Selective Inhibitor of Nuclear Export (SINET™) Compounds Show Synergistic Anti-Tumor Activity in Combination with Dexamethasone in Multiple Myeloma

Trinayan Kashyap, Boris Klebanov, William Shenapadis, Sivam Ethell, Dilara McCauley, Robert Carlson, Michael Kaufman, Sharon Shacham, and Yosef Landesman
Karyopharm Therapeutics, Newton, MA, USA

Abstract

Background: Dexamethasone is a known activator of Glucocorticoid Receptor (GR) and GR is a target of the nuclear export protein XPO1. SINET compounds are a family of small-molecule, oral selective inhibitors of XPO1. Inhibition of XPO1 results in the retention of major transcription factors like MNK2a and repressed genes like MNK2b in the cell nucleus.

Methods: Total RNA and whole protein lysates from MM cells line treated with selinexor with or without dexamethasone were analyzed by quantitative PCR and by immunoblot, respectively. Localization of GR was evaluated by immunofluorescence. GR and XIAP transcriptional activity was analyzed using ELISA assays (Chemicon). An in vivo mouse model in NOD-SCID mice was treated with selinexor (5 mg/kg) and dexamethasone (1 mg/kg), alone or in combination and tumor growth was evaluated at 17 days.

Results: Dexamethasone, but not selinexor, induced phosphorylation of GR resulting in GR nuclear localization. Selinexor potentially exerted a synergistic effect of phosphorylated GR, leading to the synergistic induction of GR-dependent transcriptional activity. RNA levels of GR dyregulated genes such as MNK2b were induced by this combination treatment. Interestingly, between the two MNK2 isoforms, the combination treatment increased the expression of MNK2a, which is a tumor suppressor protein but not the MNK2isoform. Selinexor transcriptional activity was inhibited additively by this treatment. The combination treatment of selinexor with dexamethasone showed synergistic cytoxic effects on MM cell lines, which expressed Glucocorticoid Receptor (GR). In vivo, the combination of the two drugs inhibited MM tumor growth by 96% compared to 93% and 49% by selinexor and dexamethasone, respectively.

Conclusion: Selinexor induced and stabilized the nuclear retention of GR, which is initiated by dexamethasone, increased GR transcriptional activity induced expression of tumor suppressor genes like MNK2s and repressed NFB activity. Cytoxic effects of the combination were superior to the single agents. These studies demonstrate that selinexor plus dexamethasone combination therapy is superior to either agent alone.

Selinexor Synergizes with Dexamethasone to Enhance the Transcriptional Activity of the Glucocorticoid Receptor

Combination of Selinexor and Dexamethasone Attenuates NFB Activity Better than the Single Agents

Selinexor and Dexamethasone Uplregulate MNK2 and Selinexor Traps MNK2 in the Nucleus Leading to Apoptosis and Senescence

Reduction of H929 Tumor Xenografts by Combined Selinexor- Dexamethasone Treatment Exceeds Effects of the Single Agents

Summary of Results and Conclusions

- Dexamethasone phosphorylates Glucocorticoid Receptor (GR) at site 211 and promotes nuclear localization of GR which in turn as a transcriptional activator.
- Selinexor causes nuclear retention of phosphorylated GR since GR is a XPO1 cargo.
- Combination of selinexor and dexamethasone increases transcriptional activity of GR.
- Selinexor and dexamethasone treated together inhibit the transcriptional activity of NFB better than the single agents.
- Cancer cytoxic effects of selinexor and dexamethasone combination are dependent on the expression of GR. MM cells which do not express GR are resistant to dexamethasone and show no additive/cytoxic effects of combining selinexor with dexamethasone.
- The mRNA levels of genes transcribed by GR are regulated in an additive manner by the combination of selinexor and dexamethasone.
- MNK2 RNA is processed by alternative splicing to form two isoforms: MNK2a and MNK2b.
- Intriguing combination treatment induces the tumor suppressor MNK2b isoform.
- In vivo studies of H929 MM model system in mice showed that the combination treatment of selinexor and dexamethasone led to statistically significant reduction in tumor growth.
- These studies demonstrate that selinexor plus dexamethasone combination is synergistic in MM preclinical models, which provide mechanistic understanding of action and suggest that such a combination treatment will result with synergistic therapeutic outcomes in cancer patients.

Contact information: Trinayan Kashyap
Email: trinayan@karyopharm.com