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Combination Therapies Targeting Apoptosis Pathways in Pediatric Acute Myeloid Leukemia (AML)

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Abstract : Leukaemia is the most frequently (30%) occurring type of paediatric cancer. Of these, approximately 80% are acute lymphoblastic leukaemia (ALL) with acute myeloid leukaemia (AML) cases making up the remaining 20% alongside other leukaemias. Unfortunately, children with AML do not have promising prognosis with only 60% surviving 5 years or longer. It has been highlighted recently the need for age-specific therapies for AML patients, with paediatric AML cases having a different mutational landscape compared with AML diagnosed in adult patients. Drug Repurposing is a recognized strategy in drug discovery and development where an already approved drug is used for diseases other than originally indicated. We aim to identify novel combination therapies with the promise of providing alternative more effective and less toxic induction therapy options. Our in-silico analysis highlighted 'cell death and survival' as an aberrant, potentially targetable pathway in paediatric AML patients. On this basis, 83 apoptotic inducing compounds were screened. A preliminary single agent screen was also performed to eliminate potentially toxic chemicals, then drugs were constructed into a pooled library with 10 drugs per well over 160 wells, with 45 possible pairs and 120 triples in each well. Seven cell lines were used during this study to represent the clonality of AML in paediatric patients (Kasumi-1, CMK, CMS, MV11-14, PL21, THP1, MOLM-13). Cytotoxicity was assessed up to 72 hours using CellTox™ Green reagent. Fluorescence readings were normalized to a DMSO control. Z-Score was assigned to each well based on the mean and standard deviation of all the data. Combinations with a Z-Score <2 were eliminated and the remaining wells were taken forward for further analysis. A well was considered 'successful' if each drug individually demonstrated a Z-Score <2, while the combination exhibited a Z-Score >2. Each of the ten compounds in one well (155) had minimal or no effect as single agents on cell viability however, a combination of two or more of the compounds resulted in a substantial increase in cell death, therefore the ten compounds were de-convoluted to identify a possible synergistic pair/triple combinations. The screen identified two possible 'novel' drug pairing, with BCL2 inhibitor ABT-737, combined with either a CDK inhibitor Purvalanol A, or AKT/ PI3K inhibitor LY294002. (ABT-737- 100 nM+ Purvalanol A- 1 µM) (ABT-737- 100 nM+ LY294002- 2 µM). Three possible triple combinations were identified (LY2409881+Akti-1/2+Purvalanol A, SU9516+Akti-1/2+Purvalanol A, and ABT-737+LY2409881+Purvalanol A), which will be taken forward for examining their efficacy at varying concentrations and dosing schedules, across multiple paediatric AML cell lines for optimisation of maximum synergy. We believe that our combination screening approach has potential for future use with a larger cohort of drugs including FDA approved compounds and patient material.

Keywords : AML, drug repurposing, ABT-737, apoptosis
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