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blood advances

DHODH inhibition synergizes with DNA-demethylating agents in the treatment of myelodysplastic syndromes

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Key Points

- DHODH inhibition synergizes with DNA-demethylating agents in the treatment of MDS.
- DHODH inhibition enhances the incorporation of decitabine into DNA in MDS cells.

Dihydroorotate dehydrogenase (DHODH) catalyzes a rate-limiting step in de novo pyrimidine nucleotide synthesis. DHODH inhibition has recently been recognized as a potential new approach for treating acute myeloid leukemia (AML) by inducing differentiation. We investigated the efficacy of PTC299, a novel DHODH inhibitor, for myelodysplastic syndrome (MDS). PTC299 inhibited the proliferation of MDS cell lines, and this was rescued by exogenous uridine, which bypasses de novo pyrimidine synthesis. In contrast to AML cells, PTC299 was inefficient at inhibiting growth and inducing the differentiation of MDS cells, but synergized with hypomethylating agents, such as decitabine, to inhibit the growth of MDS cells. This synergistic effect was confirmed in primary MDS samples. As a single agent, PTC299 prolonged the survival of mice in xenograft models using MDS cell lines, and was more potent in combination with decitabine. Mechanistically, a treatment with PTC299 induced intra-S-phase arrest followed by apoptotic cell death. Of interest, PTC299 enhanced the incorporation of decitabine, an analog of cytidine, into DNA by inhibiting pyrimidine production, thereby enhancing the cytotoxic effects of decitabine. RNA-seq data revealed the marked downregulation of MYC target gene sets with PTC299 exposure. Transfection of MDS cell lines with *MYC* largely attenuated the growth inhibitory effects of PTC299, suggesting *MYC* as one of the major targets of PTC299. Our results indicate that the DHODH inhibitor PTC299 suppresses the growth of MDS cells and acts in a synergistic manner with decitabine. This combination therapy may be a new therapeutic option for the treatment of MDS.

Introduction

Myelodysplastic syndrome (MDS) is a clonal bone marrow (BM) disorder characterized by ineffective and clonal hematopoiesis accompanied by morphological dysplasia and variable cytopenia. DNA methyltransferase inhibitors azacitidine and decitabine have been used as chemotherapeutic agents for high-risk MDS. They are chemical analogs of cytidine that have direct cytotoxicity and induce DNA hypomethylation by interfering with DNA methyltransferase. Overall survival has been prolonged in

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