Targeting CLL and MCL cells with DNA repair and B cell receptor inhibitors

Adam D Curtis1; Ashley A Moineau2; Daniel Pham2; Sheila S Rajan1; Rong Zhang1; Emma E Brooks1; Todd A Hoffert1; Jens Rueter1; and Lindsay S Shopland, PhD1

1Eastern Maine Medical Center Cancer Care, Brewer, ME; 2University of Maine, Orono, ME

ABSTRACT

Background: Patient-specific responses and the development of ibrutinib resistance remain significant challenges to the treatment of mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). The poly ADP ribose polymerase (PARP) inhibitor, olaparib, targets cells with high levels of DNA damage, which have the mutational potential to become drug resistant.

Methods: To improve treatment efficacy and delay ibrutinib resistance, we tested ibrutinib treatment with olaparib on CLL and MCL cell lines in vitro. Primary CLL cells from patients were obtained via collaboration with the Harold Alfond Center for Cancer Care. These and MCL cell lines were analyzed by indirect immunofluorescence, cell counting, and flow cytometry.

Results: CLL cells were found to have significant patient-to-patient differences in their levels of DNA damage. These differences correlate with increased copies of the gene, AICDA. Limitations in primary CLL cell culture have prevented testing of ibrutinib plus olaparib thus far. However, tests of these drugs on MCL cell lines revealed either additive or synergistic inhibition of culture growth. These effects correlate with the absence and presence of the DNA repair protein, ATM, respectively.

Conclusions: Our data provide a strong case for investigation of olaparib-ibrutinib combination therapy in MCL and CLL models. The additive and synergistic inhibitions of tumor cell growth support a therapeutic strategy using lower doses of each drug in combination to reduce side effects. Our data suggest that the expression of AICDA and ATM might be useful biomarkers for this combination therapy in CLL and MCL, respectively.

METHODS

1. Measurement of DNA damage load in disease cells using fluorescence microscopy and cytogenetic data from clinical diagnostics.
2. Measurement of CLL and MCL cells cultured with olaparib plus ibrutinib, ibrutinib alone, olaparib alone, or DMSO vehicle control.
3. Assessment of mechanisms of culture growth inhibition using flow cytometry.

SELECTED CELLS:

- Primary CLL bone marrow cells with high and low DNA damage levels.
- MCL cell lines: Granta-519 (DNA damage high), Z-138 (DNA damage low).

STUDY DESIGN:

1. Measure DNA damage load in disease cells using fluorescence microscopy and cytogenetic data from clinical diagnostics.
2. Measurement of CLL and MCL cells cultured with olaparib plus ibrutinib, ibrutinib alone, olaparib alone, or DMSO vehicle control.
3. Assays of mechanisms of culture growth inhibition using flow cytometry.

BACKGROUND

Chronic Lymphocytic Leukemia (CLL) and Mantle Cell Lymphoma (MCL):

- Incurable diseases
- Arise in B cells in lymph nodes
- Relatively high mutational load for heme malignancies
- Treated with ibrutinib, but develop genetic resistance

Olaparib:

- Poly ADP ribose polymerase (PARP) inhibitor
- Inhibits Bruton's Tyrosine Kinase (BTK), pro-survival signaling
- First line CLL treatment
- Second line MCL treatment

Ibrutinib:

- B-cell-specific
- Inhibits Bruton’s Tyrosine Kinase (BTK), pro-survival signaling
- Additive/synergistic inhibition of culture growth

STRATEGY: Improve ibrutinib therapy for CLL and MCL with the addition of olaparib, which targets DNA repair deficient cells and may limit tumor evolution.

GOAL OF STUDY: Initial, pre-clinical testing of the effects of combined ibrutinib plus olaparib on CLL and MCL cell growth in vitro.

ACKNOWLEDGEMENTS

We thank the patients who donated specimens to the EMMC Biobank, Erica Brooks (Harald Alfond Center for Cancer Care), and Dr. David Weinstock (Dana Farber Cancer Institute) for cell lines. Financial support was provided by the Northern New England Clinical Oncology Society, the Partridge Foundation, and the EMMC Foundation.