AMLGlobalPortal

FLT3, General AML

ATRA synergizes with FLT3 inhibition to eliminate FLT3/ITD1 leukemia stem cells *in vitro* and *in vivo*

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The chemotherapy-free therapy All-Trans Retinoic Acid and Arsenic Trioxide (ATO/ATRA) has been reported to achieve a good response in high- and low- risk Acute Promyelocytic Leukemia (APL).[1] This maybe owing to the fact that Retinoic Acid (RA) has been implicated in the differentiation of normal Hematopoietic Stem Cells (HSCs).

In Acute Myeloid Leukemia (AML), Leukemic Stem Cells (LSCs) play a role in disease initiation and conservation of malignant cells. LSCs are particularly problematic as, like healthy HSCs, they can self-renew and undergo quiescence, which is believed to be a major cause of resistance in AML treatment.

In addition to LSCs, FLT3-ITD (Internal Tandem Duplication) mutations are problematic for patients with AML. FLT3-ITD mutations are reported in approximately one third of patients diagnosed with AML. Patients with these mutations are also reported to have poor outcomes as well.

Ding Y. *et al.* conducted the first study to investigate the potential anti-cancer activity of alantolactone in AML stem and progenitor cells both in vitro and in vivo. The key published results showed that alantolactone demonstrated anti-leukemic activity through its inhibition of HL60 and K562 cells in vitro.[2]

In order to improve treatment outcomes in AML, novel therapeutic approaches that target both LSCs and FLT3-ITD mutations are necessary.

Ma H.S. et al. conducted a study to investigate the efficacy of combining ATRA and FLT3 Tyrosine Kinase Inhibitors (TKIs) to eliminate FLT3/ITD.3 The authors reported that in the FLT3/ITD+ AML cell lines and patient samples subjected to the combination therapy, there was a reduction in viable cell counts. The results of this study were published in Blood in June 2016.

This study by Ma H.S. *et al.* provides promising results on the synergistic effect of combining ATRA and FLT3 TKIs. This combination may be effective in reducing the relapse rates in AML. However, randomized clinical trials are required to further evaluate the safety and efficacy of this novel approach.

Please find the published study here.

Abstract

MYELOID NEOPLASIA All-trans retinoic acid synergizes with FLT3 inhibition to eliminate FLT3/ITD1 leukemia stem cells in vitro and in vivo

FMS-like tyrosine kinase 3 (FLT3)-mutant acute myeloid leukemia (AML) portends a poor prognosis, and ineffective targeting of the leukemic stem cell (LSC) population remains one of several obstacles in treating this disease. All-trans retinoic acid (ATRA) has been used in several clinical trials for the treatment of non-promyelocytic AML with limited clinical activity observed. FLT3 tyrosine kinase inhibitors (TKIs) used as monotherapy also achieve limited clinical responses and are thus far unable to affect cure rates in AML patients. We explored the efficacy of combining ATRA and FLT3 TKIs to eliminate FLT3/ internal tandem duplication (ITD)+ LSCs. Our studies reveal highly synergistic drug activity, preferentially inducing apoptosis in FLT3/ITD+ cell lines and patient samples. Colony-forming unit assays further demonstrate decreased clonogenicity of FLT3/ITD+ cells upon treatment with ATRA and TKI. Most importantly, the drug combination depletes FLT3/ITD+ LSCs in a genetic mouse model of AML, and prolongs survival of leukemic mice. Furthermore, engraftment of primary FLT3/ITD+ patient samples is reduced in mice following treatment with FLT3 TKI and ATRA in combination, with evidence of cellular differentiation occurring in vivo. Mechanistically, we provide evidence that the synergism of ATRA and FLT3 TKIs is at least in part due to the observation that FLT3 TKI treatment upregulates the antiapoptotic protein Bcl6, limiting the drug's apoptotic effect. However, co-treatment with ATRA reduces Bcl6 expression to baseline levels through suppression of interleukin-6 receptor signaling. These studies provide evidence of the potential of this drug combination to eliminate FLT3/ITD+ LSCs and reduce the rate of relapse in AML patients with FLT3 mutations.

References

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2. Ding Y. *et al*. Alantolactone selectively ablates acute myeloid leukemia stem and progenitor cells. J Hematol Oncol. 2016 Sep 22; 9 (1):93.

3. *Hayley H.S.et al*. Myeloid Neoplasia All-trans retinoic acid synergizes with FLT3 inhibition to eliminate FLT3/ITD1 leukemia stem cells in vitro and in vivo. Blood. 2016; 127:2867–2878. DOI:10.1182/blood-2015-05-646786