Name(s)

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Project Number

S0504

Project Title

Effects of Novel Dual PI3K-BRD4 Inhibitor SF2523 on Mantle Cell Lymphoma Survivorship

Abstract

Objectives

Mantle cell lymphoma (MCL) is a rare Non-Hodgkins B-cell lymphoma. Often overlooked in treatment development due to its rarity, MCL has a survival rate of only 5 to 10%, and most physicians notice treatment failure in less than 18 months. A major factor linked to MCL is dysregulation of the c-MYC gene, which controls cell functions including proliferation, growth, and apoptosis. SF2523 is a dual-inhibitor that suppresses PI3K and BRD4, which initiate c-MYC translation and transcription, respectively. In repressing both steps of c-MYC central dogma, SF2523 promises efficiency. This project explores the viability of SF2523 as an MCL treatment, predicting that SF2523 decreases MCL survival more than treatments of inhibitors BKM-120 (inhibits PI3K), JQ1 (inhibits BRD4), and combined BKM-120/JQ1 treatment.

Methods

Three trials of cell proliferation assay were done on MCL cell lines in vitro. Supporting experiments included three trials of IC50 (half maximal inhibitory concentration) calculations for SF2523, measuring survivability at 0 to 50 ?M (serial dilution manner), and creating a percent cell viability curve. Western blots were done to verify that SF2523 was affecting c-MYC as predicted, measuring protein expression of phospho-AKT and c-MYC.

Results

The cell proliferation assay found survivability of MCL cells with SF2523 to be 15.2%, compared to 19.0% for BKM-120/JQ1 treatment, 55.2% for BKM-120, and 55.5% for JQ1. The SF2523 IC50 value was 109.6 nM. The final blots from the western blotting show levels of phospho-AKT, a downstream protein of PI3K, and c-MYC being lowest with SF2523, rather than BKM-120, treatment.

Conclusions

These results illustrate that SF2523 decreases MCL survival more effectively than all three other treatments. This is supported by the IC50 value of 109.6 nM, which is less than published IC50 values for JQ1 and BKM-120, which are 118 nM and 116 nM, respectively. They also confirmed that SF2523 targets the c-MYC gene as expected and more effectively than other MCL treatments. SF2523 holds huge potential for MCL patient survival in the future as the first dual-inhibitor for the cancer. Further developed and tested for approval, SF2523 could contribute to saving thousands of lives annually. These implications could also extend to general B-cell lymphoma treatment, considering c-MYC plays a large role in the progression of other B-cell lymphomas, as well.

Summary Statement

I found that dual-inhibitor SF2523 more effectively reduces survival and decreases oncogenic MYC expression in Mantle Cell Lymphoma cultures than current MCL treatments.

Help Received

Dr. Donald Durden and Dr. Shweta Joshi allowed me to work at their UCSD Moore's Cancer Center lab and use their materials. Mrs. Muamera Zulcic, the Lab Manager, aided me with safety. I conducted all experiments myself but received training and guidance from Dr. Dhananjaya Pal of the same lab.