Targeting IRAK1 / IRAK4 Signaling in Waldenström's Macroglobulinemia

Poster Lay Summary (provided by the IWMF)

Dr. Guang Yang is a member of the Bing Center for WM at Dana-Farber Cancer Institute. In this poster he reports on further efforts to understand what makes WM cells grow and survive. The highly prevalent MYD88 L265P mutation in WM activates multiple B-cell signaling pathways downstream, including BTK and IRAK1/IRAK4, which support WM cell growth and survival. Analysis of bone marrow cells from WM patients following more than 6 months of continued treatment with ibrutinib, a BTK inhibitor, demonstrated highly active IRAK1 and IRAK4, but not BTK, suggesting that IRAK1/IRAK4 signaling may contribute to persistent WM cell survival even following ibrutinib treatment. Inhibition of IRAK1 and IRAK4 resulted in reduced tumor cell survival and was more pronounced with IRAK1 inhibition. Dr. Yang then showed that combined BTK and IRAK inhibition leads to decreased NF kappa B signaling, another important pathway, and enhanced WM cell killing. This study provides a framework for the development and investigation of IRAK inhibitors, alone and in combination with ibrutinib in WM patients.

Dr. Yang continues to be involved in WM research efforts at the Bing Center.
Targeting IRAK1 / IRAK4 Signaling in Waldenström's Macroglobulinemia

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Background

MYD88 L265P somatic mutations are highly prevalent in Waldenström's macroglobulinemia (WM) (NEJM 367(9): 826-33). MYD88 L265P activates multiple downstream signaling pathways including BTK and IRAK4/IRAK that support malignant cell growth and survival (Blood 122(7): 1222-32; Nature 470(7332): 115-9). Ibrutinib targets BTK, and shows high overall and major clinical response rates, though no complete responses are observed indicating alternative survival signaling.

Methods

PhosFlow analysis of IRAK1, IRAK4, and BTK was performed in primary WM cells from untreated WM patients, and those on ibrutinib therapy.

Results

Bone marrow lymphoplasmacytic cells taken from WM patients following more than 6 months of continued ibrutinib treatment indicates IRAK1 remain activated.

More pronounced apoptosis, as well as sustained reduction in tumor cell growth occurred following knockdown of IRAK1 versus IRAK4.

Treatment of MYD88 mutated WM cells with ibrutinib and IRAK4/IRAK1 inhibitor resulted in synergistic tumor cell killing in WM cell lines and at least additive tumor cell killing in the presence of microenvironment supporting cells in WM patient bone marrow mononuclear cells.

Conclusion

MYD88 L265P mutated WM cells with ibrutinib and IRAK4/IRAK1 inhibitor may contribute to persistent WM cell survival following ibrutinib treatment. Combined BTK and IRAK inhibition leads to augmented blockade of NFkB signaling and enhanced WM cell killing. The studies provide a framework for the development and investigation of IRAK inhibitors, alone and in combination with ibrutinib in WM patients.