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PARP INHIBITION INDUCES PHILADEPHIA P190 POSITIVE ACUTE LYMPHOID LEUKEMIA CELL DEATH IN LEVELS SIMILAR TO IMATINIB TREATMENT

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Objective: Acute Lymphoid Leukemia (ALL) is the most common leukemic subtype among pediatric populations. The prognosis is worse among patients which are Philadelphia chromosome positive (Ph+), detected with *BCR-ABL1 p190* translocation, and, although treatments strategies utilizing tyrosine-kinase inhibitors improved Ph+ patient's outcomes, the development of new therapeutic approaches is of utmost importance in the oncologic practice when facing the inevitable cases of resistance emergence. This study aims to evaluate the cytotoxic effect of inhibiting poly-ADP-ribose 1 (PARP1), a signaling pathway for DNA repair machinery, in an ALL Ph+ cell model. **Methodology:** Cytotoxicity analyses of the compounds AZD2461, Imatinib and Doxorubicin were performed by Alamar Blue assay in three cell lines: SUP-B15 – B-lymphoblast Ph p190+ ALL –, Raji and Namalwa – both B-lymphocyte Burkitt's lymphoma. Drug cytotoxicity was determined through serial dilutions resulting in final concentrations of 10 μM, 2 μM, 0.4 μM, 0.08 μM, 0.016 μM and 0.0032 μM for every drug. All concentrations were analyzed in triplicates for each cell line after a period of 72 hours of treatment, except for SUP-B15, which was also analyzed with all the drugs in periods of 24 and 48 hours. After the treatment period, Alamar Blue was added to each well, plates were incubated and then read for fluorescence. Viability results were analyzed through non-linear regression using GraphPad Prism (v. 5.01). **Results:** AZD2461 showed cytotoxic activity comparable to that of Imatinib in Ph+ SUP-B15, represented by an IC_{50} at 72 hours of treatment of 344.3 nM and 329.2 nM, respectively. The use of PARP inhibitors showed little to no efficacy when treating either of the remaining cell lines, with an IC_{50} that was not reached in treatment of Raji and a high IC_{50} of 20.9 μM in the treatment of Namalwa. Doxorubicin showed high cytotoxic activity against all cell lines, with IC_{50} values at 72 hours of low nanomolar levels; 20.32 nM, 85 nM and 75.93 nM for SUP-B15, Raji and Namalwa, respectively. Due to non-responsiveness of Raji and Namalwa to the targeted therapies, only SUP-B15 was evaluated at 24 and 48 hours and treatment. AZD2461 and Imatinib's IC_{50} remained comparable at 1421 nM and 1230 nM at 48 hours, respectively, and 3295 nM and 3966 nM at 24 hours, respectively. **Discussion:** The use of PARP inhibitors (PARPi) shows great clinical efficiency in the treatment of *BRCA1/ 2*-mutated tumors and other malignancies that harbor defects in double-strand-breaks repair through homologous recombination. Although Raji and Namalwa have been previously shown to considerably overexpress *PARP1* in relation to SUP-B15, the presence of *BCR-ABL1* translocation is highly associated with increased chromosomal instability through intracellular accumulation of reactive oxygen species and promotion of non-conservative repair pathways. The major cytotoxic effect of AZD2461 over SUP-B15, in levels comparable to those of Imatinib, shows that ALL Ph+ models seem to be over reliant on pathways that regulate genomic damage and minimize the instability brought by *BCR-ABL1*, specifically *PARP1*. **Conclusion:** The use of PARPis shows great effect over the viability of ALL Ph+ models and *PARP1* represents a potential new target for investigation in *BCR-ABL1* positive tumors. However, studies are being conducted to confirm cell death through on-target effects of AZD2461 and the possible effects of PARPi in the expression levels of BCR-ABL1.

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LEUCEMIA MIELOIDE AGUDA SECUNDÁRIA. RESULTADOS DE TRATAMENTOS REALIZADOS E CURVA DE SOBREVIDA EM UM HOSPITAL PÚBLICO

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Objetivos: Avaliar os resultados dos tratamentos de pacientes com Leucemia Mieloide Aguda Secundária (sLMA) do Serviço de Oncohematologia do Conjunto Hospitalar de Sorocaba (CHS), avaliar a sobrevida através da curva de Kaplan-Meier e ainda avaliar as características dos pacientes e diagnósticos prévios à transformação leucêmica. **Material e método:** trata-se de um trabalho retrospectivo com análise de prontuários dos pacientes diagnosticados com sLMA de 2016 a 2020 no ambulatório de oncohematologia do CHS. A análise ocorreu após autorização obtida via Termo de Consentimento Livre e Esclarecido (TCLE). As informações foram coletadas e transferidas para um computador, onde foram avaliadas estatisticamente. **Resultados:** 80 pacientes foram diagnosticados com Leucemia mieloide aguda (LMA) no período descrito. Destes, 22 (31.25%) foram diagnosticados com sLMA. A idade dos pacientes deste grupo variou de 28 a 81 anos, com média de 58.09 anos e mediana de 61 anos. Metade dos pacientes, ou seja, 11 tinham mais de 60 anos. Com relação à etiologia das LMA, foi observado que 18 (81.82%) eram secundárias à Síndrome Mielodisplásica (LMA/SMD), duas (9.09%) eram secundárias à Leucemia Mieloide Crônica e duas (9.09%)