IJAE
Vol. 119, n. 1 (Supplement): 90, 2014
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Effect of lenalidomide on inositide-dependent erythropoiesis and cell cycle in del(5q) myelodysplastic syndromes (mds)

Matilde Y. Follo[1], Sara Mongiorgi[1], Carlo Finelli[2], Cristina Clissa[2], Marilisa Quaranta[1], Désirée Martini[1], Anna Maria Billi[1], Lucia Manzoli[1]

[1] Department of Biomedical and Neuromotor Sciences, Cellular Signalling Laboratory, University of Bologna, via Irnerio 48, 40126 Bologna, Italy; [2]Institute of Hematology "L e A Seràgnoli", University of Bologna, via Massarenti 9, 40138 Bologna, Italy

Akt is implicated in erythropoiesis, through PI-PLCgamma1, but is also connected with cell cycle and protein synthesis, via activation of the mTOR pathway (1).

Lenalidomide is currently used in the treatment of low-risk MDS patients showing a del(5q) karyotype, as it induces erythropoiesis in non-del(5q) cells and selectively inhibits cell proliferation in del(5q) cells (2). However, the exact molecular mechanisms underlying the effect of Lenalidomide in del(5q) and non-del(5q) MDS cells are still unclear, although Lenalidomide demonstrated an effect on targeting signalling molecules involved in apoptosis, proliferation and differentiation, i.e. Akt (3).

Here we analyzed the effect of Lenalidomide on two cell lines: Namalwa CSN.70, bearing a del(5q) karyotype, and U937, with a normal 5q chromosome. In particular, we analyzed several molecules implicated in inositide signalling, such as Akt, mTOR and PI-PLCgamma1, as well as Cyclins and Globin genes, in order to assess the effect of Lenalidomide on cell cycle and erythropoiesis. Moreover, we quantified the gene expression profile of 6 patients diagnosed with del(5q) Low-Risk MDS (IPSS: Low or Int-1) who were given Lenalidomide.

In our case series, as well as in cell lines, erythropoiesis activation was associated with a response to Lenalidomide, with an induction of Akt/PLCgamma1 and an increase of Beta-Globin. Moreover, only in non-del(5q) cells, a normal proliferation was allowed, given that del(5q) cells showed a cell cycle arrest and a slight inhibition of the Akt/mTOR pathway, this latter being confirmed also by co-localization experiments performed on primary cells from MDS patients.

Therefore, our data support the hypothesis of a specific activation of both inositide-dependent proliferation and erythroid differentiation pathways in response to Lenalidomide treatment in non-del(5q) cells, whereas in the del(5q) cell clone there is a cell cycle arrest and a slower erythroid differentiation. Taken together, these results hint to a specific activation of inositide-dependent signalling pathways during Lenalidomide administration and possibly pave the way to a larger investigation aiming to assess the role of these pathways during the therapy.

References

[1] Wang et al. (2006) Akt binds to and phosphorylates phospholipase C-gamma1 in response to epidermal growth factor. Mol Biol Cell 17: 2267-2277.
[2] Komrokji RS et al. (2013) Deletion 5q MDS: molecular and therapeutic implications. Best Pract Res Clin Haematol 26:365-375.
[3] Gandhi AK, et al. (2006) Lenalidomide inhibits proliferation of Namalwa CSN.70 cells and interferes with Gab1 phosphorylation and adaptor protein complex assembly. Leuk Res. 30:849-858.

Keywords

Nuclear Inositide Signalling, Erythroid Differentiation, Cell Cycle.