The Evaluation of Mefloquine Drug Repurposing on Acute Myeloid Leukemia

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The aim of this study is to observe cell proliferation, cell viability, apoptosis, and autophagy on acute myeloid leukemia (AML) cell lines, NB4 and U937, with the drug repurposing of mefloquine (MQ). Methods: such as the 3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide (MTT) assay and trypan blue staining have shown a decrease in live cells with high concentrations of mefloquine. Using their average perspective IC50 values of MQ concentration, Western blotting was applied by means of apoptosis and autophagy markers to determine if the induction of apoptosis and inhibition of autophagy was present in MQ-treated AML cells. The experiment will be continued with more cell lines, drugs, and other means of protocol in order to contribute to cancer therapy.

**ABSTRACT**

**INTRODUCTION**

Acute leukemia is a fast-growing blood cancer with an early onset in hematopoietic stem cells. DNA mutations block normal development in lymphoid and myeloid cells, leading to an accumulation of blast cells in the bone marrow. This can result in either acute lymphocytic leukemia (ALL) or acute myeloid leukemia (AML) as shown in Fig. 1. With 2-year survival rates of less than 20% in the elderly and 60% in children [2], AML became the main focus for this project.

**RESULTS**

**MTT Assay**
1. Serial dilute 50 mM stock solution of MQ with DMSO. Seed NB4 and U937 with RPMI media (10% FBS, 1% PS) at 2 x 10⁶ cells/mL and 1 x 10⁵ cells/mL, respectively. Incubate for 24 hours.
2. Incubate plates for 48 hours. Add 10 μL of MTT reagent, incubate for 4 hours, then add 100 μL of detergent.
3. Store in the dark for 24 hours. Record absorbance at 595 nm and determine IC₅₀.

**Trypan Blue Staining**
1. Perform cell count with Trypan Blue to view cell viability at 48 h post MQ.
2. After 48 hours, perform a cell count with Trypan Blue to view cell viability at increasing MQ concentrations (include IC50, 7 µM for NB4 and 8 µM for U937 for 48h).

**RESULTS (cont.)**

**DISCUSSION/CONCLUSIONS**

We found that AML cells, NB4 and U937, had mean IC50 values respectively at 7µM and 8µM mefloquine (MQ) treatment through verification in MTT and trypan blue assays. The MTT assay uses tetrazolium dye reduction to measure metabolism as a marker for cell proliferation. Cells with increasing MQ concentration had the least metabolism by losing their ability to convert the MTT into formazan and revealing less color as a result of free heme, interacting with phosphatidylinositol, and affecting lipid metabolism by losing their ability to convert the MTT into formazan and revealing less color as a result of free heme, interacting with phosphatidylinositol, and affecting lipid metabolism.

**METHODS**

The repurposing of mefloquine (MQ) as an anti-leukemic drug will result in decreased myeloid leukemia cell proliferation due to lysosome disruption, thereby inhibiting autophagy and inducing apoptosis.

The growth maintenance of cancer cells depend partially on autophagy, a catabolic process that degrades and recycles unwanted proteins and organelles in the lysosome for cell survival. Based on previous studies, leukemic cells undergoing autophagy inhibition experience metabolic stress, triggering apoptosis [3].

The use of an antimalarial drug, mefloquine (MQ), has sparked interest in drug repurposing for leukemic cells due to its effective reduction of parasitemia from blood. Mefloquine’s current mechanism of action for malaria includes damaging the membrane of free heme, interacting with phosphatidylinositol, and affecting volume-regulated ion channels (VRAC) to bring toxicity to parasites in blood [5]. A high-throughput screening panel of leukemic cell lines identified mefloquine as an anti-leukemic compound by lysosome disruption, releasing cathepsins into the cytosol and causing permeability in the lysosome membrane [2].

**HYPOTHESIS**

The repurposing of mefloquine (MQ) as an anti-leukemic drug will result in decreased myeloid leukemia cell proliferation due to lysosome disruption, thereby inhibiting autophagy and inducing apoptosis.