THE EFFECT OF ARA-C TREATMENT ON HEMATOPOIETIC STEM CELL EXPANSION AND LEUKEMOGENESIS IN A MOUSE MODEL OF CEBPA MUTANT ACUTE MYELOID LEUKEMIA

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Acute myeloid leukemia (AML) is the most common acute leukemia in adults. AML initiating mutations originate in hematopoietic stem cells (HSCs). The original pre-malignant clones were also found in end-stage tumors and survive therapy, leading to tumor relapse. Therefore, characterization and targeting of pre-leukemic cells may finally provide the possibility to prevent or cure AML. Acquired mutations in the CEBPA gene are found in 11-14% of all AML cases and include N- and C-terminal mutations frequently found within the same patient on separate alleles. Combining N- and C- terminal mutations in mice resulted in a loss of hematopoietic stem cells (HSC) quiescence and expansion of pre-malignant pool of cells, associated with accelerated AML. Increased cycling of mutant pre-leukemic HSCs suggests that they could be susceptible to the action of anti-proliferative agents used in chemotherapy. We analyzed the effect of cytosine arabinoside (Ara-C) treatment on proliferating mutant HSCs survival, and long-term tumor development in a mouse model of CEBPA mutant AML. Treatment of mice at the pre-leukemic stage with Ara-C treatment leads to a selective mutant HSCs apoptosis and a consequent drop in mutant HCS number. However, this initial reduction in the mutant HSC number did not lead to a beneficial effect on the AML progression rates. To the contrary, mice treated with Ara-C at the pre-leukemic stage revealed: 1) earlier onset of leukocytosis; 2) earlier onset of anemia; and importantly, 3) earlier AML-associated lethality. These data demonstrate that Ara-C treatment induces pre-leukemic HSC apoptosis, but does not lead to complete mutant cell clearance, revealing that Ara-C resistant mutant HSC population exists and re-initiates leukemia progression, and even at a higher rate. Moreover, our results demonstrate that Ara-C-mediated HSC reduction does not lead to delay in leukemia progression. To the contrary, several parameters show negative long-term effects of Ara-C treatment on AML progression. Caution therefore has to be taken in evaluating of the presence of residual mutant HSC in patients' bone marrow after chemotherapy. This study points to a critical role of therapy-resistant HSCs in leukemia progression or relapse and warrants further studies on their better characterization.