The role of poly(ADP-ribose) polymerase inhibitors in the treatment of endometrial cancer: a scoping review of the current literature

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Abstract

Objective: To describe, synthesize, and interpret literature on the role of poly (ADP-ribose) polymerase inhibitors in the treatment of endometrial cancer and to identify areas of interest for future research.

Design: Scoping review of the literature covering several study designs.

Setting: Literature review.

Methods: Systematic Searches of the electronic databases PubMed® (MEDLINE®), Cochrane Library®, CINAHL®, and Web of Science™ were performed, as well as web-based searches (ClinicalTrials.gov, Canadian Clinical Trials & Cancer Trials, Australian Clinical Trials, WHO ICTRP, NIH Reporter, the CDC, and Google Scholar) for additional material, such as reports commissioned by government as well as non-governmental agencies. Literature was identified and organized into categories then synthesized to form conclusions and identify knowledge gaps.

Results: 96 records were identified after searching the literature and 69 records were subsequently reviewed.

Conclusion: There is conflicting evidence regarding the utility of proposed biomarkers in predicting sensitivity of endometrial cancer to PARP inhibitor treatment. Current in vitro and in vivo studies suggest that PARP inhibitors may be effective in the treatment of certain subsets of endometrial cancer, but further research is warranted.

Introduction

Endometrial cancer is the most common gynecologic cancer in the United States [1]. While early-stage cancer is generally cured with surgery, the therapeutic options for advanced and recurrent endometrial cancer are limited, with minimal efficacy, short-lived responses and significant toxicity [2-4]. In fact, the most effective regimens result in an overall survival of 12-15 months [5,6]. These results highlight the need for novel agents, including a shift toward targeting specific molecular and genetic pathways involved in endometrial carcinogenesis. One such target is Poly (ADP-ribose) polymerase, or PARP.

PARP is a family of 17 enzymes that catalyze the polyADP-ribosylation of proteins involved in the repair of single stranded DNA breaks via the base excision repair (BER) pathway [7,8]. PARP1 is activated in response to metabolic, chemical, or radiation-induced breaks in the DNA strand. Once a single stranded break is detected, PARP1 recruits and activates enzymes needed to repair the damaged strand via the transfer of ADP-ribose molecules from NAD+ to itself and other DNA repair proteins [7,9]. In addition to its role in the repair of single strand break (SSB) DNA, PARP aids in the prevention of formation of double strand breaks (DSB) in DNA via its recognition of stalled replication forks and recruitment of MRE11, which initiates the homologous recombination (HR) pathway [10].

Poly(ADP-ribose) polymerase inhibitors (PARP inhibitors) inhibit PARP function by two major mechanisms. First, they compete with NAD+ for access to the substrate binding site [11] and secondly, they trap PARP1 and PARP2 while complexed with DNA leading to cell death due to blocked DNA repair ability [12]. PARP inhibitors therefore lead to persistence of single stranded breaks in DNA due to impaired BER [9]. If unrepaired, these single stranded breaks lead to replication fork collapse or the generation of double-stranded breaks in DNA. Cells with intact homologous recombination (HR) DNA repair mechanisms are able to repair the double stranded breaks and the cells remain viable. However, in the absence of intact HR, cells are unable to repair double-stranded breaks and subsequently undergo apoptosis [13-15]. This exemplifies the concept of synthetic lethality, in which two specific defects, neither of which are overtly detrimental to the cell individually, but lethal when they occur together.

The synthetic lethality of PARP inhibitor treatment in tumor cells

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with defects in HR repair, including BRCA-mutated ovarian cancers has been demonstrated [16-19]. Clinical trials of monotherapy with the oral PARP inhibitor olaparib have shown objective antitumor activity in ovarian cancer [17-19]. Additional studies have focused on the efficacy of other PARP inhibitors in BRCA mutation carriers [20] and BRCA-mutated cancer cells [21].

Similarly, PARP inhibitors may have increased efficacy in tumors which exhibit "BRCAness"; that is, tumor cells deficient in HR but without a known or detectable BRCA1 or BRCA2 mutation [22]. Mutations in phosphatase and tensin homolog (PTEN) and MRE11 may cause tumor cells to exhibit a “BRCAness” phenotype, due to their role in DNA repair. PTEN is a tumor suppressor gene located on chromosome 10q23.3 that functions as an antagonist of the prosurvival/proliferative PI3K/AKT pathway [23]. In addition to its role in regulating the cell cycle, PTEN is also involved in DNA double-stranded break repair via upregulation of the gene encoding RAD51, a protein involved in DNA repair [23]. A diverse group of mutations in PTEN can lead to the generation of solid tumors; in fact, PTEN mutations are the most common molecular defect in endometrioid endometrial adenocarcinoma [24,25], seen in up to 83% of these endometrial cancers [24-27]. MRE11 is a protein that, together with RAD51 and NBS1, forms a complex involved in the detection and repair of DSBs in DNA [28,29]. The prevalence of MRE11 mutations in endometrial cancer is the subject of investigation, with studies suggesting mutation frequencies ranging from 1.9% to 50% [30,31].

Given the frequency of these mutations in endometrial and the implications of impaired DNA repair, it is plausible that endometrial cancers carrying these mutations have inadequate HR and therefore may be sensitive to PARP inhibitors. The purpose of this review is to analyze the current literature regarding the role of PARP inhibitors in the treatment of endometrial cancer, summarize results of available data, and identify areas warranting further research.

Methods

Eligibility criteria

A comprehensive literature search was conducted regarding the use of PARP inhibitors in endometrial cancer. Explicit methods aimed at minimizing bias and shadowed the recommended methodologic standards for systematic reviews set out by the Institute of Medicine. Inclusion and exclusion criteria were discussed at the beginning of the scoping process. Studies were considered eligible for inclusion if they 1. examined both endometrial cancer and PARP Inhibitors as therapy and 2. were published in English. There were no restrictions on types of studies to be included. There were no date restrictions.

Identification of literature

The scoping review was based on a search strategy using the following electronic databases: PubMed® (MEDLINE®), Cochrane Library®, CINAHL®, and Web of Science®, as well as web-based searches (ClinicalTrials.gov, Canadian Clinical Trials & Cancer Trials, Australian Clinical Trials, WHO ICTRP, NIH Reporter, the CDC, and Google Scholar) for additional material, such as reports commissioned by government as well as non-governmental agencies. The search strategies for medline CINHAL can be found in appendix A.

Permutations of search terms PARP inhibitors and Endometrial Cancer were used to collect a total of 96 bibliographical entries. The electronic search strategies were developed and executed within the databases (October 2014) by experienced information specialists. The bibliographies of included articles were reviewed for additional citations. The search was updated in February 2015 to identify any additional new records.

Review of identified studies

Prior to the initiation of screening, search results were entered into EndNote 7X Web and duplicate records were removed. Abstracts were reviewed independently by two researchers. All disagreements between reviewers regarding the articles were resolved through discussion. 52 articles were excluded from the review. 31 were excluded because they did not pertain to PARP inhibitors. 14 were excluded because they did not pertain to endometrial cancer. Four were excluded because they looked at PARP cleavage products as markers for apoptosis, no PARP inhibitors. Two were excluded because they did not include discussion of PARP inhibitors for endometrial cancer treatment and one because it did not examine PARP inhibitor efficacy (Table 1). In total, twelve published articles and five clinical trials were identified for inclusion in the review.

Results

The initial search returned 96 results, of which 17 articles met the study criteria and were subsequently reviewed (Figure 1).

Of the studies selected for analysis, 4 were in vitro [14,32-34], 2 were in vivo [35,36], 6 were reviews [3,7,37-40], and 5 were clinical trials.

In vitro studies

Dedes et al., using endometrial cancer cell lines, tested whether they were sensitive to PARP inhibition due to the loss of PTEN [14,34]. Cells lines which did not express PTEN were more sensitive to treatment with the PARP inhibitor, KU0058948. Furthermore, as proof of its critical role, they silenced PTEN in wild-type PTEN cell lines and noted and increased sensitivity to PARP inhibition. Cell lines lacking PTEN and PARP-inhibitory sensitive, when transduced with wild-type PTEN, had significantly decreased sensitivity to PARP inhibition.

In a more recent paper, investigators from Japan, using endometrial cancer cell lines, evaluated the correlation between PTEN status and olaparib sensitivity [32]. Endometrial cancer cell lines, PTEN-null and wild-type PTEN, were exposed to olaparib at varying concentrations, for 2-3 weeks and the concentration to inhibit cell survival by 50% (SF50) was calculated. The antiproliferative effects of olaparib varied depending on the cancer cell line, with SF50 ranging from 8 nM to 2500 nM. The PTEN status of cell lines was not shown to correlate with sensitivity to olaparib. However, a fourth of PTEN-deficient cells were sensitive to olaparib, with SF50 values <100 nM. RAD51 expression was not correlated with PTEN status. The authors concluded that while PTEN is not a predictive biomarker for olaparib sensitivity, PARP inhibitors may still provide a promising therapeutic strategy in certain endometrial cancers.

Koppensteiner et al. sought to determine if loss of MRE11 would result in increased sensitivity to a PARP-inhibitor [33]. Among endometrial cancers tested, nearly one third lacked MRE11 staining. When endometrial cancer cell lines were tested for PARP-inhibitor sensitivity with BMN673, the cell line lacking MRE11 expression was the most sensitive. When MRE11 was depleted via siRNA, the previously PARP-I resistant cell lines were rendered PARP inhibitor
Table 1. Excluded citations and reasons for exclusion.

<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>Title</th>
<th>Authors</th>
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<tbody>
<tr>
<td>Not About PARP Inhibitors</td>
<td>Effects of trichostatin A and paclitaxel on apoptosis and mitochondrial membrane potential of human endometrial carcinoma Ar2k cells</td>
<td>Y. N. Yang, Y. Wang, X. G. Wang and S. J. Jiang</td>
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<tr>
<td>Synuclein-gamma (SNCG) may be a novel prognostic biomarker in uterine papillary serous carcinoma</td>
<td>J. Morgan, A. V. Hokekstra, E. Chapman-Davis, J. L. Hardt, J. J. Kim and B. M. Buttin</td>
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<td>Histone deacetylase inhibitors induce apoptosis in both Type I and Type II endometrial cancer cells</td>
<td>S. J. Jiang, S. C. Dowdy, X. W. Meng, Z. Y. Wang, M. B. Jones, K. C. Podrutz and S. W. Jiang</td>
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<td>Description of the cytotoxic effect of a novel drug Abiraterone-isothiocyanate on endometrial cancer cell lines</td>
<td>T. C. Horan, M. A. Zompa, C. T. Seto, K. K. Kim, R. G. Moore and T. S. Lange</td>
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<td>Endometrial cancer cell survival and apoptosis is regulated by protein kinase C alpha and delta</td>
<td>J. M. Haughian, T. A. Jackson, D. M. Koterwas and A. P. Bradford</td>
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<td>17-Allylamino-17-demethoxygalanamycin and 17-NN-dimethyl ethylene diamine-galancamycin have cytotoxic activity against multiple gynecologic cancer cell types</td>
<td>D. R. Gossett, M. S. Bradley, X. H. Jin and Y. Y. Lin</td>
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<td>Involvement of Akt isoforms in chemoresistance of endometrial cancer cells</td>
<td>J. Giroird, M. J. Laffleur, S. Parent, V. Leblanc and E. Asselin</td>
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<td>Tumor suppressor effect of folliculin-like 1 in ovarian and endometrial carcinogenesis-02SEFs</td>
<td>Q. K. Y. Chan, H. Y. S. Ngan, P. P. C. Ip, W. V. S. Liu, W. C. Xue and A. Y. Y. Cheng</td>
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<td>Induction of apoptosis in endometrial cancer cells by psammaplysene A involves FOXO1 differential expression and functional analysis</td>
<td>E. Berry, J. L. Hardt, J. Clardy, J. R. Lurain and J. J. Kim</td>
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<td>Insulin-like growth factor-1 receptor (IGF-IR) targeting with monoclonal antibody cixutumumab (IMC-A12) inhibits IGF-I action in endometrial cancer cells</td>
<td>Z. Attiaas-Geva, I. Bentov, D. L. Ludwig, A. Fishman, I. Bruchim and H. Werner</td>
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<tr>
<td>Molecular mechanism of ursoic acid induced apoptosis in poorly differentiated endometrial cancer HEC108</td>
<td>Y. Achiwa, K. Hasegawa and Y. Udagawa</td>
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<td>Ursolic acid induces Bax-dependent apoptosis through the caspase-3 pathway in endometrial cancer SNG-II cells</td>
<td>Y. Achiwa, K. Hasegawa, T. Komiya and Y. Udagawa</td>
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<td>PARP-1 activity in normal and cancerous human endometrium and its relationship with quantity of abasic sites (AP)</td>
<td>Postawski K1, Monist M, Keith G.</td>
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<td>Poly(ADP-ribose) polymerase (PARP) and DNA-fragmentation factor (DFF45): expression and correlation in normal, hyperplastic and neoplastic endometrial tissues</td>
<td>H. Brustmann</td>
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<td>Hypomethylation of ETS transcription factor binding sites and upregulation of PARP1 expression in endometrial cancer</td>
<td>F. F. Bi, D. Li and Q. Yang</td>
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<td>Consequences of the loss of p53, RB1, and PTEN: Relationship to gefitinib resistance in endometrial cancer</td>
<td>L. Albirat, M. B. Carter, S. Davies and K. K. Leslie</td>
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<td>Changes in expression of some apoptotic markers in different types of human endometrium</td>
<td>D. Drick, M. Dvoska, I. Svandova, B. Sehnal, K. Benkova, Z. Sparkova and M. Halaska</td>
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A Study of Oral Rucaparib in Patients With a Solid Tumor (Phase I) or With gBRCA Mutation Ovarian Cancer (Phase II)  
Effects of parathyroid hormone like hormone (PTHHLH) antagonist, PTHHLH(7-34), on fetoplacental development and growth during midgestation in rats  
‘BRCAness’ and Its Implications for Platinum Action in Gynecologic Cancer  
‘Triple negative’ epithelial ovarian cancer and pathologic markers for prognosis  
Tetraiodothyronate sensitizes ovarian cancer cells to anticancer drugs doxorubicin, fenretinine, 5-fluorouracil and mitomycin C  
Pre-eclampsia and maternal anemia display reduced apoptosis and opposite invasive phenotypes of extravillous trophoblast  
PARP1 during embryo implantation and its upregulation by oestradiol in mice  
Expression of BAG-1 and PARP-1 in Precursor Lesions and Invasive Cervical Cancer Associated with Human Papillomavirus (HPV)  
The role of steroid hormones and decidual induction in the regulation of adenosine diprophosphoribosyltransferase activity in rat endometrium  
Cyclooxygenase-2 regulates survival, migration, and invasion of human endometriotic cells through multiple mechanisms  
OSU-A9, an indole-3-carbinol derivative, induces cytotoxicity in acute myeloid leukemia through reactive oxygen species-mediated apoptosis  
Reduced Mitogenicity of Sera Following Weight Loss in Premenopausal Women  
BRCA Mutation Frequency and Patterns of Treatment Response in BRCA Mutation-Positive Women With Ovarian Cancer: A Report From the Australian Ovarian Cancer Study Group  
‘Triple negative’ epithelial ovarian cancer and pathologic markers for prognosis.  
The Akt and ERK Activation by Platinum-based Chemotherapy in Ovarian Cancer is Associated with Favorable Patient Outcome  
Sojucktang induces apoptosis via loss of mitochondrial membrane potential and caspase-3 activation in KLE human endometrial cancer cell  
GRP78 induced by estrogen plays a role in the chemosensitivity of endometrial cancer  
A novel role for placental leucineaminopeptidase (P-LAP) as a determinant of chemoresistance in endometrial carcinoma cells  
A study of parietal leucineaminopeptidase (P-LAP) in endometrial cancer cells  
Reduced Mitogenicity of Sera Following Weight Loss in Premenopausal Women  
Did Not Include Discussion of PARP Inhibitors for Endometrial Cancer Treatment  
Major clinical research advances in gynecologic cancer in 2012  
Major clinical research advances in gynecologic cancer in 2013  
Veliparib, Paclitaxel, and Carboplatin in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery and Liver or Kidney Dysfunction  
Clin Med Invest, 2016  
Figure 1. Flow diagram of included studies from scoping review.
Studies have shown conflicting evidence regarding the susceptibility of PTEN null endometrial cancer cells to PARP inhibitors. Data from Dedes et al. suggest that PTEN null endometrial cancer cells are more susceptible to PARP inhibition than cells with wild type PTEN. In contrast, results from Miyasaka suggest that lack of PTEN expression does not increase sensitivity to the PARP inhibitor olaparib. The discordance of these results may stem from the difference in number and type of endometrial cell lines tested. Dedes et al. included 2 PTEN wild type cell lines, whereas Miyasaka et al. included 4 PTEN wild type cell lines, including three different PTEN mutant cell lines (HEC-6, HEC-116, and HEC-108).

The sensitivity of the tumor to PARP inhibition may be altered by the hormonal milieu of the tumor [36]. In an in vivo study by Janzen et al., in a high estrogen state, peak olaparib concentrations, comparable to serum concentrations in humans treated with the common dose of 400 mg olaparib twice daily, were achieved at 2 hours. In contrast, in a low estrogen state, the peak concentration was achieved earlier, after only 30 minutes, and reached a concentration twenty times higher than in the high estrogen state. Additionally, CYP3A4, the enzyme responsible for the majority of olaparib metabolism in humans, is reported to be regulated by estrogen concentrations. Levels of CYP3A4, mouse homolog, had transcripts in higher concentration in the estrogen treated versus estrogen depleted mice. These findings that tumors in a high estrogen environment may be more resistant to PARP inhibition than those in a low estrogen environment may ultimately have clinical implications, as the level of estrogen in endometrial cancer patients may often be elevated secondary to obesity [41] and can be manipulated with drugs such as aromatase inhibitors or oophorectomy.

In a case study reported by Forster and colleagues [35], a patient with recurrent, metastatic PTEN null endometrial cancer derived benefit, both subjective and objective, from treatment with olaparib. In addition to reporting decreased symptoms related to her metastases, imaging studies evidenced objective improvement in tumor burden.

We have reported on our thorough review of literature regarding the PARP inhibition in endometrial cancer. Available evidence suggests that PARP inhibitors hold promise in the treatment of endometrial cancer. Human studies are needed to definitively elucidate the role of these drugs in treating endometrial cancer. Patient selection will be of paramount importance and would benefit from further investigation into the role of PTEN and MRE11 mutations as potential biomarkers for sensitivity to PARP inhibitor. Patient hormonal status (i.e. estrogen level) and possible manipulation must be considered when prescribing PARP inhibitor treatment. The ideal balance of efficacy with toxicity of PARP inhibitors as monotherapy versus combination with cytotoxic chemotherapy will warrant further investigation, as well as optimal duration of treatment, long term side effects of treatment, and mechanisms of development of resistance remain to be determined and have important implications in the use of PARP inhibitors for recurrent or advanced endometrial cancer.

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