

Clonal Activation of Akt in Low-Risk MDS Patients with Del(5q) treated with Lenalidomide

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The activation of inositide signalling pathways, such as Akt/mTOR, has been demonstrated in high-risk MDS (1). Lenalidomide is currently used in the treatment of del(5q) low-risk MDS patients, where it may suppress the del(5q) clone and restore a normal erythropoiesis, via inhibition of Akt phosphorylation (2). Here, we studied the expression of inositide signalling molecules in 6 low-risk MDS patients who were given Lenalidomide by immunocytochemistry and Real-Time PCR. In our case series, 4 out of 6 del(5q) low-risk MDS patients responded to Lenalidomide and showed an activation of erythropoiesis, in that Beta-Globin levels increased, as compared with baseline. Moreover, these subjects also displayed an activation of PI-PLCgamma1 and Akt. Interestingly, Akt resulted to be specifically phosphorylated in cells not showing the 5q deletion, hinting at a clonal activation of this pathway. The 2 non responder patients early discontinued Lenalidomide for adverse events, and for these patients neither a clinical assessment of Lenalidomide effect, nor a molecular analysis, were possible. Our data show Akt/PI-PLCgamma1 activation during Lenalidomide treatment, and confirm the activation of erythropoiesis in responder patients. In addition, our results indicate that Akt is specifically phosphorylated in the 5q+ clone. Therefore, it is conceivable that Lenalidomide strengthens the proliferation of the 5q+ clone, whilst the del(5q) clone undergoes an apoptotic process, allowing the restoration of the normal erythropoiesis. This is extremely important, not only for MDS pathogenesis, but also for the development of innovative targeted therapies.

References

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Key words

Erythroid Differentiation, Akt, Cell Proliferation.