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616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Targeting Myeloid Epithelial Tyrosine Kinase (MERTK) Receptor in Acute Myeloid Leukemia Using a Novel Antibody Drug Conjugate, Rgx-019-MMAE

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Background: Myeloid epithelial reproductive tyrosine kinase receptor (MERTK) is a transmembrane protein receptor from the TAM (Tyro3, Axl, Mertk) family. It is known to be overexpressed in various solid and hematological cancers. Overexpression of MERTK is associated with reduced apoptosis, increased metastasis, and drug resistance in tumor cells, making it an attractive therapeutic target. RGX-019-MMAE, a novel humanized IgG1-MMAE antibody-drug conjugate (ADC) developed by Inspirna, selectively binds to MERTK on tumor cells, which results in internalization and degradation of the receptor, and induces cytotoxicity through the release of the payload, MMAE, which disrupts the mitosis process of actively dividing cells. Several monoclonal antibodies targeting MERTK have shown promising results against various solid cancers, however, the effect of targeting MERTK in AML progression via RGX-019-MMAE is not known. Here, we hypothesize MERTK is overexpressed in distinct subsets of AML and associated with leukemia progression, therefore, targeting MERTK via RGX-019-MMAE exerts an antileukemic effect.

Methods: To determine the clinical/prognostic relevance of MERTK, we analyzed a gene expression dataset (OHSU) and segregated the patients into low and high MERTK mRNA expression groups based on their mean expression value. To identify the specific AML subset with the highest MERTK expression, MERTK protein expression was analyzed in 818 patients with AML by performing Reverse Phase Protein Arrays (RPPA). MERTK protein expression was also measured by flow cytometry in OCI-AML3, OCI-AML2, Kasumi-1, ThP-1, Molm-13, Molm-14, MV4-11, and U937 leukemic cell lines and in the peripheral blood or bone marrow of five AML patients. Further, we treated Kasumi-1 and OCI-AML3 AML cell lines with varying doses of RGX-019-MMAE or isotype control for 72 and 120 hours and measured its effect on AML cell viability using CellTiterGlo 2.0 assay. Likewise, we treated primary cells from 5 different AML patients and determined the anti-leukemic effect of RGX-019-MMAE in primary cells. Finally, we investigated the synergistic effect of RGX-019-MMAE with Venetoclax (BCL2 inhibitor) or 5-Azacytidine *in vitro*.

Results: Analysis of AML OHSU dataset showed that patients with high MERTK mRNA expression had significantly worse overall survival than those having low MERTK mRNA expression ($p=0.02$). RPPA analysis revealed significantly higher MERTK protein expression in monocytic AML subtypes, such as M4 and M5, especially in those with PTPN11 mutation or t (9;11) translocation. Moreover, in the RPPA we noted that high expression of MERTK protein levels is significantly correlated with inferior survival. This finding suggests that MERTK could serve as a therapeutic target in AML, especially in patients with monocytic subtypes of leukemia. In addition, we observed varying degrees of MERTK protein expression in AML cell lines, with Kasumi-1 and OCI-AML3 expressing the highest amount of MERTK protein. Next, treatment of Kasumi-1 and OCI-AML3 cell lines with varying doses of anti-MERTK ADC, RGX-019-MMAE, resulted in significantly more killing of leukemic cells than the isotype control ADC in a dose-dependent manner ($p<0.01$), suggesting that RGX-019-MMAE inhibits AML cell proliferation. Further, we validated this finding in primary AML cells with high MERTK expression. As expected, we observed that treatment with RGX-019-MMAE induced significantly greater cell death (~80% apoptosis) in leukemic cells than the isotype control ADC. In addition, Kasumi-1 and OCI-AML3 cells treated in combination with RGX-019-MMAE and either Venetoclax or 5-Azacytidine showed a synergistic effect with increased cytotoxicity in a dose-dependent manner. These findings suggest that RGX-019-MMAE targets MERTK-expressing leukemic cells, sensitizes cells to chemotherapies, and promotes overall cytotoxicity.

Conclusion: RGX-019-MMAE significantly induced cell death in AML cell lines and primary AML patient samples. RGX-019-MMAE, combined with chemotherapeutic agents and targeted therapy, produces a synergistic anti-leukemic effect. Our data indicates that MERTK is a potential therapeutic target in AML patients with monocytic subtypes of leukemia.

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