Synergistic Antitumor Effect of Selinexor, Selective Inhibitor of Nuclear Export (SINE) Compound and Panobinostat in a Mouse Model of Multiple Myeloma

Sivan Elloul, Hua Chang, Boris Klebanov, Trinayan Kashyap, Maxwell Werman, Margaret Lee, Yosef Landesman, Sharon Shacham, Michael Kauffman And Sharon Friedlander
Karyopharm Therapeutics, Newton MA 02459

ABSTRACT

Introduction: Selinexor is an oral, first-in-class SINE compound that binds to the primary nuclear exporter, XPO1/Crb1. XPO1 exports over 250 cargoes, including major tumor suppressor proteins (TP53) leading to their inactivation. Inhibition of XPO1 results in nuclear retention of TP53 and restores their normal functions. XPO1 also mediates the export of key signaling molecules in multiple myeloma (MM) including o-MYC mRNA and NF-κB. Selinexor is currently being investigated in phase 2 clinical trials in MM in combination with dexamethasone, pomalidomide, lenalidomide, bortezomib and Carfilzomib.

In preclinical studies selinexor has been shown to synergize strongly with these anti-MM drugs making it an excellent candidate partner for combination therapy in MM. To identify additional synergistic pairings, we investigated the use of selinexor in combination with panobinostat, a pan-histone deacetylase inhibitor (HDAC), recently approved by the FDA in combination with bortezomib for 3rd line treatment of MM, as a potential treatment for MM both in vitro and in vivo.

METHODS: The effects of selinexor and panobinostat alone or in combination on cell viability were tested on MM.15 cell line using the MTT assay. Treatment groups included: A) vehicle control, B) 0.01 μM selinexor, C) 0.01 μM panobinostat, D) combination of A & B. Drug inactivation was analyzed by Western blot.

RESULTS: XPO1, MYC and Nuclear NFκB Proteins in Combination Treated MM1S Cells

The effects of selinexor and panobinostat alone or in combination on cell viability were tested on MM.15 cell line using the MTT assay. Treatment groups included: A) vehicle control, B) 0.01 μM selinexor, C) 0.01 μM panobinostat, D) combination of A & B. Drug inactivation was analyzed by Western blot.

Reduction in XPO1, MYC and Nuclear NFκB Proteins in Combination Treated MM1S Cells

The effects of selinexor and panobinostat alone or in combination on cell viability were tested on MM.15 cell line using the MTT assay. Treatment groups included: A) vehicle control, B) 0.01 μM selinexor, C) 0.01 μM panobinostat, D) combination of A & B. Drug inactivation was analyzed by Western blot.

Selinexor-Panobinostat Combination Treatment is Synergistic in MM1S-Derived Mouse Xenografts

The effects of selinexor and panobinostat alone or in combination on cell viability were tested on MM.15 cell line using the MTT assay. Treatment groups included: A) vehicle control, B) 0.01 μM selinexor, C) 0.01 μM panobinostat, D) combination of A & B. Drug inactivation was analyzed by Western blot.

DISCUSSION AND CONCLUSIONS

The NFκB and o-MYC transcription factors play key roles in the survival and proliferation of MM cells. NFκB is activated by classical and/or alternative pathways and o-MYC transcriptional deregulation is achieved via at least three different mechanisms including transcription, modifications and amplification. Therefore, simultaneous inhibition of NFκB and o-MYC, ideally with a combination of drugs that will target multiple activation mechanisms of these transcription factors, is an attractive therapeutic approach for MM. Selinexor and panobinostat are potent drugs with unique mechanisms of action affecting multiple cellular processes. Here we show that the combination of these drugs results in synergistic reduction in MM cell viability, decrease in o-MYC mRNA and protein levels and an overall decrease in NFκB mRNA and nuclear protein levels. Simultaneously, the immediate cellular response to selinexor is induction of XPO1 expression, panobinostat treatment leads to inhibition of XPO1 expression. This result may be the basis for the synergistic effect observed when combining selinexor with panobinostat in vitro and in vivo and suggests a potential way to overcome possible development of mechanisms of resistance to selinexor.

Conclusions: Selinexor-panobinostat combination synergizes to induce apoptosis in MM cells and amplifies anti-tumor effect in a MM xenograft model. These data provide rational support for study of selinexor/panobinostat combination in clinical trials.

Website: www.karyopharm.com contact: Sharon Friedlander, email: sfriedlander@karyopharm.com