

POSTER PRESENTATION

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New targeted therapies in myelodysplastic syndrome: the role of farnesyltransferase and proteasome inhibitors

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From 16th International Charles Heidelberger Symposium on Cancer Research
Coimbra, Portugal. 26–28 September 2010

One of the main mechanisms responsible for MDS molecular pathogenesis involves the activation of tyrosine-kinase receptors, such as FLT3, RAS proteins, and deregulation of apoptotic pathways. Regarding this, new drugs have been developed to target pathways involved in malignancy, such as Farnesyltransferase Inhibitors (IFTs) and proteasome inhibitors (PI). This work aims to clarify the role of IFTs and PI as potential therapeutic agents in Myelodysplastic Syndrome (MDS).

For this, F-36P cells, were incubated with different concentrations of α -HFPA (IFT) and MG262 (PI), as single agents and in association with the conventional therapeutic drug, Cytosine Arabinoside (Ara-C). Cell growth and viability was evaluated by Trypan Blue test. Cell death was analyzed by optic microscopy and flow cytometry (FC). Expression of proteins involved in apoptosis and cell cycle regulation was evaluated by FC. The detection of RAS and FLT3 mutations was accessed by sequentiation and PCR, respectively.

Our results show that α -HFPA and MG262, in monotherapy, induce a decrease in cell growth and viability in a time and dose-dependent manner (IC_{50} , α -HFPA 125 μ M; MG262 100 nM). The antiproliferative effect of α -HFPA could be related to RAS/MAPK pathway inhibition, as we observed a decrease in cyclin D1 levels, while the cytotoxicity induced by MG262 to an increase in BAX expression. Our results show that α -HFPA is effective independently of RAS mutations, once we didn't identify mutations in none of the isoforms studied, but we observe ITD mutations in *FLT3* gene.

These results suggest that IFTs and PIs may constitute a potential therapeutic approach as single agents in MDS.

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Published: 24 September 2010

doi:

Cite this article as: Gonçalves et al.: New targeted therapies in myelodysplastic syndrome: the role of farnesyltransferase and proteasome inhibitors. *BMC Proceedings* 2010 **4**(Suppl 2):P44.

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