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614. ACUTE LYMPHOBLASTIC LEUKEMIA - THERAPY, EXCLUDING TRANSPLANTATION: POSTER I | NOVEMBER 16, 2012

Identification of Non-Cardiotoxic hERG1 Blockers to Overcome Chemoresistance in Acute Lymphoblastic Leukemias

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Abstract

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Although cure rates for children with acute lymphoblastic leukemia (ALL), the most common pediatric malignancy, have markedly improved over the last two decades, chemotherapy resistance remains a major obstacle to successful treatment in a significant proportion of patients (Pui CH et al. N Engl J Med., 360:2730–2741, 2009). Increasing evidence indicates that bone marrow mesenchymal cells (MSCs) contribute to generate drug resistance in leukemic cells (Konopleva M et al., Leukemia, 16:1713–1724, 2002). We contributed to this topic, describing a novel mechanism through which MSCs protect leukemic cells from chemotherapy (Pillozzi S. et al., Blood, 117:902–914, 2011.). This protection depends on the formation of a macromolecular membrane complex, on the plasma membrane of leukemic cells, the

major players being i) the human ether-a-gò-gò-related gene 1 (hERG1) K^+ channel, ii) the $\beta_1$integrin subunit and iii) the SDF-1α receptor CXCR4. In leukemic blasts, the formation of this protein complex activates both the ERK 1/2 MAP kinases and the PI3K/Akt signalling pathways triggering antiapoptotic effects. hERG1 exerts a pivotal role in the complex, as clearly indicated by the effect of hERG1 inhibitors to abrogate MSCs protection against chemotherapeutic drugs. Indeed, E4031, a class III antiarrhythmic that specifically blocks hERG1, enhances the cytotoxicity of drugs commonly used to treat leukemia, both in vitro and in vivo. The latter was tested in a human ALL mouse model, consisting of NOD/SCID mice injected with REH cells, which are relatively resistant to corticosteroids. Mice were treated for 2 weeks with dexamethasone, E4031, or both. Treatment with dexamethasone and E4031 in combination nearly abolished bone marrow engraftment while producing marked apoptosis, and strongly reducing the proportion of leukemic cells in peripheral blood and leukemia infiltration of extramedullary sites. These effects were significantly superior to those obtained by treatment with either dexamethasone alone or E4031 alone. This model corroborated the idea that hERG1 blockers significantly increase the rate of leukemic cell apoptosis in bone marrow and reduced leukemic infiltration of peripheral organs.

From a therapeutic viewpoint, to develop a pharmacological strategy based on hERG1 targeting we must consider to circumvent the side effects exerted by hERG1 blockers. Indeed, hERG1 blockers are known to retard the cardiac repolarization, thus lengthening the electrocardiographic QT interval, an effect that in some cases leads to life threatening ventricular arrhythmias (torsades de points). On the whole, it is mandatory to design and test non-cardiotoxic hERG1 blockers as a new strategy to overcome chemoresistance in ALL.

On these bases, we tested compounds with potent anti-hERG1 effects, besides E4031, but devoid of cardiotoxicity (e.g. non-torsadogenic hERG1 blockers). Such compounds comprise erythromycin, sertindole and CD160130 (a newly developed drug by BlackSwanPharma GmbH, Leipzig, Germany). We found that such compounds exert a strong anti-leukemic activity both in vitro and in vivo, in the ALL mouse model described above.

This is the first study describing the chemotherapeutic effects of non-torsadogenic hERG1 blockers in mouse models of human ALL.

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No relevant conflicts of interest to declare.

Author notes

* Asterisk with author names denotes non-ASH members.