

Treatment with AS101 sensitizes acute myeloid leukemia cells (AML) to chemotherapy by disrupting the interaction between the integrin VLA-4 and Fibronectin: Mechanisms of action and clinical applications

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Bone marrow minimal residual disease (MRD) causes relapse after chemotherapy in patients with acute myelogenous leukemia (AML) due to acquired drug resistance - this is induced by the attachment of the integrin receptor VLA-4 on leukemic cells to its ligand fibronectin (FN) on bone marrow stromal cells. We show that the non toxic compound AS101, previously shown to exert anti tumoral effects in-vitro and in-vivo, sensitizes AML cells to ARA-C only when leukemic cells are plated on FN but not on BSA-coated plates. This was associated with a significant decrease in pAkt and Bcl-2. The sensitizing effect of AS101 was also correlated with the ability of AS101 to deactivate VLA on AML cells. In a model of SCID mice implanted with leukemic cells either from established AML cell lines or with leukemic cells expressing high VLA-4, obtained from AML patients, co-treatment with AS101 and chemotherapy significantly increased mice survival while chemotherapy alone exerted only a modest effect. Furthermore, the combined treatment resulted in the elimination of leukemic cells from all organs tested. Moreover, mice transplanted with AML cells that express low VLA-4, considerably reacted to chemotherapy alone as expressed by increased survival, while co-treatment with AS101 resulted in similar effects. Importantly, AS101 increases migration of leukemic cells expressing high VLA-4 from the Bone-Marrow to the peripheral blood enabling their sensitization to chemotherapy.

We propose that treatment with AS101 currently used in treatment of cancer patients, combined with chemotherapy, has a potential to eradicate MRD and prolong survival of AML patients.

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