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Poly ADP-ribose polymerase (PARP) inhibitors- new therapeutic strategies in Acute Myeloid Leukemia: a literature review

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Abstract
The use of poly (ADP-ribose) polymerase (PARP) inhibitors has recently increased as a result of demonstrating their superior efficacy compared to traditional chemotherapy in various cancer subtypes in many preclinical studies and clinical trials. A better understanding of the molecular mechanisms of PARP and their underlying foci that can be used as screening markers for potential new therapeutic options would aid rational treatment strategies and improve long-term patient outcomes. The available data on acute leukemia suggest potential windows for effective treatment of PARPi in disease subgroups. In this review, we summarize the current advances in the most common PARP-based adjuvant therapies and combination strategies for the treatment of acute leukemia and discuss the future prospects and challenges of therapy with PARP inhibitors. We also discuss reports describing an increased risk of cancer treatment in patients receiving PARP inhibitors for solid tumors.
The research material were publications, the search was carried out using a combination of keywords such as: "PARP inhibitor", "acute leukemia", "therapy", "PARP clinical trials". The first step was to find relevant publications from the last 15 years. The second step was to review the publications found.
Studies have shown that PARP inhibitors play an increasing role in the treatment of leukemia. In addition, focusing research efforts on identifying the most effective drug combinations and sequences could help to further shape the role of PARPi in the treatment of acute myeloid leukemia (AML).

Keywords: PARP inhibitor; Drug targets; Combination therapies; Acute leukemia; Acute Myeloid Leukemia

INTRODUCTION AND PURPOSE
Acute myeloid leukemia (AML) is a malignancy of the stem cell precursors of the myeloid lineage (red blood cells, platelets, and white blood cells other than B and T cells) [1]. Like other malignancies, it is due to genetic variations that lead to neoplastic changes and clonal proliferation. Identifying these genetic abnormalities is crucial in assigning patients to a given risk group and determining the appropriate treatment [2]. Despite the progress of modern medicine, clinical outcomes for AML have not significantly improved, with only 20–30% of patients achieving long-term disease-free survival [3]. Especially in the era of personalized treatment, there is a great clinical need for innovative therapies that are more effective and less toxic than conventional chemotherapy. While some AML patients achieve complete remission after conventional chemotherapy or a combination of a hypomethylating agent and venetoclax, de novo or acquired drug resistance is often an insurmountable challenge, especially in the remaining patients [4]. Potent anti-

leukemic effects have consistently been reported in human AML cell lines and preclinical models treated with numerous PARPi [5,6].

Over the past decade, poly (ADP-ribose) polymerases (PARP) have emerged as a new target for the treatment of solid tumors and have been approved for subgroups of patients with ovarian, breast, prostate and pancreatic cancer [7]. PARP proteins are involved in several cellular processes including stress response, chromatin remodeling, DNA repair, and stress apoptosis, as well as deficiencies in DNA repair pathways. Four PARP inhibitors, olaparib, rucaparib, niraparib and talazoparib, have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and another three are being tested in Phase III studies (veliparib, pamiparib and flusoparib) [8].

PPARP Poly (ADP-ribose) polymerases are a family of 17 proteins, and the most recognized and most characterized member of the PARP protein family is PARP1, initially identified for its role in detecting and repairing single-stranded DNA breaks. Following DNA damage, PARP1 is rapidly recruited into single strand breaks (SSBs) and double strand breaks (DSBs) where other proteins are PARylated upon binding to single stranded DNA (ssDNA) leading to recruitment of downstream DNA repair factors [9]. BRCA1 and BRCA2 are then recruited further downstream to regulate one of two major pathways in DSB repair during the S and G2 phases of the cell cycle: homologous recombination (HR) [10]. Unlike other DSB repair paths, HR repair is largely flawless. BRCA1 is required for HR initiation by promoting DSB endresection and then works further along with BRCA2 and PALB2 to stimulate RAD51 recruitment into the excised DNA single strand. HR then allows the DNA damage to be accurately repaired using the newly replicated sister chromatid as template. In addition to their role in HR, BRCA1 and BRCA2 are also critical during the S phase of the cell cycle, where they protect blocked replication forks from degradation by nucleases such as MRE11 [11]. As a consequence of the above-mentioned roles of BRCA1 and BRCA2, heterozygous germline mutations in each of these genes confer a strong predisposition to cancer that arise from the loss of the remaining wild-type alleles and are associated with high levels of genomic instability due to loss of HR [12]. BRCA1/2-deficient tumors also often show a marked level of sensitivity to other DNA damaging agents, including platinum-based chemotherapy, topoisomerase inhibitors (TOP), and bifunctional alkylators, which are likely to produce lethal classes of DNA changes into BRCA1/2-deficient cells [13]. The interaction between BRCA1/2 and PARP1 is the most known synthetic lethal compound to date [14].

Although BRCA1/2 mutations are rare in haematological malignancies, clinical experience has shown the benefit of using PARPi in HR deficient tumors due to myriad mutations in other genes [15]. Leukemia cells are characterized by a high degree of chromosomal instability, believed to be due to defective DNA damage repair mechanisms, including dysregulation of several genes involved in HR such as ATM, ATR, CHK1 and RAD51[16]. Moreover, evidence has emerged that DNA polymorphisms and/or aberrant transcriptional regulation may result in faulty DNA-damage response (DDR) in myeloid blasts differentiation, leukemia pathogenesis, and treatment resistance. These analyzes led to the evaluation of PARP inhibition as an intervention strategy for AML, especially in the case of demonstrated genomic instabilities and chromosomal aberrations [17].

In this review, we summarize the current advances in the most common PARP-based adjuvant therapies and combination strategies for the treatment of acute leukemia, and discuss the future prospects and challenges of therapy with PARP inhibitors. We also discuss reports describing an increased risk of cancer treatment in patients receiving PARP inhibitors for solid tumors.

Description of the state of knowledge

Almost a decade ago, Gaymes and colleagues suggested that patients with myelodysplastic syndromes (MDS) and AML might be good candidates for PARPi therapy. More specifically, the microsatellite instability found in MDS/AML patients correlated with downregulation of HR repair genes. Indeed, monoallelic mutations in CtIP (high-risk MDS) and primary MRE11 AML samples (2 out of 18.11%) and mutations in CtIP (4 out of 56.7%) in high-risk MDS made the leukemic cells sensitive to PARPi [18]. Futhermore, it was noticed that samples taken from myeloproliferative tumors prone to develop AML were more sensitive to olaparib and veliparib compared to normal bone marrow cells. In addition, JAK2-V617F's ability to activate transcription via a signal transducer and transcription activator and inhibit apoptosis, making JAK2 unmutated myeloblasts more sensitive to PARPi than JAK2-V617F mutant samples [19,20].

Mufti and colleagues presented their study of the PARP inhibitor talazoparib in adult patients with advanced hematologic malignancies in a phase I single-drug study (NCT01399840) [21]. Thirty-three participants were enrolled: twenty-one with AML and four with MDS (10 females and 23 males), and the median age was 71 years (range 22–86). Dosage levels ranged from 100-2000 μg/day on a continuous daily schedule in 21-day cycles with ascending dose levels. Investigators reported the most common adverse events associated with talazoparib, which were fatigue (27%), neutropenia (27%), nausea (24%), infection (21%), and thrombocytopenia (12%). Disease stabilization was noted in 13 of the 24 AML or MDS patients evaluated, and one MDS patient who received 24 cycles of talazoparib became red cell transfusion independent.

Consider the limited activity of a single agent, other studies focus on adjuvant therapies with PARPi. 48 patients with relapsed/refractory AML were enrolled in a phase I study in which veliparib was combined with temozolomide (NCT01139970) [22]. The age of the patients was 69 years (range 20-88 years) with relapsed or refractory AML (RR-AML); newly diagnosed AML resulting from previous MDS, Myeloproliferative neoplasms (MPN) or chemotherapy; or patients ≥ 60 years of age with untreated AML with unfavorable cytogenetic results and/or ineligibility for intensive care were enrolled in the 3+3 regimen. Veliparib was administered orally once on day 1 and then twice daily on days 4–12 of cycle 1. In subsequent cycles it was administered twice daily on days 1–8. Temozolomide was given once daily on days 3–9 in cycle 1 and days 1–5 in cycle 2 and beyond. The most common non-hematologic adverse events of any grade were nausea/vomiting (35%), fatigue (24%), mucositis (13%), diarrhea (10%), and constipation (11%). The most common serious adverse events were infections (24%); febrile neutropenia (20%); and oropharyngeal mucosistis/esophagitis (4%). Complete remission (CR) was documented in 8 of 48 patients (16.6%), with seven of these patients achieving CR after the first cycle. An additional eight patients experienced haematological improvement (HI) or disease stabilization. The median overall survival (OS) for all patients was 5.3 months. Patients who achieved CR had a median OS of 20 months, while patients who achieved HI or disease stabilization had a median OS of 9.4 months. Notably, responders showed a veliparib-induced increase in H2AX in CD34+ cells as a marker of DNA damage accumulation. Moreover, three out of four patients with O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation achieved CR, making methylated MGMT a possible biomarker of sensitivity to this regimen.

Veliparib was also evaluated in combination with topotecan and carboplatin in a Phase 1 study in 99 patients with relapsed/refractory AML, chronic myelomonocytic leukemia (CMML), or aggressive MPN (NCT00588991) [23]. The median age of all patients was 56 years (range 25-76 years) with a median of two prior treatments (range 0-4), including 16 patients with a prior allogeneic hematopoietic stem cell transplantation (allo-HSCT). Veliparib doses were escalated, 10–100 mg twice daily. They were administered standard doses of topotecan (1.0–1.3 mg/m2/day) and carboplatin (120–150 mg/m2/day) in 21-day cycles. The MTD of veliparib was 80 mg twice daily for up to 21 days, with two out of four patients (50%) receiving 90 mg twice daily developing grade ≥3 mucositis. Across the entire cohort, at least 33% of patients achieved partial remission. Among patients with de novo AML, the overall response rate was 25% (19/77). Patients with aggressive MPN, CMML, or secondary AML responded in 64% (14/22), of whom 11 went on to allo-HSCT) with donor cell engraftment. The median OS was 15.3 months for responders compared with 4.2 months for non-responders. At higher drug doses, decreased pADPr content and increased H2AX phosphorylation in circulating CD34+ blasts were observed. In addition, impaired FANCD2 monoubiquitination was detected in 28 out of 49 samples tested (57%) and correlated with a small increase in survival (median 6 .1 month vs 4.8 months and 1-year survival 39% vs 5%). A phase II study is currently underway in patients with newly diagnosed or relapsed refractory AML with prior MPN in the form of adjuvant therapy with topotecan/carboplatin/veliparib.

There is currently much research on subtypes of AML with molecular deficits that contribute to HR deficiency and may have increased sensitivity to PARP inhibition. A Phase 1/2 clinical trial is underway at the University of Maryland evaluating the combination of PARPi and DNA methyltransferase inhibitors (DNMTi) (NCT02878785) in adult patients with untreated AML who are considered unfit for intensive chemotherapy or RR-AML. Patients receive daily intravenous decitabine for five days every 28 days with increasing doses of talazoparib administered orally once daily continuously starting from day 1 of cycle 1. In addition, olaparib is being evaluated in a phase II IDH1/2 mutant AML study (NCT03953898). While, a phase I study is evaluating Talazoparib in patients with AML with a cohesin mutation (NCT03974217).

Despite the clinical effectiveness of PARPi in oncology, the risk-benefit ratio of DDR inhibition pathways in cancer patients is under constant review. PARPi serves as a potential therapeutic agent for the bone marrow, but it is also emerging as a cause of these disorders [24]. When comparing de novo myeloid malignancies, myeloid malignancies associated with PARPi therapy are more likely to contain mutations in components of the DDR pathway, such as TP53 and PPM1D. Similarly, chemotherapy and radiotherapy can select and promote the expansion of hematopoietic stem cell clones with TP53 and PPM1D mutations [25]. In addition, unfavorable cytogenetics, especially complex karyotypes, were found in the vast majority of cases. The development of a secondary myeloid tumor (t-MN) following the use of PARPi in ovarian, breast and pancreatic cancer highlighted the potential toxicity of PARP1 inhibition in healthy hematopoietic precursors [26]. Indeed, the overall prevalence of t-MN ranges from 0.3 to 3% of patients, depending on primary tumor subtypes and the type of PARPi used in the study. Nevertheless, the incidence of t-MN after PARPi is significantly lower than the incidence of t-MN after conventional chemotherapy (overall incidence 0.8% to 6.3%) [27].

Since the role of PARPi is being investigated in clinical trials of AML subtypes, shortening the duration of therapy with these drugs to achieve synergy with chemotherapy in the initial treatment of leukemia may have a different risk profile than long-term use as maintenance therapy for solid tumors, but careful analyzes are needed to confirm this [28]. To achieve the most optimal benefit from PARPi therapy, patients at increased risk of developing treatment-related myeloid malignancies should be selected based on the baseline clonal hematopoiesis (CH) landscape and stratified for acute leukemia patients who are likely to benefit from PARPi-based therapeutic regimens [29]. It is equally important to identify agents that may be effective in treating these PARPi-emergent myeloid malignancies. Achieving these goals

could reduce the incidence of secondary malignancies as well as better inform the design of effective treatment regimens for PARPi-related myeloid cancers.

Summary

Studies have shown that PARP inhibitors play an increasing role in the treatment of leukemia. Despite the promising results that have emerged from studies evaluating PARPi (particularly talazoparib, and veliparib) as single agents or in a study with chemotherapy in haematological malignancies, further studies of cross-expression and regulation of different members of the PARP family are still needed to identify possible biomarkers, provide more prospects for the optimal outline of PARPi-based combinations and expand their therapeutic prospects. In addition, focusing research efforts on identifying the most effective drug combinations and sequences could help to further shape the role of PARPi in the treatment of acute myeloid leukemia (AML). The range of risks and benefits associated with the use of PARPi in the treatment of ovarian cancer, breast cancer and other solid tumors is still being presented to patients, so a deeper understanding of the risk of bone marrow cancer associated with therapy with these drugs is equally important. While the incidence of PARPi therapy-related myeloid malignancies remains low, raising awareness of the role of PARPi and their potential complications is becoming increasingly important as these agents continue to be used in increasing numbers of cases and clinicians prescribing PARPi should remain vigilant about with these possible complications.

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