NAMPT inhibitor KPT-9274 as an alternative treatment for Acute Myeloid Leukemia

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Introduction

- Acute Myeloid Leukemia (AML) is a cancer characterized by abnormal cell growth of immature myeloid cells.
- It is believed that most patients have multiple malignant clones of leukemic stem cells, each differing in their responses to treatment.
- NAMPT is a rate-limiting mechanism that produces nicotinamide adenine dinucleotide (NAD), a key metabolite essential for sustaining cellular energy metabolism.
- NAD is an important cofactor and serves as a metabolite required for a number of cellular processes such as mitochondrial function, genomic stability, DNA repair, calcium homeostasis and gene expression.
- NAMPT is over-expressed in various types of cancerous cells. They are reliant on the NAMPT salvage pathway for NAD production and do not efficiently utilize other pathways to produce NAD.
- Suppression of NAD production by inhibiting the NAMPT leads to loss of ATP, resulting in cell death without potentially toxic effects on non-cancerous cells.
- NAMPT inhibition has potential to become an alternative treatment of AML by eradicating leukemic stem cells and malignant stem colonies.

Aim

- Previous studies have displayed anti-tumor effects of NAMPT inhibitors in tumor models in vitro and in vivo.
- The purpose of this study is to evaluate the ability of KPT-9274, a novel, potent and selective NAMPT small molecule inhibitor to decrease colony formation in AML patient samples.
- In addition, self-renewal capacity is being evaluated in AML patient samples by assessing the ability of KPT-9274 to eradicate leukemic stem cell colonies.

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Methods

- Six AML leukemic patient cells were diluted down to a specific number of cells (1,000-10,000 cells/plate) then treated with KPT-9274 or the vehicle control (DMSO).
- Cells were plated and incubated on a 6-well culture plate, along with a control group in a semi-solid medium.
- After two weeks, leukemic cell colonies were counted using an inverted light microscope.
- The cells were washed with 20% RPMI media, underwent a dilution process to achieve a desired amount of cells, then re-plated to assess self-renewal capacity.

KPT-9274 Decreases Colony Formation in AML Leukemic Patient Cell Lines

- Inhibition of NAMPT by KPT-9274 resulted in an overall decrease in acute myeloid leukemic colonies by 39.7 to 75.9 percent.
- NAMPT inhibitors have anti-leukemic properties and have potential to be an alternative treatment for AML.
- Future considerations include assessing the self-renewal capacity of the AML patient cell lines. Regrowth of cells would indicate resistance to the NAMPT inhibitor as a result of clonal mutations within the cell.

References


Figure 1. Schematic of NAMPT inhibition

Figure 2. Experimental design

Figure 3. A) Patient colony counts after 2 weeks; B) Colony formation assay in patient 1361 after treatment with KPT-9274 and re-plating (day 26); C) Patient mutational status and cytogenetics.

Figure 4. Treatment of AML patient cell lines with KPT-9274 shows an overall decrease in cell colonies relative to the vehicle.