolomide, irinotecan and irradiation. The first clinical trial of a PARPi in cancer patients was in 2003, in which rucaparib (AG014699) was given in combination with temozolomide [15].

More recently, PARPi have been shown to be synthetically lethal in cells lacking another DNA repair pathway: homologous recombination repair (HRR). Synthetic lethality explains the phenomenon in which blocking two complementary enzymes or pathways together results in cell death, but blocking either alone does not compromise viability. The tumour suppressors BRCA1 and BRCA2 play important roles in HRR and mutations in these genes are associated with breast, ovarian and some other cancers. As only tumours are HRR-defective and normal tissues retain HRR function (except in cases of rare genetic diseases), this represents a nontoxic, tumour-selective therapeutic manoeuvre. These exciting developments have led to an expansion in the field and there are currently five PARPi in advanced pre-registration clinical trials, mostly in BRCA/HRR-defective breast or ovarian cancer [16].

RATIONALE FOR POLY(ADP-RIBOSE) POLYMERASE INHIBITOR THERAPY IN EWING SARCOMA

There are two potential justifications for considering PARPi therapy in Ewing sarcoma: first, its potential as a single agent based on the association of PARP-1 with ETS transcription factors and secondly as a chemotherapy/radiotherapy potentiating agent in combination with either ionizing radiation, temozolomide or topotecan, all used for the treatment of relapsed Ewing sarcoma.

POLY(ADP-RIBOSE) POLYMERASE INHIBITORS AS SINGLE AGENTS

The first publication to suggest that PARPi may be active as single agents in Ewing sarcoma came from the group at the University of Michigan, who were first to publish on the interaction between EWS-FLI1 and PARP-1, and the sensitivity of Ewing sarcoma cells to PARP inhibition.

The group had previously shown that the protein product of *TMPRSS2-ERG*, an ETS fusion

gene, in prostate cancer interacts with PARP-1 and that PARPi inhibited ETS-positive prostate xenograft growth [17]. Based on these findings, they investigated ETS fusion genes in Ewing sarcoma, *EWS-FLI1* or *EWS-ERG*. Immunoprecipitation experiments using either FLI1 or ERG antibodies, which recognized the respective fusion proteins, pulled down PARP-1 in a DNA-independent manner. Clonogenic assays in soft agar demonstrated that cells overexpressing EWS-FLI1 or EWS-ERG were sensitive to the PARPi olaparib. Ewing sarcoma cell lines, including those from heavily pretreated patients, were similarly highly sensitive to continuous single agent olaparib exposure, whereas control cell lines from rhabdomyosarcomas or osteosarcomas showed unhindered growth. These findings were confirmed in a mouse xenograft model, in which single agent olaparib delayed subcutaneous Ewing sarcoma (RD-ES) tumour growth to a comparable extent as single agent temozolomide. They also demonstrated that the ETS fusion protein was associated with increased levels of DNA damage, measured by γH2A.X foci and COMET assays, which could be potentiated by PARP inhibition. Interestingly, in cell invasion assays, siRNAs against PARP-1 and EWS reduced cell invasion, but knock-down of other key DNA repair enzymes (XRCC1; base excision repair; XRCC3; HRR and XRCC4; nonhomologous end joining) had no effect. The group therefore concluded that PARP-1 has a DNA repair-independent role in Ewing sarcoma cell migration. Finally, they demonstrated that EWS-FLI1 maintains PARP-1 mRNA expression, as knockdown of EWS-FLI1 decreased PARP-1 protein expression and promotor activity. In conclusion, they postulated a EWS-FLI1:PARP-1-positive feedback loop in transcriptional activation, together with the potentiation of DNA damage by PARP-1 inhibition as the two mechanisms contributing to the PARPi sensitivity of Ewing sarcoma (Fig. 1).

Shortly afterwards, the large collaboration of the Cancer Genome Project [6■■] published the screening results of more than 600 human cancer cell lines against 130 different drugs under clinical and preclinical investigation, in which the particular sensitivity of cells harbouring the EWS-FLI1 oncogene to PARPi was revealed as an unexpected finding. In cell viability and clonogenic assys, cell lines carrying the EWS-FLI1 translocation were significantly more sensitive to two PARPi (olaparib and rucaparib), than their EWS-FLI1-negative controls. The consortium also determined whether the *EWS-FLI1* fusion gene was essential for the sensitivity to PARPi, or whether it was intrinsic to the mesenchymal precursor cells from which Ewing sarcoma originates. They therefore compared the PARPi sensitivity of mouse mesenchymal cells transformed with either
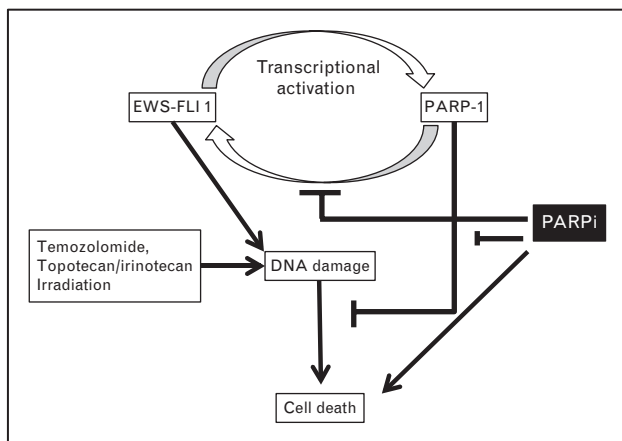
FIGURE 1. Proposed model for interaction of PARP-1 and *EWS* fusion genes and the potential role for PARPi. *EWS* fusion gene (exemplified by EWS FLI1) promotes PARP-1 expression, which in turn promotes EWS FLI1 transcriptional activation, creating a positive feedback loop that promotes EWS FLI1-driven malignancy. EWS FLI1 expression results in higher levels of DNA damage that requires PARP-1 for repair. Temozolomide, irinotecan/topotecan and ionizing radiation all cause DNA damage that is repaired in a PARP-dependent manner. PARPi may have single-agent activity in Ewing sarcoma by blocking the positive feedback loop thereby removing the oncogenic driving force, and inhibiting the repair of EWS FLI1-generated DNA damage. PARPi increase the efficacy of temozolomide, irinotecan/topotecan and ionizing radiation by inhibiting repair of the DNA damage they cause. PARP, poly(ADP-ribose) polymerase; PARPi, poly(ADP-ribose) polymerase inhibitor.

EWS-FLI1 or the liposarcoma-associated translocation FUS-CHOP. Cells transformed with EWS-FLI1 were as sensitive as human Ewing sarcoma cell lines to olaparib, whereas FUS-CHOP transformed cells were resistant, and transient depletion of EWS-FLI1 in Ewing sarcoma cells led to reduced PARPi sensitivity. They concluded therefore that the sensitivity of Ewing sarcoma cells to PARP inhibition might be caused by EWS-FLI1 transcriptional activity.

Despite these promising preclinical results for single agent PARPi, this did not translate into the successful application of single agent PARPi in xenograft models. The Paediatric Preclinical Testing Programme (PPTP) evaluated the PARPi BMN 673 in a range of different xenograft mouse models, and all tested Ewing sarcoma models ($n = 5$ cell lines) showed progressive disease when treated with single agent BMN 673 continuously over 28 days [18]. Another group tested single agent olaparib in a similar Ewing sarcoma xenograft model to the Michigan group (RD-ES), and found that olaparib did not improve survival [19▪▪].

POLY(ADP-RIBOSE) POLYMERASE INHIBITORS AS CHEMOTHERAPY AND RADIOTHERAPY-POTENTIATING AGENTS

The DNA damage caused by the two groups of chemotherapeutic agents most commonly used in second-line treatment of Ewing sarcoma (topoisomerase I poisons, i.e. topotecan, irinotecan, and methylating agents, i.e. temozolomide), and also radiotherapy, can be potentiated by PARPi, as already described in a previous paragraph (PARP and the therapeutic utility of its inhibitors). For Ewing sarcoma, the potentiating effects of olaparib in combination with temozolomide were first published by the Michigan group [5▪▪] who demonstrated that in mice bearing Ewing sarcoma xenografts concomitant treatment with temozolomide and olaparib caused tumour regressions and sustained complete responses. Our own group demonstrated that Ewing sarcoma cells can be sensitized *in vitro* to temozolomide, and to a lesser extent to ionizing radiation, by co-treatment with the PARPi inhibitor rucaparib (AG014699) [20▪]. In colony formation survival assays, $0.4\,\mu mol/l$ of rucaparib caused a 15–28 fold sensitization of temozolomide and a 1.5-fold radiosensitization in CADO-Ewing sarcoma and TC-71 Ewing sarcoma cells. In-vitro data for the combinations of irinotecan or its active metabolite SN-38 with olaparib have demonstrated strong synergy for both combinations in Ewing sarcoma cell lines (RD-ES and TC-71), with a combination index of approximately 0.35 and 0.25 [19▪▪].

The effect of PARPi treatment in combination with temozolomide and irinotecan in Ewing sarcoma tumour graft models has also been published for the PARPi niraparib [21▪▪] and BMN 673 [18]. The Wilcoxon group presented impressive in-vivo evidence for combining either irinotecan or temozolomide with niraparib, with complete regression of patient-derived Ewing sarcoma tumours in all tested mice using two different schedules: full-dose temozolomide (daily for 5 days) or irinotecan (once weekly) combined with niriparib (daily for 5 days), or half-dose temozolomide or irinotecan and continuous niriparib. Interestingly, although toxicity was observed with the former schedule, there was none with the latter and continuous niriparib alone slowed tumour growth. The PPTP group also presented impressive data on the PARPi BMN 673, which potentiates the activity of temozolomide *in vitro*, exceeding 50-fold for some Ewing sarcoma cell lines. They also tested 10 different Ewing sarcoma xenograft models, and five of 10 showed a maintained complete response when treated with a combination of BMN 673 and low-dose temozolomide.

Table 1. Overview of clinical trials for Ewing sarcoma patients utilizing PARP inhibitors

PARP inhibitor	Company	Monotherapy	Combination treatments	Age of eligible patients	Trial status	Reference
Olaparib	Astra Zeneca	Phase II trial NCT01583543		>18 years	Closed	[23■■]
			Phase I with temozolomide NCT01858168	>18 years	Open	
			With radiotherapy		In preparation	[22■■]
BMN 673	BioMarin	Phase I trial NCT01286987		>18 years, not exclusively in Ewing patients	Open	[18,24]
Niraparib	Tesaro		Phase I with temozolomide NCT02044120	>13 years	To open March 2014	[21■■]
E7449	Esai		Other PARP inhibitors in Phase II/III clinical trials not currently tested in Ewing sarcoma			
Rucaparib	Clovis					
Veliparib	Abott					
CEP-9722	Cephalon					

PARP, poly(ADP-ribose) polymerase.

Further preclinical evidence that PARPi potentiate the effects of ionizing radiation in Ewing sarcoma has recently been published [22■■]. In this study, Ewing sarcoma cells, but not non-Ewing sarcoma cells, were sensitized to radiotherapy by olaparib, and this also translated to a xenograft mouse model, in which olaparib in combination with a single dose of ionizing radiation substantially delayed tumour growth. These findings open new potential treatment strategies for patients with unresectable Ewing sarcoma tumours, to either improve the efficacy of radiation, or to potentially achieve the same efficacy with reduced radiation doses. A first clinical trial to combine radiation with PARP inhibition is currently in preparation.

POLY(ADP-RIBOSE) POLYMERASE INHIBITORS IN CLINICAL TRIALS

These encouraging preclinical results, both *in vitro* and *in vivo*, have led to early clinical trials with different PARPi in patients with Ewing sarcoma (overview in Table 1) [18,21■■–23■■,24]. In a phase II pilot study with olaparib (NCT01583543), 12 patients with advanced Ewing sarcoma progressing after chemotherapy were treated with 400 mg of olaparib twice daily, and response was assessed by computed tomography or MRI at regular intervals. There was tolerable grade 3 toxicity in two of 12 patients, but unfortunately no partial or complete responses could be observed. Best responses were four patients with stable disease but eight patients had progressive disease and further enrolment was stopped [23■■]. This somewhat disappointing result

is now being followed up with a phase I combination trial of olaparib (50–200-mg twice daily) and temozolomide (50–75 mg/m^2), begun in July 2013 (NCT01858168), in patients with metastatic and/or unresectable, relapsed or refractory Ewing sarcoma. Another trial is testing the PARPi BMN 673 as a single agent in a range of advanced or recurrent solid tumours, including patients with Ewing sarcoma (NCT01286987), but so far without any objective responses in nine of 14 patients, the remaining five were too early to be evaluated [24]. All ongoing trials so far are limited to adult patients. Apart from these three trials, there are several combination studies currently being designed or in preparation. All results are eagerly awaited, so that also the paediatric/adolescent age group can at some point hopefully benefit from combinations of PARPi with chemotherapy or radiotherapy.

CONCLUSION

Since the two groundbreaking publications in 2012, showing Ewing sarcoma cells to be particularly sensitive to PARP inhibition, PARPi have emerged as a new class of drugs to treat Ewing sarcoma. PARPi monotherapy in xenograft models showed some moderate effects, but in a first clinical trial in patients with relapsed Ewing sarcoma, monotherapy did not translate into sufficient responses, despite being well tolerated. However, combinations of PARPi with temozolomide, topoisomerase I poisons and/or radiotherapy have shown excellent in-vivo results and are therefore currently the most favoured strategy for upcoming clinical trials.

Conflicts of interest

B.V. has no conflicts of interest.

N.J.C. has received funding from Pfizer, Clovis and BioMarin for work on PARP inhibitors and has (or had) consultancy agreements with Abbott, BioMarin, Eisai and Tesaro. She is inventor on a patent concerning rucaparib therapy but receives no revenue from this source. She declares no conflicts of interest.

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