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

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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


Keywords

Nuclear Inositide Signalling, Erythroid Differentiation, Cell Cycle.