Abstract: P1770

Title: ANTILEUKEMIC ACTIVITY OF CD33-DIRECTED MUTATION-AGNOSTIC LINTUZUMAB-AC225 IN KMT2A MUTANT AML

Abstract Type: e-Poster Presentation

Topic: Acute myeloid leukemia - Biology & translational research

Background:

Acute myeloid leukemia (AML) is a highly heterogeneous hematologic malignancy with a poor survival prognosis. Menin is critical for leukemogenesis in AML patient subsets driven by the rearrangement of the lysine methyltransferase 2A (*KMT2A*) gene (also known as mixed lineage leukemia, *MLL*) that can impair transcriptional networks. Small molecule inhibitors of menin-KMT2A have shown promise in treating eligible patients, but most patients eventually relapse. Combining KMT2A inhibition with an AML targeted radionuclide could leverage radiation-induced DNA damage to mitigate incomplete responses. We have shown that leukemic cells are broadly targeted by lintuzumab-Ac225, a CD33-directed monoclonal antibody conjugated with the alpha particle-emitting radionuclide actinium-225. In clinical trials, the addition of lintuzumab-Ac225 to chemotherapy regimen CLAG-M has shown substantial improvement in clinical outcomes in heavily pretreated relapsed/refractory AML patients, including venetoclax failures and those harboring TP53 mutations. To investigate if AML patients with *KMT2A* rearrangement may benefit from lintuzumab-Ac225, we compared the anti-leukemic response to lintuzumab-Ac225 or menin inhibitors as single agents and in combination using AML preclinical models.

Aims:

In this study, we evaluated the cytotoxic and anti-leukemic activity of lintuzumab-Ac225 in the *KMT2A* mutant AML cell line MV-4-11 as a single agent or in combination with menin inhibitors revumenib or ziftomenib.

Methods:

Lintuzumab-Ac225 was generated by conjugating lintuzumab with *p*-SCN-Bn-DOTA and subsequent radiolabeling with Ac-225. A viability assay was performed using flow cytometry to assess cytotoxic effects of lintuzumab-Ac225 and the menin inhibitor as single agents or in combination on the *KMT2A* rearranged AML cell line MV-4-11. The efficacy of lintuzumab-Ac225 and menin inhibitor combinations on AML cell line growth was further investigated in a subcutaneous xenograft model of MV-4-11 leukemia in nude mice.

Results:

Lintuzumab-Ac225 caused a potent dose-dependent reduction of MV-4-11 leukemic cells relative to cold lintuzumab ($p<0.0001$). Single agent cytotoxicity of revumenib and ziftomenib was also observed, but the combination of lintuzumab-Ac225 with menin inhibitors potentiated the response at all dose levels studied ($p<0.001$). Both lintuzumab-Ac225 and revumenib delayed tumor growth as single agents in a preclinical AML model, while the combination of the two agents demonstrated enhanced tumor control in the MV-4-11 AML model compared to the monotherapies ($p<0.01$).

Summary/Conclusion:

Our findings demonstrate that lintuzumab-Ac225 has potent anti-leukemic activity in AML cells harboring *KMT2A* genetic aberrations. Combination of CD33-targeted radionuclide therapy with menin inhibitor significantly improves AML control, demonstrating that targeted radiotherapy approaches can augment menin-targeted therapy. Based on these findings, the combination of lintuzumab-Ac225 with mutation-targeted agents may enhance anti-leukemic response compared to single-agent approaches.

Keywords: Acute myeloid leukemia, KMT2A, CD33, Radiotherapy