5-Fluorotroxacitabine displays potent anti-leukemic effects and circumvents resistance to Ara-C

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INTRODUCTION

Cytarabine has been a major backbone of Acute Myeloid Leukemia (AML) treatment. But eventually, 60-70% patients relapse. Several mechanisms of drug resistance for Ara-C have been described one of which is increased Cytidine deaminase (CDA) deaminating Ara-C, thereby preventing generation of the triphosphorylated active metabolite.

We evaluated a novel nucleoside analogue, 5FTRX, for its efficacy in Acute Myeloid Leukemia (AML) and ability overcome resistance due to increased CDA.

RESULTS

5FTRX overcomes resistance due to increased CDA

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<th>Basal levels of CDA do not correlate with 5FTRX efficacy in AML cell lines</th>
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<td>Control</td>
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<td>CDA (17 kDa)</td>
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5FTRX displayed robust and dose-dependent inhibition of OCI-AML2 and MV4-11 tumors in mouse xenograft models, with complete tumor regressions and long-lasting tumor growth delays with no changes in body weight.

5FTRX reduced engraftment in mouse xenograft models

5FTRX induced DNA damage and increased Phospho H2A.X levels

5FTRX reduced colony formation in primary AML samples

CONCLUSION

• CDA-overexpressing cells were more sensitive to 5FTRX, and less sensitive to Ara-C.
• 5FTRX reduced viability in AML cell lines.
• 5FTRX decreased colony formation of AML patient samples.
• 5FTRX reduced AML engraftment in mice.

5FTRX (100 mg/kg i.p., 5 days) reduced primary and secondary AML engraftment >95% compared to controls without toxicity.