CANCER DIAGNOSIS & PROGNOSIS
4: 592-598 (2024) doi: 10.21873/cdp.10368

Association of PARP1 Expression Levels and Clinical Parameters in Different Leukemic Subtypes With *BCR::ABL1 p190+* Translocation

GUILHERME PASSOS DE MORAIS[1*], CAIO BEZERRA MACHADO[2*], BEATRIZ MARIA DIAS NOGUEIRA[2], FLÁVIA MELO CUNHA DE PINHO PESSOA[2], DEIVIDE DE SOUSA OLIVEIRA[3], RODRIGO MONTEIRO RIBEIRO[3], JEAN BRENO SILVEIRA DA SILVA[3], ALINE DAMASCENO SEABRA[4], FERNANDO AUGUSTO RODRIGUES MELLO JÚNIOR[4], ROMMEL RODRIGUEZ BURBANO[4,5], ANDRÉ SALIM KHAYAT[5], MANOEL ODORICO DE MORAES FILHO[2], MARIA ELISABETE AMARAL DE MORAES[1] and CAROLINE AQUINO MOREIRA-NUNES[1,2,5,6]

[1]*Unichristus University Center, Faculty of Biomedicine, Fortaleza, Brazil;*
[2]*Pharmacogenetics Laboratory, Drug Research and Development Center (NPDM), Department of Physiology and Pharmacology, Federal University of Ceará, Fortaleza, Brazil;*
[3]*Department of Hematology, Hospital Geral de Fortaleza (HGF), Fortaleza, Brazil;*
[4]*Molecular Biology Laboratory, Ophir Loyola Hospital, Belem, Brazil;*
[5]*Department of Biological Sciences, Oncology Research Center, Federal University of Pará, Belem, Brazil;*
[6]*Clementino Fraga Group, Central Unity, Molecular Biology Laboratory, Fortaleza, Brazil*

Abstract. *Background/Aim: Although the reciprocal translocation t(9;22)(q34;q11) is a hallmark of chronic myeloid leukemia (CML), it is also present in acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Depending on the gene's breakpoint, it is possible to obtain three isoforms, among which p190 stands out for the poor prognosis it induces whenever it appears. Due to the genomic instability induced by BCR::ABL1, it is proposed to expand the applicability of poly-ADP-ribose polymerase-1 (PARP1) and its inhibitors in hematological neoplasms. Materials and Methods: We measured the expression levels of PARP1 by quantitative real-time PCR (qPCR) using TaqMan®, correlating its expression with BCR::ABL1 p190+, to evaluate its influence in the clinic of adult patients. Results: We found that PARP1 is expressed differently in ALL, AML and CML and that p190 transcripts do not follow a linear pattern in these populations. We also found that PARP1 expression is not correlated with age, white blood cell and the amount of p190 transcripts. Conclusion: Despite the lack of statistical correlation between the variables analyzed, the role of PARP1 in BCR::ABL1 leukemia cannot be ruled out, given the instability profile promoted by this translocation. Finally, further studies involving a larger sample of patients are needed, as well as investigations into other molecular pathways that may impact on the pathogenesis of different BCR::ABL1 leukemic subtypes.*

*These Authors contributed equally to the study.

Correspondence to: Caroline Aquino Moreira-Nunes, Federal University of Ceará, Coronel Nunes de Melo st, n 1000, Rodolfo Teófilo, CEP: 60416-000 Fortaleza, CE, Brazil. Tel: +55 8533668033, e-mail: carolfam@gmail.com

Key Words: Biomarker, PARP polymerase, hematological malignancies, BCR::ABL.

Leukemia is a group of hematological malignancies, presenting a high clonal expansion of malignant cells, originating from myeloid and lymphoid lineages (1). Despite the higher frequency of the t(9;22)(q34;q11) chromosomal translocation in patients with chronic myeloid leukemia (CML) (2), the worst prognosis is observed in patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), when they harbor the Philadelphia chromosome (Ph+), being classified as high risk, which tends to worsen with age (3, 4).

This cytogenetic alteration leads to creation of the chimeric gene *BCR activator of RhoGEF and GTPase::ABL proto-oncogene 1 (BCR::ABL1)*. The gene has three primary isoforms, namely $p190^{BCR::ABL1}$, $p210^{BCR::ABL1}$, and $p230^{BCR::ABL1}$, depending on the different gene breakpoints (5, 6). The $p210^{BCR::ABL1}$ is the main isoform responsible for pathogenesis in CML patients (7). Although p190 is detected in only 1-2% of CML patients (8, 9), the *p190* transcript confers a higher risk of treatment failure in chronic-phase patients, as well as being associated with distinct clinical characteristics (9). Among the acute leukemias, ALL exhibits the highest frequency of $p190^{BCR::ABL1}$ (10). Although treatment with tyrosine kinase inhibitors (TKIs) has shown a significant benefit for Ph+ patients, adult patients still suffer from low response of the p190 isoform to TKIs (10-12).

Regardless of leukemia type, the isoform $p190^{BCR::ABL1}$ produces a protein with 190 kDa, the lowest molecular weight compared to the others. This is associated with a more aggressive leukemia phenotype, due to shorter transcripts causing the loss of important *BCR* regulatory sequences (13, 14).

The presence of *BCR::ABL1* induces genomic instability in neoplastic clones through deregulation of mitochondrial membrane potential by the accumulation of reactive oxygen species. In addition, *BCR::ABL1* induces greater dependence on non-homologous repair pathways, contributing to increased genomic instability and decreasing the ability of these neoplastic clones to reliably repair damage to the DNA molecule (15-17).

The enzyme poly-ADP-ribose polymerase-1 (PARP1) has emerged as a potential therapeutic target in certain types of solid tumors (18–21) with excessive dependence on non-conservative repair pathways, with the aim of exploiting a distinctive feature of cancer proposed by Hanahan, genomic instability (22). Among a family of 17 enzymes, PARP1 is the main enzyme responsible for molecular signaling for DNA repair by adding ADP-ribose chains in a process known as PARylation (23).

PARP inhibitors (PARPi) act by the principle of synthetic lethality, increasing damage to the genetic material through the accumulation of DNA damage and genomic instability. In addition to the cytotoxicity exerted by direct inhibition of the PARylation process, PARPi acts on the PARP trapping process, forming insoluble complexes between DNA molecules and PARP. This trapping prevents DNA repair and induces greater genetic damage to neoplastic clones (23, 24).

PARP1 expression may play an important role in the pathogenesis of adult patients with *BCR::ABL1 p190+*, as the Ph+ chromosome confers a profile of greater genetic instability in tumor cells by inducing DNA damage (15, 16). In this study, we measured PARP1 expression levels in patients and correlated its expression with *BCR::ABL1 p190+*, to assess its influence on the clinical outcome of adult patients and propose PARP1 as a potential molecular biomarker for future therapeutic applications.

Materials and Methods

Patients and ethical issues. The study group consisted of a total of 59 adult patients diagnosed with *CML, AML* and *ALL* who had the *BCR::ABL1 p190+* from the Ophir Loyola Hospital, Para, Brazil and Fortaleza General Hospital, Ceara, Brazil. Peripheral blood and bone marrow samples from the patients were used. The analysis also included a control group with 10 peripheral blood samples from healthy individuals, for statistical comparison of gene expression. The patients were brought into the study only after understanding and accepting the terms and informed written consent was obtained from each of them. All methods were carried out in accordance with the Helsinki guidelines and regulations. The research was submitted to the Brazil Platform and was approved by the Research Ethics Committee under registration number 5.207.521.

Expression analysis. Total RNA was extracted from the leucocyte layer using TRIzol Reagent® (Invitrogen™ , Carlsbad, CA, USA). Extracted RNA was quantified utilizing the equipment NanoDrop (Thermo Scientific, Carlsbad, CA, USA) and 20 ng were used for cDNA confection using the High-Capacity cDNA Reverse Transcriptase kit (Life Technologies, Carlsbad, CA, USA). The samples were quantified by quantitative real-time PCR (qPCR) using TaqMan® Gene expression assays (Applied Biosystems®, Foster City, CA, USA) for the *PARP1* (Hs00242302_m1), *BCR::ABL1 p190+* (e1a2) (Hs03024844_ft) and *ABL* (Hs_01104728_m1) and *ACTB* (Hs01060665_g1) genes, which were used as endogenous controls.

The commercial kit TaqMan® Expression Master Mix (Applied Biosystems®, Foster City, CA, USA) was used to detect expression analysis by qPCR begin performed using QuantStudio 5 Real-Time PCR system (Applied Biosystems®). The experiments were performed in triplicate and the standard requirements for performing the technique were followed (25). For calculating relative expression levels of PARP1 the $2^{-\Delta\Delta CQ}$ (delta delta cycle quantification) method was used (26), using the health donor samples as the calibrator/control, considering that the amplification of the target gene and the amplification efficiency of the internal control should be approximately equal. A standard curve was applied to determine the *p190*/ng copy number values.

Statistical analysis. The Chi-square test was conducted to assess the correlation between clinical variables. The Shapiro–Wilk test was used to evaluate the sample's distribution. Comparison tests were performed by Analysis of Variance (ANOVA) Kruskal–Wallis test and Dunn's Multiple Comparison post-test were compared in non-parametric tests. The data is based on the mean±standard deviation of the mean of the experimental groups in biological triplicates. The Spearman rank test was applied for correlation between PARP expression and p190/ng copy number values. All statistics were performed using GraphPad Prism (version 8.0.1) and significant differences were considered with an interval of confidence of 95% ($p<0.05$).

Results

A total of 59 samples from adults diagnosed with *BCR::ABL1 p190+* leukemia were used, distributed as ALL (n=28), AML (n=7) and CML (n=24). Among the patients with ALL, 21 were males (75.0%) and 7 females (25.0%),

Table I. *Clinical data of patients included in the study.*

Characteristics	ALL	AML	CML	*p*-Value
Sex (n, M/F)	21/7	4/3	12/ 12	0.1687
Age [years, M (range)]	46.0 (20.0-90.0)	47.5 (24.0-68.0)	56.0 (34.0-90.0)	0.0111
WBC [*10^9/l, M (range)]	75.36 (0.92-533.2)	10.59 (2.26-511.4)	7.15 (3.65-388.6)	0.2623
BM blast [%, M (range)]	50.1 (2.0-96.0)	72 (5.0-96.0)	3.6 (2.5-6.0)	0.1257
Karyotype				0.6520
Diploidy	9	1	2	
CK	6	2	1	
Unknown	13	4	21	

WBC: White blood cell; BM: bone marrow; CK: complex karyotype; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CML: chronic myeloid leukemia.

with an average age of 46 years. The average leukometry in peripheral blood was 75.36 (10^9/l) with an average of 50.1% blasts in the bone marrow.

The patients with AML were 4 males (57.14%) and 3 females (42.85%), with a mean age of 47.5 years. The average leukometry in peripheral blood was 10.59 (10^9/l) with an average of 72% blasts in the bone marrow. Of the patients with CML, 12 were males (50.0%) and 12 females (50.0%), with a mean age of 56 years. The average leukometry in peripheral blood was 7.15 (10^9/l) with an average of 3.6% blasts in the bone marrow.

Using the Chi-Square test, we evaluated the influence of clinical variables on the type of leukemia. A significant correlation was identified between age (p=0.0111) on the types of ALL, AML, and CML. However, no significant correlations were found within the other comparisons (Table I).

Due to the high prevalence of the *p190* transcript in the ALL population (10), we decided to evaluate the clinical variables of this isolated group. We stratified these patients into two groups according to PARP1 expression (Table II), to assess the influence of the patient clinical status on PARP1 expression. Similarly, no significant correlations were found between the variables analyzed.

The differential expression of PARP1 ($F [2,56] = 5,949$; $p < 0.005$; ηp^2, = 0,175 "large effect") concerning the types of leukemia was analyzed and statistically significant values were found between the expression in the group with ALL and CML (Δ: 19,29 [37,91; 18,63] p=0.0002) and between AML and CML (Δ: 18,73 [37,36; 18,63] p=0.0334) (Figure 1).

Subsequently, to analyze the correlation between PARP1 and p190 transcript, we stratified the patients who had a PARP1 expression higher than 1.5-Fold Change. All these patients were diagnosed with ALL and AML, representing 22.03% of the total patients used in the study. We found that in this group with a Fold-Change greater than 1.5, the number of copies of p190/ng of RNA transcripts did not show direct proportionality with PARP1 expression.

Table II. *Chi-square analysis of clinical data of patients with acute lymphoblastic leukemia, separated by fold change.*

Characteristics	ALL		*p*-Value
	Fold change >1.5	Fold change <1.5	
Sex (n, M/F)			
Male	7	14	0.3809
Female	4	3	
Age (years)			
20-39	7	10	0.4376
40-59	2	6	
>60	2	1	
WBC (*10^9/l)			
≤10	2	10	0.0972
>10	6	4	
>100	3	3	
BM blast (%)			
≤50	2	3	0.5275
≤80	5	2	
>80	3	3	
Unknown	1	9	

WBC: White blood cell; BM: bone marrow; ALL: acute lymphoblastic leukemia.

In CML, all the patients had a Fold Change of less than 1.5, showing reduced PARP1 expression. In addition, most of these patients had a low concentration of p190 copies/ng RNA.

Using the Spearman's rank test, we compared all the PARP1, p190/ng copies, age and white blood cell (WBC) variables with each other. No statistically significant correlations were found between PARP1 relative expression and the number of p190/ng copies (r=–0.093), age (r=–0.099) and WBC (r=0.247) (Table III).

Table III. *Spearman correlation analyses of PARP1, BCR::ABL1 p190+ transcripts, age and WBC of patients with increased expression in more than 1.5-fold of PARP1.*

	PARP1/relative expression	*BCR::ABL1 p190+* transcripts	Age	WBC
PARP1/relative expression	r=1.000	r=–0.093	r=–0.099	r=0.247
		p=0.765	*p*=0.751	*p*=0.415
p190	r=–0.09	r=1.000	r=–0.066	r=–0.170
	p=0.765		*p*=0.835	*p*=0.579
Age	r=–0.10	r=–0.066	r=1.000	r=0.319
	p=0.751	*p*=0.835		*p*=0.289
WBC	r=0.25	r=–0.170	r=0.319	r=1.000
	p=0.415	*p*=0.579	*p*=0.289	

BCR::ABL1 p190+: copy number of p190/nanogram of RNA, WBC: white blood cell (10^9/l).

Discussion

BCR::ABL1 p190+ leukemia continues to be a complex disease with the worst prognosis in ALL, AML and CML, posing a greater risk and aggressiveness to patients due to p190 (3, 4, 9). ALL patients exhibit the highest frequency of *p190* (10). Due to various advances in the diagnosis and treatment of pediatric ALL, mortality rates have fallen (27, 28). However, adult patients continue to suffer from a poor prognosis that tends to worsen with age and the lack of targeted therapies (29).

Given that *BCR::ABL1* is an important inducer of genetic instability (15, 16), it is hypothesized that patients afflicted with malignant hematological tumors harboring this translocation might benefit from the applicability of PARP as a therapeutic target (30, 31). Considering this, we investigated PARP1 expression as a potential biomarker for prognosis in this population.

Although the Chi-square test showed no significant associations between the clinical variables and types of leukemia, the clinical heterogeneity observed suggests that the relationship between these factors may be more complex. The literature describes that patients with *p190+* CML have distinct clinical characteristics, increased leukemic progression and, especially high rates of resistance/failure to treatment using first-generation TKIs (32–34).

BCR::ABL1 in AML is still a rare entity (35) and for this reason data on its main clinical characteristics and responses to TKIs are still scarce. Some case reports with the presence of *p190+* in adults describe that the presence of mutations and co-expression of other rare transcripts can affect the response to treatment and induce a more aggressive leukemia (36, 37).

Epidemiologically corroborating our results in ALL, one study showed a higher frequency of the *p190* isoform in adult male patients than in female patients (38). Due to the heterogeneity of clinical characteristics and responses to treatment, we have tried to evaluate alterations in the genome of these patients. The most recurrent alterations are deletions in the *IKZF1*, *PAX5* and *CDKN2A/B* genes, which are negatively associated with patient outcomes (39, 40).

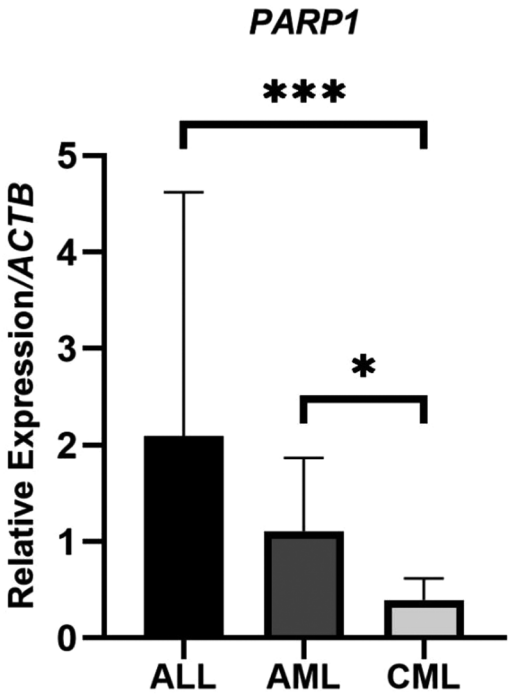

Figure 1. *Expression of poly-ADP-ribose polymerase 1 (PARP1) in patients by type of leukemia BCR::ABL p190+. Expression in patients with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) was compared using analysis of Kruskal's variance and multiple comparisons of Dunn's.. PARP1 expression was normalized using the endogenous gene actin beta (ACTB). Comparisons between CML, AML and ALL were statistically significant with *p=0.0334 and ***p=0.0002. ALL: Acute lymphoblastic leukemia; AML: acute myeloid leukemia; CML: chronic myeloid leukemia.*

When we evaluated the expression of PARP1 between leukemia types (Figure 1), we found significant differences, showing that the expression in patients with ALL was higher than in patients with AML (p=0.0334) and substantially higher than in patients with CML (p=0.0002). Indeed, the differential expression of PARP1 found a 2-fold increase in ALL compared to healthy patients, and reduced expression in CML (31).

As for AML, studies have shown that high PARP1 expression is associated with complex cytogenetic abnormalities (41). Another study revealed that AML patients with high PARP1 expression had a shorter overall survival and had high levels of blasts, WBC in peripheral blood and were associated with a higher frequency of mutations in *FLT3* (42). In addition, a cell culture study showed that PARP2 is also overexpressed in AML cell lines. This suggests that in addition to PARP1, PARP2 may contribute to the pathogenesis of AML (43).

Although PARP1 is overexpressed in CML cell lines (30), our results show that there were no statistically significant correlations between the relative expression of PARP1 and the amount of *p190* transcripts in patients with CML, demonstrating that the two events are apparently independent. Although this lack of statistical correlation is evident in this study, the role of PARP1 in *BCR::ABL1* leukemia cannot be ruled out, given that cells expressing *BCR::ABL1* have homologous recombination (HR) defects and that this expression increases DNA damage and reactive oxygen species (44). In addition, it has been described that this oncogene is capable of inducing leukemia on its own in Ph+ tumors that tend to be extremely dependent on *BCR::ABL1* expression (45, 46), giving rise to an increased anti-leukemic effect in *BCR::ABL1* positive cells in combination with TKI and PARPi therapies (47).

Finally, the characterization of the genetic background of mutations, cytogenetic alterations and DNA repair capacity must be considered so that PARPi therapy can benefit leukemia patients in the future (48).

Conclusion

BCR::ABL1 p190+ leukemia remains a complex disease with a poor prognosis and distinct clinical features. We found that PARP1 is differentially expressed in ALL, AML and CML and that *p190* transcripts do not follow a linear pattern in these populations. We also found that PARP1 expression is not correlated with age, white blood cell and the amount of *p190* transcripts. Despite the lack of statistical correlation between the variables analyzed, the role of PARP1 in *BCR::ABL1* leukemia cannot be ruled out, given the instability profile promoted by this translocation. Finally, further studies involving a larger sample of patients are needed, as well as investigations into other molecular pathways that may impact on the pathogenesis of different *BCR::ABL1* leukemic subtypes.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Morais GP, Machado CB and Moreira-Nunes CA, performed the study design; Morais GP, Machado CB and JBSS performed the performed gene expression analysis; Morais GP, Machado CB, FMCPP and Nogueira BMD performed the molecular and statistical analysis; Morais GP, Machado CB, and Nogueira BMD, Moraes-Filho MO, Moraes MEA, and Moreira-Nunes CA wrote the article. All Authors read and approved the final article.

Acknowledgements

This study was supported by Brazilian funding agencies National Counsel of Technological and Scientific Development (CNPq; to ASK; MEAM, MOMF and CAMN).

References

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

2 Rashid K, Hassan A, Tanvir I, Ehsan K: Significance of Philadelphia chromosome in chronic myeloid leukemia patients of Anmol Hospital, Lahore, Pakistan. Pakistan Biomed J 1(1), 2018. DOI: 10.52229/pbmj.v1i1.47

3 Döhner H, Wei AH, Appelbaum FR, Craddock C, Dinardo CD, Dombret H, Ebert BL, Fenaux P, Godley LA, Hasserjian RP, Larson RA, Levine RL, Miyazaki Y, Niederwieser D, Ossenkoppele G, Röllig C, Sierra J, Stein EM, Tallman MS, Tien H, Wang J, Wierzbowska A, Löwenberg B: Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood 140(12): 1345-1377, 2022. DOI: 10.1182/blood.2022016867

4 DeAngelo DJ, Jabbour E, Advani A: Recent advances in managing acute lymphoblastic leukemia. Am Soc Clin Oncol Educ Book (40): 330-342, 2020. DOI: 10.1200/edbk_280175

5 Ren R: Mechanisms of BCR–ABL in the pathogenesis of chronic myelogenous leukaemia. Nat Rev Cancer 5(3): 172-183, 2005. DOI: 10.1038/nrc1567

6 Hantschel O: Structure, regulation, signaling, and targeting of abl kinases in cancer. Genes Cancer 3(5-6): 436-446, 2012. DOI: 10.1177/1947601912458584

7 Molica M, Zacheo I, Diverio D, Alimena G, Breccia M: Long-term outcome of chronic myeloid leukaemia patients with p210 and p190 co-expression at baseline. Br J Haematol 169(1): 148-150, 2015. DOI: 10.1111/bjh.13184

8 Verma D, Kantarjian HM, Jones D, Luthra R, Borthakur G, Verstovsek S, Rios MB, Cortes J: Chronic myeloid leukemia (CML) with P190 BCR-ABL: analysis of characteristics, outcomes, and prognostic significance. Blood 114(11): 2232-2235, 2009. DOI: 10.1182/blood-2009-02-204693

9 Awad SA, Hohtari H, Javarappa KK, Brandstoetter T, Kim D, Potdar S, Heckman CA, Kytölä S, Porkka K, Doma E, Sexl V, Kankainen M, Mustjoki S: BCR-ABL1 p190 in CML: a minor breakpoint with a major impact. Blood 134(Suppl_1): 190, 2019. DOI: 10.1182/blood-2019-126584

10 El Fakih R, Jabbour E, Ravandi F, Hassanein M, Anjum F, Ahmed S, Kantarjian H: Current paradigms in the management of Philadelphia chromosome positive acute lymphoblastic leukemia in adults. Am J Hematol 93(2): 286-295, 2018. DOI: 10.1002/ajh.24926

11 Jiao Q, Bi L, Ren Y, Song S, Wang Q, Wang YS: Advances in studies of tyrosine kinase inhibitors and their acquired resistance. Mol Cancer 17(1): 36, 2018. DOI: 10.1186/s12943-018-0801-5

12 Mishra S, Zhang B, Cunnick JM, Heisterkamp N, Groffen J: Resistance to imatinib of Bcr/Abl P190 lymphoblastic leukemia cells. Cancer Res 66(10): 5387-5393, 2006. DOI: 10.1158/0008-5472.CAN-05-3058

13 Komorowski L, Fidyt K, Patkowska E, Firczuk M: Philadelphia chromosome-positive leukemia in the lymphoid lineage-similarities and differences with the myeloid lineage and specific vulnerabilities. Int J Mol Sci 21(16): 5776, 2020. DOI: 10.3390/ijms21165776

14 Qin R, Wang T, He W, Wei W, Liu S, Gao M, Huang Z: Jak2/STAT6/c-Myc pathway is vital to the pathogenicity of Philadelphia-positive acute lymphoblastic leukemia caused by P190(BCR-ABL). Cell Commun Signal 21(1): 27, 2023. DOI: 10.1186/s12964-023-01039-x

15 Pawlowska E, Blasiak J: DNA repair—a double-edged sword in the genomic stability of cancer cells—the case of chronic myeloid leukemia. Int J Mol Sci 16(11): 27535-27549, 2015. DOI: 10.3390/ijms161126049

16 Popp HD, Kohl V, Naumann N, Flach J, Brendel S, Kleiner H, Weiss C, Seifarth W, Saussele S, Hofmann WK, Fabarius A: DNA damage and DNA damage response in chronic myeloid leukemia. Int J Mol Sci 21(4): 1177, 2020. DOI: 10.3390/ijms21041177

17 Abdulmawjood B, Costa B, Roma-Rodrigues C, Baptista PV, Fernandes AR: Genetic biomarkers in chronic myeloid leukemia: what have we learned so far? Int J Mol Sci 22(22): 12516, 2021. DOI: 10.3390/ijms222212516

18 O'Malley DM, Krivak TC, Kabil N, Munley J, Moore KN: PARP inhibitors in ovarian cancer: a review. Target Oncol 18(4): 471-503, 2023. DOI: 10.1007/s11523-023-00970-w

19 Mateo J, Lord CJ, Serra V, Tutt A, Balmaña J, Castroviejo-Bermejo M, Cruz C, Oaknin A, Kaye SB, de Bono JS: A decade of clinical development of PARP inhibitors in perspective. Ann Oncol 30(9): 1437-1447, 2019. DOI: 10.1093/annonc/mdz192

20 Taylor AK, Kosoff D, Emamekhoo H, Lang JM, Kyriakopoulos CE: PARP inhibitors in metastatic prostate cancer. Front Oncol 13: 1159557, 2023. DOI: 10.3389/fonc.2023.1159557

21 Gout J, Perkhofer L, Morawe M, Arnold F, Ihle M, Biber S, Lange S, Roger E, Kraus JM, Stifter K, Hahn SA, Zamperone A, Engleitner T, Müller M, Walter K, Rodriguez-Aznar E, Sainz B Jr, Hermann PC, Hessmann E, Müller S, Azoitei N, Lechel A, Liebau S, Wagner M, Simeone DM, Kestler HA, Seufferlein T, Wiesmüller L, Rad R, Frappart PO, Kleger A: Synergistic targeting and resistance to PARP inhibition in DNA damage repair-deficient pancreatic cancer. Gut 70(4): 743-760, 2021. DOI: 10.1136/gutjnl-2019-319970

22 Hanahan D: Hallmarks of Cancer: New dimensions. Cancer Discov 12(1): 31-46, 2022. DOI: 10.1158/2159-8290.CD-21-1059

23 Lord CJ, Ashworth A: PARP inhibitors: Synthetic lethality in the clinic. Science 355(6330): 1152-1158, 2017. DOI: 10.1126/science.aam7344

24 Murai J, Huang SY, Renaud A, Zhang Y, Ji J, Takeda S, Morris J, Teicher B, Doroshow JH, Pommier Y: Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. Mol Cancer Ther 13(2): 433-443, 2014. DOI: 10.1158/1535-7163.MCT-13-0803

25 Bustin SA, Benes V, Garson JA, Hellemans J, Huggett J, Kubista M, Mueller R, Nolan T, Pfaffl MW, Shipley GL, Vandesompele J, Wittwer CT: The MIQE Guidelines: Minimum information for publication of quantitative real-time PCR experiments. Clin Chem 55(4): 611-622, 2009. DOI: 10.1373/clinchem.2008.112797

26 Schmittgen TD, Livak KJ: Analyzing real-time PCR data by the comparative CT method. Nat Protoc 3(6): 1101-1108, 2008. DOI: 10.1038/nprot.2008.73

27 Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, Reaman GH, Carroll WL: Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncol 30(14): 1663-1669, 2012. DOI: 10.1200/JCO.2011.37.8018

28 Inaba H, Mullighan CG: Pediatric acute lymphoblastic leukemia. Haematologica 105(11): 2524-2539, 2020. DOI: 10.3324/haematol.2020.247031

29 Aldoss I, Stein AS: Advances in adult acute lymphoblastic leukemia therapy. Leuk Lymphoma 59(5): 1033-1050, 2018. DOI: 10.1080/10428194.2017.1354372

30 Machado CB, DA Silva EL, Dias Nogueira BM, DE Moraes Filho MO, Montenegro RC, DE Moraes MEA, Moreira-Nunes CA: PARP1 is overexpressed in hematological malignant cell lines: a framework for experimental oncology. Anticancer Res 41(5): 2397-2402, 2021. DOI: 10.21873/anticanres.15014

31 Machado CB, da Silva EL, Ferreira WAS, Pessoa FMCP, de Quadros AU, Fantacini DMC, Furtado IP, Rossetti R, Silveira RM, de Lima SCG, Mello Júnior FAR, Seabra AD, Moreira ECO, de Moraes Filho MO, de Moraes MEA, Montenegro RC, Ribeiro RM, Khayat AS, Burbano RMR, de Oliveira EHC, Covas DT, de Souza LEB, Moreira-Nunes CFA: PARP1 characterization as a potential biomarker for BCR::ABL1 p190+ acute lymphoblastic leukemia. Cancers (Basel) 15(23): 5510, 2023. DOI: 10.3390/cancers15235510

32 Adnan-Awad S, Kim D, Hohtari H, Javarappa KK, Brandstoetter T, Mayer I, Potdar S, Heckman CA, Kytölä S, Porkka K, Doma E, Sexl V, Kankainen M, Mustjoki S: Characterization of p190-Bcr-Abl chronic myeloid leukemia reveals specific signaling pathways and therapeutic targets. Leukemia 35(7): 1964-1975, 2021. DOI: 10.1038/s41375-020-01082-4

33 Arun AK, Senthamizhselvi A, Mani S, Vinodhini K, Janet NB, Lakshmi KM, Abraham A, George B, Srivastava A, Srivastava VM, Mathews V, Balasubramanian P: Frequency of rare *BCR-ABL1* fusion transcripts in chronic myeloid leukemia patients. Int J Lab Hematol 39(3): 235-242, 2017. DOI: 10.1111/ijlh.12616

34 Xue M, Wang Q, Huo L, Wen L, Yang X, Wu Q, Pan J, Cen J, Ruan C, Wu D, Chen S: Clinical characteristics and prognostic significance of chronic myeloid leukemia with rare BCR-ABL1 transcripts. Leuk Lymphoma 60(12): 3051-3057, 2019. DOI: 10.1080/10428194.2019.1607329

35 Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 127(20): 2391-2405, 2016. DOI: 10.1182/blood-2016-03-643544

36 Piedimonte M, Ottone T, Alfonso V, Ferrari A, Conte E, Divona M, Bianchi MP, Ricciardi MR, Mirabilii S, Licchetta R, Campagna A, Cicconi L, Galassi G, Pelliccia S, Leporace A, Lo Coco F, Tafuri A: A rare BCR-ABL1 transcript in Philadelphia-positive acute myeloid leukemia: case report and literature review. BMC Cancer 19(1): 50, 2019. DOI: 10.1186/s12885-019-5265-5

37 Kim H, Kim IS, Kim H: Emergence of BCR-ABL1 (p190) in acute myeloid leukemia post-gilteritinib therapy. Ann Lab Med 43(4): 386-388, 2023. DOI: 10.3343/alm.2023.43.4.386

38 Haider S, Mahmood A, Akhtar F, Mahmood R, Muzafar S, Batool M: BCR-ABL1 gene mutation in acute lymphoblastic leukemia. Ann Pak Inst Med Sci 18(3): 181-185, 2022. DOI: 10.48036/apims.v18i3.629

39 Fedullo AL, Messina M, Elia L, Piciocchi A, Gianfelici V, Lauretti A, Soddu S, Puzzolo MC, Minotti C, Ferrara F, Martino B, Chiusolo P, Calafiore V, Paolini S, Vignetti M, Vitale A, Guarini A, Foà R, Chiaretti S: Prognostic implications of additional genomic lesions in adult Philadelphia chromosome-positive acute lymphoblastic leukemia. Haematologica 104(2): 312-318, 2019. DOI: 10.3324/haematol.2018.196055

40 Mullighan CG, Miller CB, Radtke I, Phillips LA, Dalton J, Ma J, White D, Hughes TP, Le Beau MM, Pui C, Relling MV, Shurtleff SA, Downing JR: BCR–ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature 453(7191): 110-114, 2008. DOI: 10.1038/nature06866

41 Pashaiefar H, Yaghmaie M, Tavakkoly-Bazzaz J, Ghaffari SH, Alimoghaddam K, Momeny M, Izadifard M, Kasaeian A, Ghavamzadeh A: Significance of PARP1 expression levels in patients with acute myeloid leukemia. Ann Oncol 29: ix87, 2018. DOI: 10.1093/annonc/mdy437

42 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, Jin J: High PARP-1 expression predicts poor survival in acute myeloid leukemia and PARP-1 inhibitor and SAHA-bendamustine hybrid inhibitor combination treatment synergistically enhances anti-tumor effects. EBioMedicine 38: 47-56, 2018. DOI: 10.1016/j.ebiom.2018.11.025

43 Gil-Kulik P, Dudzińska E, Radzikowska-Büchner E, Wawer J, Jojczuk M, Nogalski A, Wawer GA, Feldo M, Kocki W, Cioch M, Bogucka-Kocka A, Rahnama M, Kocki J: Different regulation of PARP1, PARP2, PARP3 and TRPM2 genes expression in acute myeloid leukemia cells. BMC Cancer 20(1): 435, 2020. DOI: 10.1186/s12885-020-06903-4

44 Hiroki H, Ishii Y, Piao J, Namikawa Y, Masutani M, Honda H, Akahane K, Inukai T, Morio T, Takagi M: Targeting Poly(ADP)ribose polymerase in BCR/ABL1-positive cells. Sci Rep 13(1): 7588, 2023. DOI: 10.1038/s41598-023-33852-2

45 Bavaro L, Martelli M, Cavo M, Soverini S: Mechanisms of disease progression and resistance to tyrosine kinase inhibitor therapy in chronic myeloid leukemia: an update. Int J Mol Sci 20(24): 6141, 2019. DOI: 10.3390/ijms20246141

46 Stepanenko AA, Dmitrenko VV: Pitfalls of the MTT assay: Direct and off-target effects of inhibitors can result in over/underestimation of cell viability. Gene 574(2): 193-203, 2015. DOI: 10.1016/j.gene.2015.08.009

47 Nieborowska-Skorska M, Sullivan K, Dasgupta Y, Podszywalow-Bartnicka P, Hoser G, Maifrede S, Martinez E, Di Marcantonio D, Bolton-Gillespie E, Cramer-Morales K, Lee J, Li M, Slupianek A, Gritsyuk D, Cerny-Reiterer S, Seferynska I, Stoklosa T, Bullinger L, Zhao H, Gorbunova V, Piwocka K, Valent P, Civin CI, Muschen M, Dick JE, Wang JC, Bhatia S, Bhatia R, Eppert K, Minden MD, Sykes SM, Skorski T: Gene expression and mutation-guided synthetic lethality eradicates proliferating and quiescent leukemia cells. J Clin Invest 127(6): 2392-2406, 2017. DOI: 10.1172/JCI90825

48 Padella A, Ghelli Luserna Di Rorà A, Marconi G, Ghetti M, Martinelli G, Simonetti G: Targeting PARP proteins in acute leukemia: DNA damage response inhibition and therapeutic strategies. J Hematol Oncol 15(1): 10, 2022. DOI: 10.1186/s13045-022-01228-0

Received May 22, 2024
Revised June 21, 2024
Accepted July 12, 2024