Preclinical activity in non-Hodgkin’s lymphoma of selinexor, a Selective Inhibitor of Nuclear Export (SINE), is enhanced through combination with standard-of-care therapies.

ABSTRACT

Introduction: The nuclear export protein Exportin 1 (XPO1) is overexpressed in diffuse large B-cell lymphoma (DLBCL), follicular lymphoma cell lines have been previously developed at Wayne State University. All lines are GCB type with the exception of OCI-LY3 (ABC), WSU-DLCL2 (neither) and A3/KAW (unknown). Cell growth inhibition was performed using trypan blue viability assay and MTT values were calculated using GraphPad Prism software. Apoptosis was detected using Annexin V FITC assay. Changes in protein expression was evaluated using western blotting. For xenograft model of DLBCL, pieces of serially passaged WSU-DLCL2 tumors were transplanted into the flanks of 4-5 wk old ICR-SCID mice and vehicle or drug treatments were started one week later. 10X10 (~50 mg) of serially passaged WSU-DLCL2 tumors were transplanted into the tail veins of ICR-SCID mice and vehicle or drug treatments were started one week later.

METHODS

Methods: Diffuse large B cell lymphoma (WSU-DLCL2) and follicular small cleaved cell lymphoma (WSU-FSCCL) cell lines were inoculated IV in the tail veins of ICR-SCID mice and vehicle or drug treatments were started one week later. 10X10 (~50 mg) of serially passaged WSU-DLCL2 tumors were transplanted into the flanks of 4-5 wk old ICR-SCID mice and vehicle or drug treatments were started one week later. 10X10 (~50 mg) of serially passaged WSU-DLCL2 tumors were transplanted into the flanks of 4-5 wk old ICR-SCID mice and vehicle or drug treatments were started one week later.

RESULTS

Selinexor synergizes with either DEX or EVER. WSU-DLCL2 or WSU-FSCCL cells were incubated with 100 nM selinexor (SEL) or 100 nM dexamethasone (DEX) or 1.25 μM everolimus (EVER), each drug alone, SEL+DEX or SEL+EVER. [Left Panel] Resulting cell viability was determined using trypan blue staining and cell counting. [Right Panel] Annexin V FITC apoptosis assay (Sel 100 nM, DEX 100 nM and EV 2.5 μM).

CONCLUSIONS

The enhanced in vitro and in vivo efficacy of selinexor in combination with DEX or the mTOR inhibitor everolimus provides rationale for further clinical investigation.

Conclusion: Phase 2 study of selinexor in DLBCL is currently recruiting patients. (Study of Selinexor (KPT-330) in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma” SADAL – NCT02227251).

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