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Review

PARP Inhibitors as Therapeutic Options for Tyrosine Kinase-dependent Leukemia: A Review

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Abstract. *The idea of utilizing poly-ADP-ribose polymerase inhibitors (PARPi) as therapeutics for cancer has grown in popularity since its original approval for clinical usage in treatment of BRCA DNA repair-associated-mutated ovarian cancer. In this study, we evaluated experimental data regarding in vitro studies utilizing PARPi as a treatment for tyrosine kinase (TK)-dependent leukemia. Studies from 2015 to 2019 were compiled and the ones with most relevant TK pathways and PARP inhibition were analyzed. PARPi showed activity against many leukemia cell lines and samples from patients with primary leukemia, especially when combined with other signaling pathway inhibitor drugs, improving upon the hypothesis that the utilization of PARPi has potential as a new therapeutic approach in treatment of primary leukemia and TK-dependent leukemia.*

The term 'leukemia' is used to represent a cohort of hematopoietic malignancies in which a deregulation of the production of mature leukocytes and their precursors is present. Leukemia is one of the most common types of cancer involving pediatric patients in the world, and its distribution may be associated with a wide array of factors such as socioeconomic status and ethnicity (1, 2).

Even though in recent years the treatment of different leukemia subtypes has steadily advanced, there are still many obstacles to overcome. As an example, the occurrence of therapy-related neoplasms is highly associated with exposure to conventional chemotherapy for primary leukemia. Moreover, the development of multidrug resistance in cancer cells may occur even after few chemotherapy cycles and is considered to be one of the main challenges in leukemia treatment (3-5).

Conventional oncology therapies with cytotoxic agents still has its limitations and has shown itself to be ineffective when treating many malignancies by causing patients side-effects. Knowing that, it is of the utmost importance in oncology to strive always for innovation in the search for new pathways and targeted molecular therapies to improve prognosis and quality of life for patients with neoplasms (6, 7).

The development of targeted molecular therapies has completely changed the dynamics in the treatment of most neoplasms, being less toxic and more effective alternatives than conventional chemotherapy (8).

Poly-ADP-Ribose Polymerase (PARP) Activity and Clinical Usage

The inhibition of PARP is becoming more popular as a target in the treatment of BRCA1/2 DNA repair-associated (BRCA1/2)-deficient tumors that present defects in the homologous recombination (HR) repair pathway (9).

The PARP family is composed of 17 enzymes with different functions in the cellular matrix, however, PARP1 is primarily the one responsible for DNA damage repair (DDR) activity attributed to these enzymes and, therefore, is the main target in molecular therapies utilizing PARP inhibitors (PARPi) in the treatment of cancer. The mechanism of action of PARP1 is related to its capacity to execute post-translation modifications of proteins through the addition of PARP chains, inducing structural and functional changes in a process called PARylation (10, 11).

PARP1 possesses three zinc-finger domains, two of which are responsible for recognizing and binding the enzyme to DNA (Figure 1A). When genetic damage is identified, PARP1 auto-PARylates and signalizes for the recruitment of other enzymes which initializes the DDR mechanism. Before

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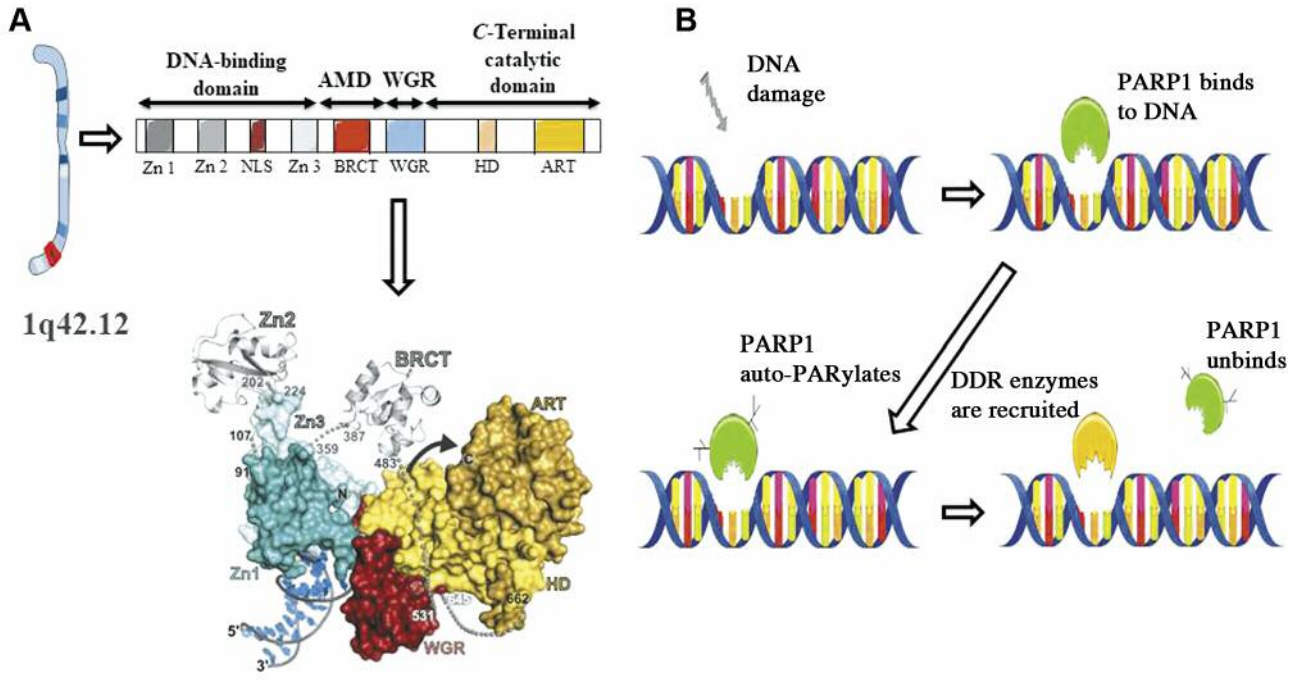

Figure 1. *Poly-ADP-ribose polymerase 1 (PARP1) structure and DNA-repair mechanism. A: Representation of PARP1 structure and functioning domains. Zn1: Zinc-finger 1; Zn2: Zinc-finger 2; NLS: nuclear localization signal; Zn3: Zinc-finger 3; AMD: auto-modification domain; BRCT: breast-cancer-susceptibility protein carboxy terminus; HD: helical subdomain; ART: ADP-ribosyl transferase subdomain. B. Multifactorial DNA damage generates single-strand breaks which are then recognized by PARP1. After binding, PARP1 auto-PARylates, signaling for the recruitment of proteins involved in the repairing mechanism. PARP1 unbinds from DNA due to charge repulsion and DNA damage-repair (DDR) enzymes initiate the repair.*

DDR initiation, PARP1 unbinds from the DNA due to accumulation of negative charges from the PARP chains and the PARylation process is reverted, returning PARP1 to its original conformation (Figure 1B) (12-14).

PARPi in treatment of neoplasms represents the first ever clinical application of the synthetic lethality concept, which describes cell death when a series of intrinsic and extrinsic cell factors are activated through pharmacological manipulation (15). PARP1 is responsible for signalizing the repair of single-strand breaks in DNA, therefore, its inhibition induces escalation of these injuries and conversion into double-strand breaks. Tumors which are deficient in HR mechanism, such as BRCA1/2-deficient tumors, are unable to effectively repair double-strand breaks and are induced to undergo apoptosis when treated with PARPi as a consequence (16, 17).

Another means through which PARPi exerts cytotoxicity is by forming insoluble PARP–DNA complexes, in a process known as PARP trapping. When PARP binds to DNA and is unable to be released, the DDR mechanisms are unable to bind and act on that sequence, impairing DNA repair and inducing genetic damage. Some PARPi agents are more efficient than others in binding PARP to DNA, and some even induce PARP release; this difference in their activity has no direct correlation with their capability of inhibiting PARylation itself (18-20).

The current usage of PARPi in clinical practice is still restricted to treatment of solid tumors and most indications for their use revolve around treatment of BRCA-mutated tumors (21). However, a series of recent experimental and clinical studies demonstrated that PARPi may also be useful when treating a great variety of leukemia subtypes and related diseases that may present other mutation categories, without damage to the DDR mechanism. Even though experimental evidence attests the efficacy of these drugs, their antitumor mechanism has not been fully elucidated in many of the leukemia subtypes in which they are active (22).

Tyrosine Kinases and Carcinogenesis

TKs are a large protein family that is involved in a variety of cellular signaling pathways and other survival and replication mechanism in a way that grants them a major role in the carcinogenesis of many tumor type (Figure 2). Approximately 100 TKs have been characterized in the human genome and are divided into receptor TKs, these being proteins with transmembrane domains, and non-receptor TKs, characterized as being cytoplasmic or nuclear proteins (23-25).

The first TK inhibitor (TKI) to be approved as a therapeutic in neoplasms was designated for the treatment of chronic

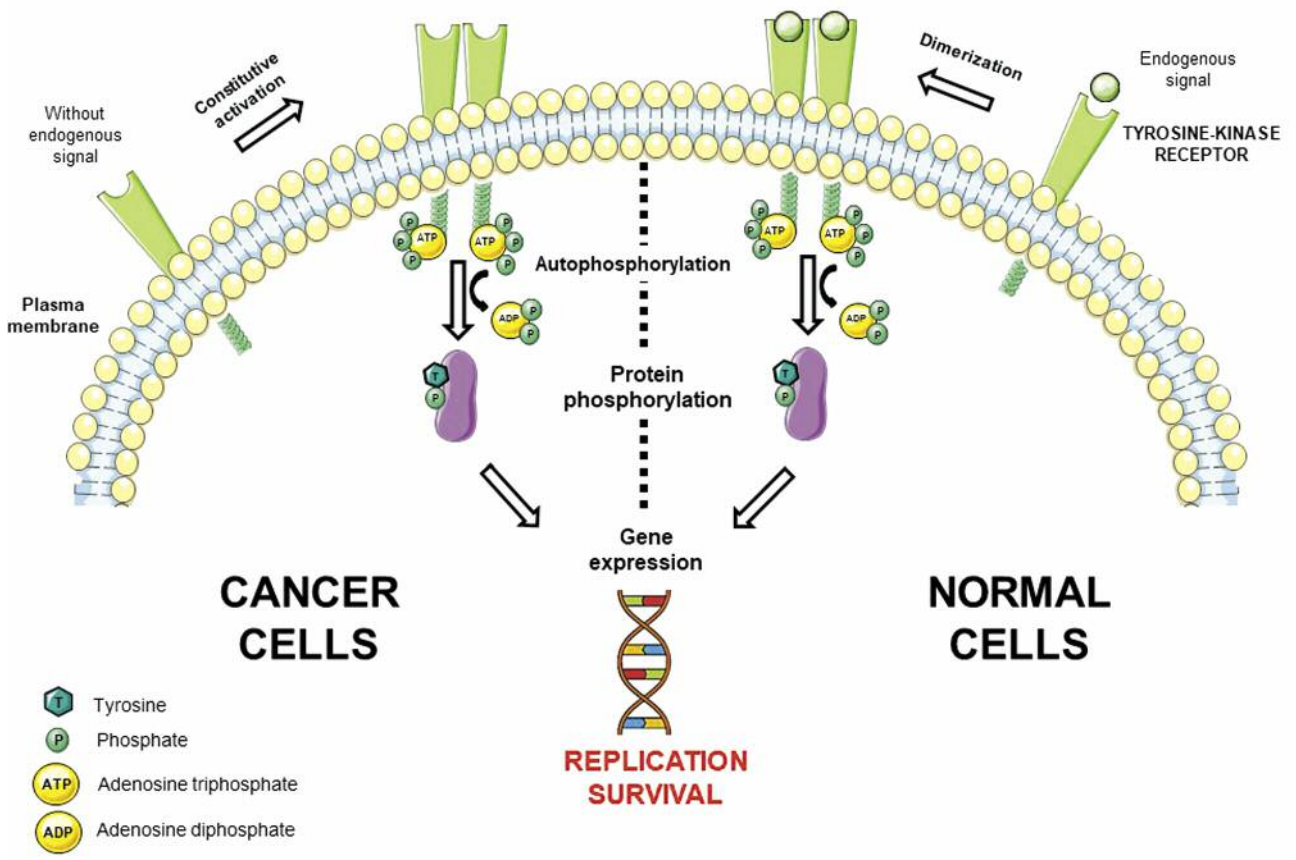

Figure 2. *Tyrosine-kinase signaling pathway. Tyrosine-kinase mutations may induce constitutive activation or overexpression in cancer cells, leading to signaling pathways deregulation and malignant cells replication and survival.*

myeloid leukemia (CML) due to the high frequency of expression of the chimeric TK breakpoint cluster region - Abelson murine leukemia (*BCR–ABL*) in this subtype. Currently, the roles of many TKs in carcinogenesis have been well characterized for other leukemia subtypes and are used as targets of inhibition for the treatment of neoplasms. The development of TKIs astoundingly changed the prognosis of patients suffering from TK-dependent leukemia by drastically increasing the rates of cure and overall survival (25-27).

However, malignant cells are easily mutated and the selective pressure exerted by treatment with TKIs usually results in emergence of resistant tumors, especially in relapsed leukemias. The mechanism involving resistance may vary depending on the drugs used and the leukemia subtype being treated with strategies to overcome resistance mostly consisting of increases in TKI dosage or utilization of second generation TKIs. Both strategies represent more risks to the patients, due to the increased drug toxicity, and will not necessarily provide a longer overall survival (28–31).

New Therapeutic Strategies

The development of alternative therapeutic approaches is extremely necessary in the goal of tackling the inevitable cases of resistance originated from the selective pressure of conventional and targeted therapies (32).

Even though some mechanisms remain to be elucidated, the utilization of PARPi has been shown to be a promising therapeutic strategy in the treatment of many leukemia subtypes (22). It is also important to note that some PARPi may have off-target effects beyond inhibition of PARylation and PARP trapping and may interfere directly with kinase activity pathways (33). In this review, we aimed to evaluate experimental data in the literature regarding *in vitro* studies utilizing PARPi as a treatment for TK-dependent leukemia.

Table I comprises a number of relevant studies from 2015 to 2019 reporting *in vitro* PARPi activity against leukemia cell lines and in samples of patients with different leukemia subtypes.

Table I. *In vitro studies of poly-ADP-ribose polymerase inhibitors (PARPi) in leukemia cells and samples from patients described in the literature.*

Leukemia	Genetic mutation	PARPi	Synergy	Mechanism	Cell lines	Reference
AML	*RUNX1–ETO; cKIT; CBFB–MYH11*	Olaparib	Avapritinib	Synthetic lethality by HR down-regulation	Kasumi-1; patient samples from primary AML	Nieborowska-Skorska *et al.*, 2019 (34)
MDS/CMML and AML	*ASXL1; FLT3–ITD; JAK2; RUNX1*	Talazoparib	APE1 inhibitor III; decitabine	-	Bone marrow samples	Kohl *et al.*, 2019 (35)
DLBCL and T-ALL	*LMO2*	Olaparib	Doxorubicin	Synthetic lethality by DSB-induction in HR-deficient cells	VAL; OCI-LY8; OCI-LY19; DOHH2; MOLT16; MOLT4	Parvin *et al.*, 2019 (36)
CML	*BCR–ABL*	Talazoparib	Chloroquine	Inhibition of Talazoparib-induced autophagy	Peripheral blood from pediatric patients with CML	Liu *et al.*, 2019 (37)
CML	*BCR–ABL*	Perezone	-	Apoptosis through PARP1 inhibition and redox alterations	K562	Hernández-Rodríguez *et al.*, 2019 (38)
MPN	*JAK2^{V617F}; CALR*	Veliparib	Busulfan	Double-strand DNA breaks	SET2; HEL; HL-60; K562; patient blood samples	Patel *et al.*, 2019 (39)
AML	*RUNX1–ETO*	Olaparib	BMS; daunorubicin	PARylation, HR and NHEJ deregulation	KG1α; Kasumi-1	Li *et al.*, 2019 (40)
AML	*NPM1; FLT3–ITD; CEBPA; DNMT3A; IDH1; IDH2*	Talazoparib	NL101	Impairment of cell cycle and apoptosis induction	Samples from patients with AML; MV4-11; MOLM-13; HL-60; Kasumi-1	Li *et al.*, 2018 (41)
CML	*BCR–ABL1*	Olaparib; talazoparib	5F02; imatinib	Accumulation of DSB	Samples from patients with CML	Nieborowska-Skorska *et al.*, 2019 (42)
CML	*BCR–ABL1*	Talazoparib	Imatinib	Accumulation of DSB	Samples from patients with CML	Podszywalow-Bartnicka *et al.*, 2019 (43)
AML	*FLT3–ITD*	Olaparib; talazoparib	Quizartinib; gilteritinib; crenolanib	Accumulation of DSB and cell death induction	Patient samples from primary AML; MV-4-11; HL-60; REH; BaF3	Maifrede *et al.*, 2018 (44)
AML	*NPM1mutA; FLT3–ITD*	Olaparib	-	Up-regulation of death receptors	Samples from patients with AML	Faraoni *et al.*, 2018 (45)
AML	*IDH1/2^{MUT}*	Olaparib; talazoparib	Daunorubicin	Down-regulation of AML level	Samples from patients with AML	Molenaar *et al.*, 2018 (46)
AML	*MLL–AF9*	Olaparib	5-Azacytidine; decitabine; doxorubicin	Increased DNA damage, cell-cycle arrest and increase in apoptosis	MML-AF9 murine leukemia cells; MOLM13	Zhao and So, 2017 (47)
AML and ALL	*MLL; FLT3; NPM1; DNMT3A; TP53; ETV6–RUNX1*	Olaparib	AZD1775	Impairment of HR, increase in DNA damage and apoptosis	Jurkat; Molm13; MV4-11; REH; OCI-AML3; 32D	Garcia *et al.*, 2017 (48)
CML, AML and ALL	*TCF3–HLF*	Olaparib; veliparib	-	Impairment of HR and accumulation of DSB	MOLT3; Jurkat; NALM6; REH; RS4-11; Raji; Daudi; BV137; K562; MEG-01; KG-01; NB4; HL-60; ML-1; THP-1; U-937; Kasumi-1; CMK; HAL-01; YCUB-2; AR230	Piao *et al.*, 2017 (49)

Table I. *Continued*

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Leukemia	Genetic mutation	PARPi	Synergy	Mechanism	Cell lines	Reference
AML	*FLT3–ITD*	Veliparib; talazoparib	Decitabine; 5-azacytidine	Increase in PARP trapping and DSB accumulation	Patient samples from primary AML; MV411; MOLM13; MOLM-14; KASUMI	Muvarak *et al*., 2016 (50)
CML and ALL	*BCR–ABL TP53*	P10	SAHA	Accumulation of DSB, cell-cycle arrest and induced apoptosis	K562; MOLT4; Nalm6; REH	Hegde *et al*., 2016 (51)
MPN	*JAK2^{V617F}; BRCA1; CHEK2; RAD50*	Veliparib; olaparib	-	Synthetic lethality by HR pathway dysfunction	Samples from patients with diverse MPN	Pratz *et al*., 2017 (52)
AML	*RUNX1–ETO; PML–RARα; MLL–AF9*	Olaparib; veliparib	LiCl	Synthetic lethality by HR pathway dysfunction	Human primary AML cells; NB4-LR2; THP1; Kasumi-1; GP2; NIH3T3	Esposito *et al*., 2015 (53)
ATLL	*p53*	PJ-34	-	Cell-cycle arrest, accumulation of DSB and reactivation of p53 pathways	Patient-derived ATLL cells; MT-4; MT-2; C8166; C91PL; MT-1; ATL-T; ED-40515(–); ALT-25; ATL-43T; KOB; ATL-55T	Bai *et al*., 2015 (54)
AML and ALL	*NPM1; TP53*	Rucaparib	5FU	Increase in DNA damage and induction of apoptosis	OCI-AML2; RPMI-8402	Falzacappa *et al*., 2015 (55)
AML	*FLT3; NPM1*	Olaparib	-	Increase in DNA damage	Patient samples from primary AML; HL-60; U937; NB4; HL-60R; OCI-AML2; OCI-AML3	Faraoni *et al*., 2015 (56)

ALL: Acute lymphocytic leukemia; AML: acutemyeloid leukemia; ATALL: adult T-cell leukemia/lymphoma; CML: chronic myeloid leukemia; CMML: chronic myelomonocytic leukemia; DLBCL: diffuse large B-cell lymphoma; DSB: double-strand break; HR: homologous recombination; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; NHEJ: non-homologous end joining; PARP1: poly-ADP-ribose polymerase; TALL: T-cell acute lymphoblastic leukemia.

PARPi Studies

Most studies that were found in the literature, reported the effects of combined therapy utilizing one of the inhibitors already used in clinical practice for treatment of solid tumors, alongside inhibitors of other cellular pathways and some TKIs (34-37, 39-44, 46-48, 50, 51, 53, 55). The most commonly described leukemia subtype was acute myeloid leukemia (AML) harboring mutations such as Runt-related transcription factor1–eight twenty-one (*RUNX1–ETO)* and fms-like tyrosine kinase 3-internal tandem duplication (*FLT3–ITD)* (34, 35, 40, 41, 44, 45, 48, 50, 53, 56).

While *RUNX1–ETO* AML cells displayed increased sensitivity to treatment with olaparib, when accompanied by *cKIT* mutation, these cell lines tended to lose this sensitivity (34, 53). *RUNX1* is a well-known transcription factor involved in normal hematopoiesis and its mutation into *RUNX1–ETO* causes deficiency in BRCA1/2 status and deregulation of normal DDR pathways, conferring sensitivity to PARPi. However, *cKIT* mutations have experimentally been shown to restore tumor HR capacity, conferring increased resistance to treatment with PARPi that would benefit from synthetic lethality. This resistance was shown to be overcomed when using a combination treatment with $cKIT_{MUT}$ inhibitors (34, 53, 57, 58).

In regards to *FLT3–ITD* mutation, experimental data have shown low sensitivity to PARPi treatment as a monotherapy, while it was efficient when combined with *FLT3–ITD* inhibitors (44). This lack of sensitivity may be attributed to the capacity of *FLT3–ITD* mutation in restoring cellular HR activity through increased expression

of DNA-binding protein 51 (RAD51) (59-61). Garcia *et al*. also demonstrated that inhibition of other kinase pathways, such as WEE1-like protein kinase (WEE1), impaired HR in *FLT3–ITD*-mutated AML cells and synergized with PARPi treatment (48).

Studies analyzing cohorts of samples from patients with AML have demonstrated that high PARP1 expression in AML cells is related both to increased *FLT3-ITD* mutation rate (41), as well as reduced sensitivity to PARPi (56), indicating that the overexpression of PARP1 might be a potential predictive marker to the resistance to PARPi treatment in AML mediated by *FLT3–ITD* mutation, however further investigation is required on this topic. AML cell lines expressing no *FLT3–ITD* or relevant levels of PARP1 are still capable of resisting PARPi treatment through other mechanisms, such as the aforementioned overexpression of RAD51 (56).

Another TK found to have an important role in hematological malignancies is Janus kinase 2 (*JAK2*) harboring the point mutation V617F, which is often expressed in myeloproliferative neoplasms. Contrasting data found in the literature make it still unclear if $JAK2^{V617F}$ cells are indeed sensitive or not to treatment with PARPi, more specifically to veliparib (39, 52). In a similar mechanism to that of *FLT3-ITD*, $JAK2^{V617F}$ mutation is known to increase RAD51 expression and up-regulate HR activity, which would, in theory, reduce $JAK2^{V617F}$ cell sensitivity to PARPi treatment (60).

One of the most common leukemia subtypes associated with TK dependence is CML as a result of its high BCR–ABL1 expression. Even though TKI development has greatly improved prognosis of patients with CML, cases of primary and secondary resistance are still reported in clinical practice and represent a major obstacle in treatment (62, 63). *BCR–ABL* mutations are known to deregulate cellular signaling pathways, down-regulating BRCA1 protein expression and consequentially inhibiting HR activity (64, 65).

In accordance with the concept of synthetic lethality, the utilization of different PARPi was able to inhibit growth of CML *BCR–ABL* cells *in vitro* mainly through increase in genomic instability and consequent apoptosis. This inhibitory activity was shown to be even more relevant when combined with different synergistic drugs (37, 38, 42). Liu *et al*. demonstrated that the utilization of chloroquine potentiated the activity of talazoparib in samples from patients with CML by inhibiting talazoparib-induced autophagy which may play a cytoprotective role in tumor cells (37). Moreover, Nieborowska-Skorska *et al*. demonstrated that a combination of NAD-like PARPi, such as olaparib and talazoparib, and non-NAD-like PARPi, as well as combination with the commonly used TKI imatinib, may potentiate NAD-like PARPi inhibitory activity against cell in samples from patients with CML (42).

In the above mentioned studies, as well as those described in Table I, the cytotoxicity of PARPi has been shown for different leukemia subtypes *in vitro,* especially when combined with other drugs capable of deregulating cellular signaling pathways and DDR mechanisms, reinforcing its capability for selectively killing malignant cells through synthetic lethality (66), and improving upon the hypothesis that their use has the potential to improve prognosis of many patients afflicted by TK-dependent leukemia.

Conclusion

The highly significant experimental data support the utilization of PARPi as a potential new therapeutic approach in the treatment of primary leukemia and TK-dependent leukemia through a series of different mechanisms, such as synthetic lethality, PARP trapping and synergy with other signaling pathway inhibitors. The confirmation of this evidence in clinical trials is needed in order to further improve upon this hypothesis.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Machado CB and Moreira-Nunes CA designed the study; Machado CB, Silva EL and Moreira-Nunes CA prepared the figures; Machado CB, Silva EL, Moraes-Filho MO, Moraes MEA and Moreira-Nunes CA wrote the article; Machado CB and Moreira-Nunes CA revised the final version. All Authors read and approved the final article.

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References

1 Juliusson G and Hough R: Leukemia. Prog Tumor Res *43*: 87-100, 2016. PMID: 27595359. DOI: 10.1159/000447076

2 Reis RDS, Santos MDO, De Camargo B, Oliveira JFP, Thuler LCS and Pombo-De-Oliveira MS: Early childhood leukemia incidence trends in Brazil. Pediatr Hematol Oncol *33*: 83-93, 2016. PMID: 26925506. DOI: 10.3109/08880018.2015.1130763

3 Kantarjian HM, Keating MJ and Freireich EJ: Toward the potential cure of leukemias in the next decade. Cancer *124*: 4301-4313, 2018. PMID: 30291792. DOI: 10.1002/cncr.31669

4 McNerney ME, Godley LA and Le Beau MM: Therapy-related myeloid neoplasms: When genetics and environment collide. Nat Rev Cancer *17*: 513-527, 2017. PMID: 28835720. DOI: 10.1038/nrc.2017.60

5 Du Y and Chen B: Detection approaches for multidrug resistance genes of leukemia. Drug Des Devel Ther *11*: 1255-1261, 2017. PMID: 28458519. DOI: 10.2147/DDDT.S134529

6 Kansagra A, Dahiya S and Litzow M: Continuing challenges and current issues in acute lymphoblastic leukemia. Leuk Lymphoma *59*: 526-541, 2018. PMID: 28604239. DOI: 10.1080/10428194.2017.1335397

7 Taylor KN and Eskander RN: PARP inhibitors in epithelial ovarian cancer. Recent Pat Anticancer Drug Discov *13*: 145-158, 2017. PMID: 29205122. DOI: 10.2174/1574892813666171204094822

8 Lee YT, Tan YJ and Oon CE: Molecular targeted therapy: Treating cancer with specificity. Eur J Pharmacol *834*: 188-196, 2018. PMID: 30031797. DOI: 10.1016/j.ejphar.2018.07.034

9 Francica P and Rottenberg S: Mechanisms of PARP inhibitor resistance in cancer and insights into the DNA damage response. Genome Med *10*, 2018. PMID: 30593284. DOI: 10.1186/s13073-018-0612-8

10 McCann KE and Hurvitz SA: Advances in the use of PARP inhibitor therapy for breast cancer. Drugs Context *7:* 212540, 2018. PMID: 30116283. DOI: 10.7573/dic.212540

11 Gibson BA and Kraus WL: New insights into the molecular and cellular functions of poly(ADP-ribose) and PARPs. Nat Rev Mol Cell Biol *13*: 411-424, 2012. PMID: 22713970. DOI: 10.1038/nrm3376

12 Leung AKL: Poly(ADP-ribose): An organizer of cellular architecture. J Cell Biol *205*: 613-619, 2014. PMID: 24914234. DOI: 10.1083/jcb.201402114

13 Langelier MF, Planck JL, Roy S and Pascal JM: Crystal structures of poly(ADP-ribose) polymerase-1 (PARP1) zinc fingers bound to DNA: Structural and functional insights into DNA-dependent PARP1 activity. J Biol Chem *286*: 10690-10701, 2011. PMID: 21233213. DOI: 10.1074/jbc.M110.202507

14 Wang L, Liang C, Li F, Guan D, Wu X, Fu X, Lu A and Zhang G: PARP1 in carcinomas and PARP1 inhibitors as antineoplastic drugs. Int J Mol Sci *18*, 2017. PMID: 28991194. DOI: 10.3390/ijms18102111

15 Lord CJ and Ashworth A: PARP inhibitors: Synthetic lethality in the clinic. Science *355*: 1152-1158, 2017. PMID: 28302823. DOI: 10.1126/science.aam7344

16 D'Andrea AD: Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair *71*: 172-176, 2018. PMID: 30177437. DOI: 10.1016/j.dnarep.2018.08.021

17 Jiang X, Li W, Li X, Bai H and Zhang Z: Current status and future prospects of PARP inhibitor clinical trials in ovarian cancer. Cancer Manag Res *11*: 4371-4390, 2019. PMID: 31191001. DOI: 10.2147/CMAR.S200524

18 Murai J, Huang SYN, Das BB, Renaud A, Zhang Y, Doroshow JH, Ji J, Takeda S and Pommier Y: Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res *72*: 5588-5599, 2012. PMID: 23118055. DOI: 10.1158/0008-5472.CAN-12-2753

19 Murai J, Huang SYN, Renaud A, Zhang Y, Ji J, Takeda S, Morris J, Teicher B, Doroshow JH and Pommier Y: Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. Mol Cancer Ther *13*: 433-443, 2014. PMID: 24356813. DOI: 10.1158/1535-7163.MCT-13-0803

20 Zandarashvili L, Langelier M-F, Velagapudi UK, Hancock MA, Steffen JD, Billur R, Hannan ZM, Wicks AJ, Krastev DB, Pettitt SJ, Lord CJ, Talele TT, Pascal JM and Black BE: Structural basis for allosteric PARP1 retention on DNA breaks. Science *368*: eaax6367, 2020. PMID: 32241924. DOI: 10.1126/science.aax6367

21 Min A and Im SA: PARP inhibitors as therapeutics: Beyond modulation of parylation. Cancers *12(2):* 394, 2020. PMID: 32046300. DOI: 10.3390/cancers12020394

22 Faraoni I, Giansanti M, Voso MT, Lo-Coco F and Graziani G: Targeting ADP-ribosylation by PARP inhibitors in acute myeloid leukaemia and related disorders. Biochem Pharmacol *167*: 133-148, 2019. PMID: 31028744. DOI: 10.1016/j.bcp.2019.04.019

23 Kim M, Baek M and Kim DJ: Protein Tyrosine signaling and its potential therapeutic implications in carcinogenesis. Curr Pharm Des *23*: 4226-4246, 2017. PMID: 28625132. DOI: 10.2174/1381612823666170616082125

24 Gross S, Rahal R, Stransky N, Lengauer C and Hoeflich KP: Targeting cancer with kinase inhibitors. J Clin Invest *125*: 1780-1789, 2015. PMID: 25932675. DOI: 10.1172/JCI76094

25 Fernandez S, Desplat V, Villacreces A, Guitart A V., Milpied N, Pigneux A, Vigon I, Pasquet JM and Dumas PY: Targeting tyrosine kinases in acute myeloid leukemia: Why, who and how? Int J Mol Sci *20(14):* 3429, 2019. PMID: 31336846. DOI: 10.3390/ijms20143429

26 Zhou T, Medeiros LJ and Hu S: Chronic Myeloid Leukemia: Beyond BCR-ABL1. Curr Hematol Malig Rep *13*: 435-445, 2018. PMID: 30370478. DOI: 10.1007/s11899-018-0474-6

27 Fleuren EDG, Zhang L, Wu J and Daly RJ: The kinome "at large" in cancer. Nat Rev Cancer *16*: 83-98, 2016. PMID: 26822576. DOI: 10.1038/nrc.2015.18

28 Rosti G, Castagnetti F, Gugliotta G and Baccarani M: Tyrosine kinase inhibitors in chronic myeloid leukaemia: Which, when, for whom? Nat Rev Clin Oncol *14*: 141-154, 2017. PMID: 27752053. DOI: 10.1038/nrclinonc.2016.139

29 Jiao Q, Bi L, Ren Y, Song S, Wang Q and Wang Y shan: Advances in studies of tyrosine kinase inhibitors and their acquired resistance. Mol Cancer *17:* 36, 2018. PMID: 29455664. DOI: 10.1186/s12943-018-0801-5

30 Yan F, Al-Kali A, Zhang Z, Liu J, Pang J, Zhao N, He C, Litzow MR and Liu S: A dynamic N 6-methyladenosine methylome regulates intrinsic and acquired resistance to tyrosine kinase inhibitors. Cell Res *28*: 1062-1076, 2018. PMID: 30297871. DOI: 10.1038/s41422-018-0097-4

31 Liu L, Shi B, Wang X and Xiang H: Strategies to overcome resistance mutations of Bruton's tyrosine kinase inhibitor ibrutinib. Future Med Chem *10*: 343-356, 2018. PMID: 29347836. DOI: 10.4155/fmc-2017-0145

32 Daver N, Cortes J, Ravandi F, Patel KP, Burger JA, Konopleva M and Kantarjian H: Secondary mutations as mediators of resistance to targeted therapy in leukemia. Blood *125*: 3236-3245, 2015. PMID: 25795921. DOI: 10.1182/blood-2014-10-605808

33 Antolin AA, Ameratunga M, Banerji U, Clarke PA, Workman P and Al-Lazikani B: The kinase polypharmacology landscape of clinical PARP inhibitors. Sci Rep *10:* 2585, 2020. PMID: 32066817. DOI: 10.1038/s41598-020-59074-4

34 Nieborowska-Skorska M, Paietta EM, Levine RL, Fernandez HF, Tallman MS, Litzow MR and Skorski T: Inhibition of the mutated cKIT kinase in AML1-ETO-positive leukemia cells restores sensitivity to PARP inhibitor. Blood Adv *3*: 4050-4054, 2019. PMID: 31816060. DOI: 10.1182/bloodadvances.2019000756

35 Kohl V, Flach J, Naumann N, Brendel S, Kleiner H, Weiss C, Seifarth W, Nowak D, Hofmann WK, Fabarius A and Popp HD: Antileukemic efficacy *in vitro* of talazoparib and APE1 inhibitor III combined with decitabine in myeloid malignancies. Cancers *11(10):* 1493, 2019. PMID: 31623402. DOI: 10.3390/cancers11101493

36 Parvin S, Ramirez-Labrada A, Aumann S, Lu XQ, Weich N, Santiago G, Cortizas EM, Sharabi E, Zhang Y, Sanchez-Garcia I, Gentles AJ, Roberts E, Bilbao-Cortes D, Vega F, Chapman JR,

Verdun RE and Lossos IS: LMO2 confers synthetic lethality to PARP inhibition in DLBCL. Cancer Cell *36*: 237-249.e6, 2019. PMID: 31447348. DOI: 10.1016/j.ccell.2019.07.007

37 Liu Y, Song H, Song H, Feng X, Zhou C and Huo Z: Targeting autophagy potentiates the anti-tumor effect of PARP inhibitor in pediatric chronic myeloid leukemia. AMB Express *9:* 108, 2019. PMID: 31309361. DOI: 10.1186/s13568-019-0836-z

38 Hernández-Rodríguez M, Mendoza Sánchez PI, Macias Perez ME, Rosales Cruz E, Mera Jiménez E, Nicolás Vázquez MI and Miranda Ruvalcaba R: *In vitro* and computational studies showed that perezone inhibits PARP1 and induces changes in the redox state of K562 cells. Arch Biochem Biophys *671*: 225-234, 2019. PMID: 31063714. DOI: 10.1016/j.abb.2019.05.002

39 Patel PR, Senyuk V, Rodriguez NS, Oh AL, Bonetti E, Mahmud D, Barosi G, Mahmud N and Rondelli D: Synergistic cytotoxic effect of busulfan and the PARP inhibitor veliparib in myeloproliferative neoplasms. Biol Blood Marrow Transplant *25*: 855-860, 2019. PMID: 30615982. DOI: 10.1016/j.bbmt.2018.12.841

40 Li D, Luo Y, Chen X, Zhang LY, Wang T, Zhuang Y, Fan Y, Xu J, Chen Y and Wu L: NF-kB and poly (ADP-ribose) polymerase 1 form a positive feedback loop that regulates DNA repair in acute myeloid leukemia cells. Mol Cancer Res *17*: 761-772, 2019. PMID: 30559256. DOI: 10.1158/1541-7786.MCR-18-0523

41 Li X, Li C, Jin J, Wang J, Huang J, Ma Z, Huang X, He X, Zhou Y, Xu Y, Yu M, Huang S, Yan X, Li F, Pan J, Wang Y, Yu Y and Jin J: High PARP1 expression predicts poor survival in acute myeloid leukemia and PARP1 inhibitor and SAHA-bendamustine hybrid inhibitor combination treatment synergistically enhances anti-tumor effects. EBioMedicine *38*: 47-56, 2018. PMID: 30472087. DOI: 10.1016/j.ebiom.2018.11.025

42 Nieborowska-Skorska M, Maifrede S, Ye M, Toma M, Hewlett E, Gordon J, Le BV, Sliwinski T, Zhao H, Piwocka K, Valent P, Tulin AV, Childers W and Skorski T: Non-NAD-like PARP1 inhibitor enhanced synthetic lethal effect of NAD-like PARP inhibitors against BRCA1-deficient leukemia. Leuk Lymphoma *60*: 1098-1101, 2019. PMID: 30277116. DOI: 10.1080/10428194.2018.1520988

43 Podszywalow-Bartnicka P, Maifrede S, Le BV, Nieborowska-Skorska M, Piwocka K and Skorski T: PARP1 inhibitor eliminated imatinib-refractory chronic myeloid leukemia cells in bone marrow microenvironment conditions. Leuk Lymphoma *60*: 262-264, 2019. PMID: 29932782. DOI: 10.1080/10428194.2018.1471602

44 Maifrede S, Nieborowska-Skorska M, Sullivan-Reed K, Dasgupta Y, Podszywalow-Bartnicka P, Le BV, Solecka M, Lian Z, Belyaeva EA, Nersesyan A, Machnicki MM, Toma M, Chatain N, Rydzanicz M, Zhao H, Jelinek J, Piwocka K, Sliwinski T, Stoklosa T, Ploski R, Fischer T, Sykes SM, Koschmieder S, Bullinger L, Valent P, Wasik MA, Huang J and Skorski T: Tyrosine kinase inhibitor-induced defects in DNA repair sensitize FLT3(ITD)-positive leukemia cells to PARP1 inhibitors. Blood *132*: 67-77, 2018. PMID: 29784639. DOI: 10.1182/blood-2018-02-834895

45 Faraoni I, Aloisio F, De Gabrieli A, Consalvo MI, Lavorgna S, Voso MT, Lo-Coco F and Graziani G: The poly(ADP-ribose) polymerase inhibitor olaparib induces up-regulation of death receptors in primary acute myeloid leukemia blasts by NF-κB activation. Cancer Lett *423*: 127-138, 2018. PMID: 29526802. DOI: 10.1016/j.canlet.2018.03.008

46 Molenaar RJ, Radivoyevitch T, Nagata Y, Khurshed M, Przychodzen B, Makishima H, Xu M, Bleeker FE, Wilmink JW, Carraway HE, Mukherjee S, Sekeres MA, van Noorden CJF and Maciejewski JP: Idh1/2 mutations sensitize acute myeloid leukemia to parp inhibition and this is reversed by IDH1/2-mutant inhibitors. Clin Cancer Res *24*: 1705-1715, 2018. PMID: 29339439. DOI: 10.1158/1078-0432.CCR-17-2796

47 Zhao L and So CWE: PARPi potentiates with current conventional therapy in MLL leukemia. Cell Cycle *16*: 1861-1869, 2017. PMID: 28886273. DOI: 10.1080/15384101.2017.1288325

48 Garcia TB, Snedeker JC, Baturin D, Gardner L, Fosmire SP, Zhou C, Jordan CT, Venkataraman S, Vibhakar R and Porter CC: A small-molecule inhibitor of WEE1, AZD1775, synergizes with olaparib by impairing homologous recombination and enhancing DNA damage and apoptosis in acute leukemia. Mol Cancer Ther *16*: 2058-2068, 2017. PMID: 28655785. DOI: 10.1158/1535-7163.MCT-16-0660

49 Piao J, Takai S, Kamiya T, Inukai T, Sugita K, Ohyashiki K, Delia D, Masutani M, Mizutani S and Takagi M: Poly (ADP-ribose) polymerase inhibitors selectively induce cytotoxicity in TCF3-HLF-positive leukemic cells. Cancer Lett *386:* 131-140, 2017. PMID: 27894958. DOI: 10.1016/j.canlet.2016.11.021

50 Muvarak NE, Chowdhury K, Xia L, Robert C, Choi EY, Cai Y, Bellani M, Zou Y, Singh ZN, Duong VH, Rutherford T, Nagaria P, Bentzen SM, Seidman MM, Baer MR, Lapidus RG, Baylin SB and Rassool FV: Enhancing the cytotoxic effects of PARP inhibitors with DNA demethylating agents - a potential therapy for cancer. Cancer Cell *30*: 637-650, 2016. PMID: 27728808. DOI: 10.1016/j.ccell.2016.09.002

51 Hegde M, Mantelingu K, Pandey M, Pavankumar CS, Rangappa KS and Raghavan SC: Combinatorial study of a novel poly (ADP-ribose) polymerase inhibitor and an HDAC inhibitor, SAHA, in leukemic cell lines. Target Oncol *11*: 655-665, 2016. PMID: 27188390. DOI: 10.1007/s11523-016-0441-x

52 Pratz KW, Koh B, Patel AG, Flatten KS, Poh W and James G: Poly(ADP-ribose) polymerase inhibitor hypersensitivity in aggressive myeloproliferative neoplasms. Clin Cancer Res *22(15)*: 3894-3902, 2017. PMID: 26979391. DOI: 10.1158/1078-0432.CCR-15-2351

53 Esposito MT, Zhao L, Fung TK, Rane JK, Wilson A, Martin N, Gil J, Leung AY, Ashworth A and Eric So CW: Synthetic lethal targeting of oncogenic transcription factors in acute leukemia by PARP inhibitors. Nat Med *21*: 1481-1490, 2015. PMID: 26594843. DOI: 10.1038/nm.3993

54 Bai XT, Moles R, Chaib-Mezrag H and Nicot C: Small PARP inhibitor PJ-34 induces cell cycle arrest and apoptosis of adult T-cell leukemia cells. J Hematol Oncol *8*: 1-12, 2015. PMID: 26497583. DOI: 10.1186/s13045-015-0217-2

55 Falzacappa MVV, Ronchini C, Faretta M, Iacobucci I, Di Rorà AGL, Martinelli G, Meyer LH, Debatin KM, Orecchioni S, Bertolini F and Pelicci PG: The combination of the PARP inhibitor rucaparib and 5FU is an effective strategy for treating acute leukemias. Mol Cancer Ther *14*: 889-898, 2015. PMID: 25667168. DOI: 10.1158/1535-7163.MCT-14-0276

56 Faraoni I, Compagnone M, Lavorgna S, Angelini DF, Cencioni MT, Piras E, Panetta P, Ottone T, Dolci S, Venditti A, Graziani G and Lo-Coco F: BRCA1, PARP1 and γH2AX in acute myeloid leukemia: Role as biomarkers of response to the PARP inhibitor olaparib. Biochim Biophys Acta - Mol Basis Dis *1852*: 462-472, 2015. PMID: 25483710. DOI: 10.1016/j.bbadis.2014.12.001

57 Lam K and Zhang DE: RUNX1 and RUNX1-ETO: Roles in hematopoiesis and leukemogenesis. Front Biosci *17*: 1120-1139, 2012. PMID: 22201794. DOI: 10.2741/3977

58 Wichmann C, Quagliano-Lo Coco I, Yildiz, Chen-Wichmann L, Weber H, Syzonenko T, Döring C, Brendel C, Ponnusamy K, Kinner A, Brandts C, Henschler R and Grez M: Activating cKIT mutations confer oncogenic cooperativity and rescue RUNX1/ETO-induced DNA damage and apoptosis in human primary $CD34^+$ hematopoietic progenitors. Leukemia *29*: 279-289, 2015. PMID: 24897507. DOI: 10.1038/leu.2014.179

59 Klein HL: The consequences of RAD51 overexpression for normal and tumor cells. DNA Repair *7*: 686-693, 2008. PMID: 18243065. DOI: 10.1016/j.dnarep.2007.12.008

60 Gaymes TJ, Mohamedali A, Eiliazadeh AL, Darling D and Mufti GJ: FLT3 and JAK2 mutations in acute myeloid leukemia promote interchromosomal homologous recombination and the potential for copy neutral loss of heterozygosity. Cancer Res *77*: 1697-1708, 2017. PMID: 28108507. DOI: 10.1158/0008-5472.CAN-16-1678

61 Bhat KP and Cortez D: RPA and RAD51: Fork reversal, fork protection, and genome stability. Nat Struct Mol Biol *25*: 446-453, 2018. PMID: 29807999. DOI: 10.1038/s41594-018-0075-z

62 Talati C and Pinilla-Ibarz J: Resistance in chronic myeloid leukemia: Definitions and novel therapeutic agents. Curr Opin Hematol *25*: 154-161, 2018. PMID: 29266016. DOI: 10.1097/MOH.0000000000000403

63 Loscocco F, Visani G, Galimberti S, Curti A and Isidori A: BCR-ABL independent mechanisms of resistance in chronic myeloid leukemia. Front Oncol *9*: 939, 2019. PMID: 31612105. DOI: 10.3389/fonc.2019.00939

64 Farmer H, McCabe H, Lord CJ, Tutt AHJ, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NMB, Jackson SP, Smith GCM and Ashworth A: Targeting the DNA repair defect in *BRCA*-mutant cells as a therapeutic strategy. Nature *434*: 917-921, 2005. PMID: 15829967. DOI: 10.1038/nature03445

65 Podszywalow-Bartnicka P, Wolczyk M, Kusio-Kobialka M, Wolanin K, Skowronek K, Nieborowska-Skorska M, Dasgupta Y, Skorski T and Piwocka K: Downregulation of BRCA1 protein in BCR-ABL1 leukemia cells depends on stress-triggered tiar-mediated suppression of translation. Cell Cycle *13*: 3727-3741, 2014. PMID: 25483082. DOI: 10.4161/15384101.2014.965013

66 Lord CJ, Tutt ANJ and Ashworth A: Synthetic lethality and cancer therapy: lessons learned from the development of PARP inhibitors. Annu Rev Med *66*: 455-470, 2015. PMID: 25341009. DOI: 10.1146/annurev-med-050913-022545

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