Clinical Implications of Targeting XPO1-mediated Nuclear Export in Multiple Myeloma

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Abstract

Multiple myeloma (MM) is a malignancy of plasma cells that is typically chronic, and relapse is common. Current therapeutic strategies include combination and sequential treatments with corticosteroids, alkylating agents, proteasomal inhibitors, immunomodulators, and monoclonal antibodies. These drugs prolong survival but ultimately become ineffective. Exportin 1 (XPO1), a nuclear export protein, is overexpressed in MM cells, and knockdown studies have suggested that XPO1 is essential for MM cell survival. Selective inhibitor of nuclear export (SINE) compounds are novel, orally bioavailable class of agents that specifically inhibit XPO1. Selinexor (KPT-330) is the first-in-human SINE compound. Early phase clinical trials have established the safety profile of this agent and have shown promising efficacy in combination with low-dose dexamethasone and other anti-MM agents. The combination of selinexor and dexamethasone has demonstrated activity in "penta-refractory" MM, (ie, MM refractory to the 5 most active anti-MM agents currently used in treatment). We have reviewed the available data on the molecular implications of XPO1 inhibition in MM. We also reviewed the pertinent early phase clinical data with SINE compounds and discuss management strategies for common toxicities encountered with use of selinexor.

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Introduction

Multiple myeloma (MM) is a clonal B-cell neoplasm of post-germinal center plasma cells.[1] MM develops from plasma cell cytogenetic abnormalities (ie, secondary IgH translocations, activation of NF-κB pathway, or p53 mutations), cell cycle dysregulation, changes to the bone marrow microenvironment, and clonal heterogeneity.[2,3]

The 5-year relative survival rates of MM have nearly doubled during the past 3 decades (26.3% in 1975 vs. 52.7% in 2009)[4] owing to advancements such as immunomodulatory/cereblon-binding drugs (IMiDs; thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (PIs; bortezomib, carfilzomib, ixazomib), and monoclonal antibodies targeting CD38 (daratumumab) and SLAMF7 (elotuzumab). These therapies complement the traditional use of high-dose chemotherapy followed by autologous hematopoietic cell transplantation.[5] Nevertheless, MM invariably relapses as tumor cells become refractory to successive regimens owing to the increasingly complex cytogenetics and clonal changes.

Selective inhibitor of nuclear export (SINE) compounds present a novel approach to specifically target clonal changes and drug resistance in MM. These compounds target exportin 1 (XPO1; also known as chromosome region maintenance 1 [CRM1]), a prominent nuclear exporter that controls the nuclear–cytoplasmic localization of many proteins. XPO1 is overexpressed in many cancers, including MM.[6,7] Selinexor (KPT-330) is a SINE compound that is currently in advanced clinical development for the treatment of relapsed/refractory MM (RRMM). We have outlined the mechanism of action of SINE compounds, summarized the available

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preclinical and clinical data, and discussed the management of drug toxicity in patients with MM.

Role of XPO1 in Cancer

Nuclear-cytoplasmic protein transport is fundamental to maintain normal intracellular signaling and cell cycle regulation. XPO1 is one of the best-characterized nuclear exporters, involved in the shuttling of > 200 nuclear export signal containing cargo proteins.[8,9] Figure 1A demonstrates the process of XPO1-mediated nuclear export. Importantly, it is the sole nuclear exporter of several classes of critical cancer-related proteins,[10] including (1) tumor suppressor proteins (TSPs; eg, p53, p73, adenomatous polyposis coli [APC], retinoblastoma [Rb], forkhead box protein O [FOXO], breast cancer 1 [BRCA1], nucleophosmin [NPM1], and merlin)[11-18]; (2) cell cycle regulators (eg, p21, p27, galectin-3, Tob)[19-22]; (3) immune response regulators (eg, inhibitor of NF-κB, IκB)[23]; (4) oncogenes (eg, BCR-ABL)[24]; and (5) chemotherapeutic targets (eg, DNA topoisomerases I and II).[25] In addition, XPO1 forms a complex with the messenger RNA (mRNA) cap-binding protein eukaryotic initiation factor 4E (eIF4E) to transport multiple oncoprotein mRNAs (eg, c-Myc, cyclin D1, MDM2) to the cytoplasm, promoting synthesis of oncoproteins.[26]

The enhanced export of tumor suppressor and regulatory proteins due to XPO1 overexpression can lead to aberrant cellular growth signaling and prevent apoptosis.[27] It is very likely that disruption of nuclear-cytoplasmic trafficking is oncogenic and serves as a mechanism for cancer cell evasion of cell cycle checkpoint controls and chemotherapeutic resistance.[10,28,29] The enhanced nuclear transport mechanism due to XPO1 overexpression has been identified in a variety of malignancies, including osteosarcoma, pancreatic cancer, ovarian cancer, glioma, leukemia, lymphoma, and MM.[30-38] Inhibition of XPO1 with SINE compounds is a therapeutic strategy to force nuclear retention of tumor suppressor proteins and growth regulators, resulting in cancer cell apoptosis.

Small Molecule Inhibitors of XPO1

Leptomycin B (LMB; Elactocin or CI 940), derived from *Streptomyces* sp., was the first and most widely studied nuclear export inhibitor (NEI) before SINE compounds.[10] An irreversible inhibitor of XPO1, LMB was found to have highly potent antitumor activity in various cell lines and murine xenograft models[39,40]; however, further development halted after a phase I clinical trial showed only modest efficacy with severe dose-limiting, acute toxicities.[41] Subsequently, semisynthetic derivatives of LMB (eg, anguinomycins),[42] natural LMB analogs (eg, goniothalamin),[43] and the synthetic LMB analog, KOS 2464,[40] demonstrated in vitro potency with narrow therapeutic windows but have not been studied in the clinical setting.

Ratjadone C, derived from myxobacterium *Sorangium cellulosum*, is another LMB analog with a potent inhibitory effect on XPO1.[44] To the best of our knowledge, it is the first NEI to be studied in MM cell lines. Turner et al[45] have demonstrated that human MM cell lines (HMCLs), NCI-H929 and RPMI-8226, treated with ratjadone C were fourfold more sensitive to apoptosis induction from topoisomerase IIα (TOP2A) inhibitors (doxorubicin and etoposide) as a result of blocked nuclear export of TOP2A.[45]

CBS9106 (SL-801) is a notable, orally available, synthetic compound that has been shown to exert nuclear export inhibition through depletion of XPO1 protein levels in multiple cancer cell lines, including HMCLs.[46] Bortezomib abrogates the effects of CBS9106, suggesting a role for the ubiquitin/proteasome pathway in CBS9106-mediated XPO1 degradation,[46] limiting the clinical potential of this combination (or with any other PI) in treating myeloma. CBS9106 is being studied in a phase I trial of patients with advanced solid malignancies (ClinicalTrial.gov identifier, NCT02667873). Comprehensive reviews of LMB and other NEIs have been previously reported.[40,47]

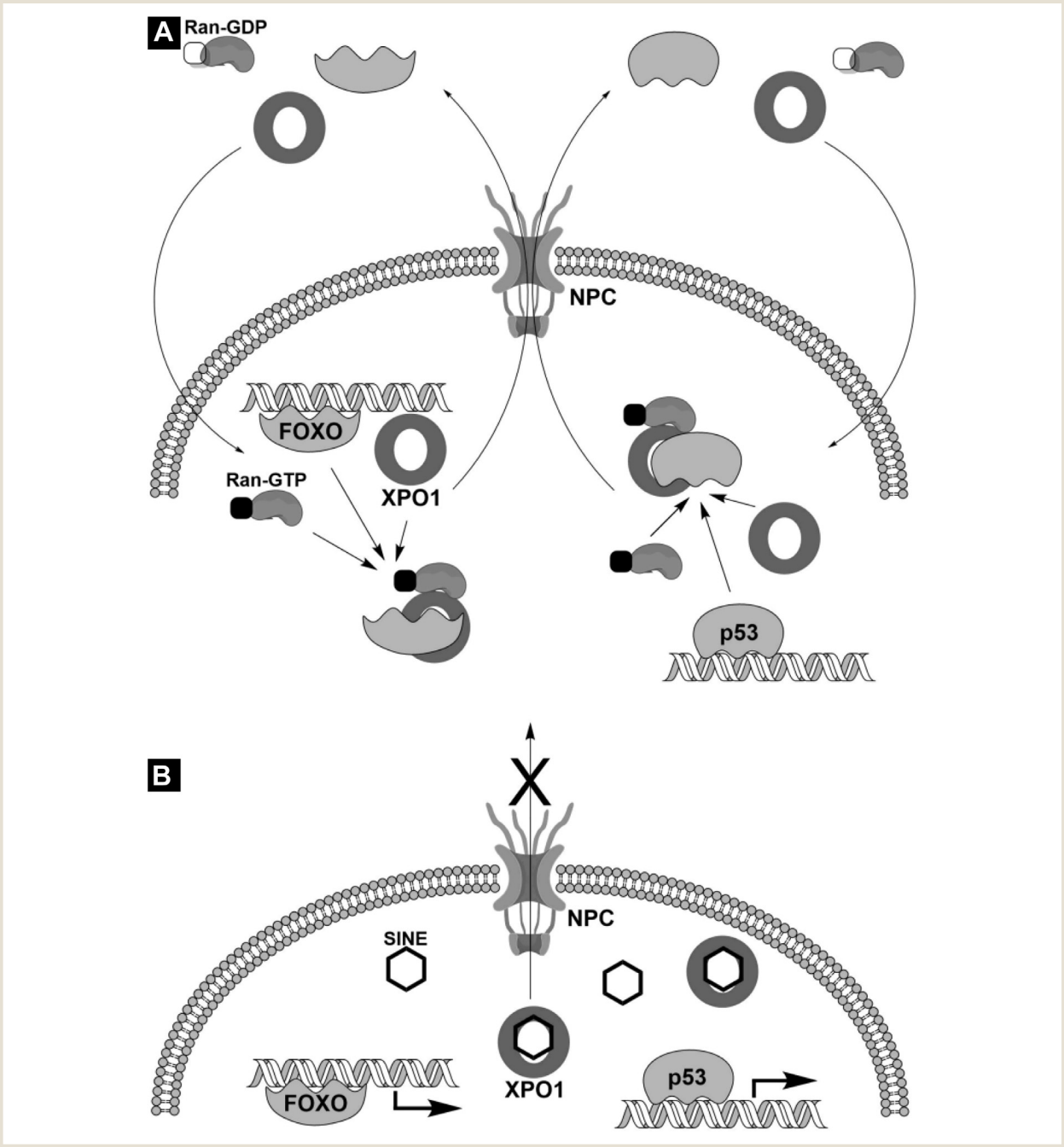
SINE compounds, including KPT-185, KPT-251, KPT-276, KPT-330 (selinexor), KPT-335 (verdinexor), and KPT-8602 (eltanexor), were developed through the combination of traditional structural-activity relationship and novel computational methods such as consensus induced fit docking.[7,48] These orally bioavailable compounds covalently bind to residue Cys^{528} in the cargo-binding groove of XPO1 in a slowly reversible manner, abrogating its nuclear transport activity (Figure 1B).[6] KPT-185 is a well-studied, potent in vitro SINE compound; however, it is limited by poor pharmacokinetics in vivo.[34,49] KPT-251 and KPT-276 are less potent analogs of KPT-185 with better oral bioavailability.[34,37,49] Selinexor is nearly as potent as KPT-185, has acceptable oral bioavailability,[50] and is currently in phase II/III trials in advanced malignancies. Eltanexor, a second-generation SINE compound with minimal blood–brain barrier penetration and improved tolerability profile in preclinical studies,[51] is currently in phase I clinical studies. Significant antitumor activity of SINE compounds has been reported in preclinical studies of solid organ malignancies such as pancreatic cancer,[52] breast cancer,[53] lung cancer,[54] renal cancer,[55] and melanoma,[56] as well as hematologic malignancies such as acute myeloid leukemia,[57] chronic lymphocytic leukemia,[34] and mantle cell lymphoma,[37] which have been reviewed previously.[6,7,58] In the present review, we have focused on the effects of SINE compounds in MM.

SINE Compounds Target Vulnerability of XPO1 in MM

A high-throughput small interfering RNA-based lethality screen using 3 HMCLs identified ~55 highly expressed MM survival genes, including *MCL1*, *RRM1 CDK11*, *TNK2*, 26S proteasomal subunits, and *XPO1*. Subsequently, XPO1 knockdown proved lethal in all 3 representative HMCLs evaluated (ie, KMS11, RPMI-8826, and JJN3).[59] Furthermore, increased XPO1 expression is present in $CD138^+$ plasma cells from patients with active MM and has been correlated with worse clinical outcomes.[36,60] These observations led to the investigation of the effects of XPO1 inhibition in MM.

KPT-276 reduced the viability of MM cells in vitro and ex vivo, with a median concentration at which 50% of the cells are inhibited of 160 nM.[36] When HMCLs were cocultured with bone marrow stromal cells or osteoclasts, SINE compounds induced cytotoxicity selectively in the MM cells, leaving the support cells intact and viable.[60] In vivo, treatment with SINE compounds decreased M-spike concentrations in the Vk*MYC mouse model,[36] which closely mimics human MM, and had a positive predictive value of

Figure 1 Exportin 1 (XPO1)-mediated Nuclear Export in Multiple Myeloma (MM)—Selective Inhibitor of Nuclear Export (SINE) Compound. (A) XPO1 Chaperones Nuclear Proteins Out of the Nucleus. Cargo Proteins Such as FOXO or p53 That Are Marked for Export From the Nucleus Bind a Pocket in XPO1 in the Presence of the Activated Small G-protein, Ran. The Active Ran-GTP:XPO1:Cargo Complex Is Exported From the Nucleus Through the Nuclear Pore Complex (NPC) Driven by the Concentration Gradient of Ran-GTP Across the Nuclear Membrane. Once in the Cytoplasm, Ran-GTP Is Hydrolyzed to Ran-GDP, and the XPO1:Cargo Complex Dissociates. (B) SINE Compounds (Hexagons) Bind to XPO1-Cys^{528} and Occupy the Cargo-binding Pocket of XPO1 and Prevent Formation of the Ran-GTP:XPO1:Cargo Complex. The Result Is Increased Nuclear Localization of Tumor Suppressor Cargo Proteins and Upregulation of Their Transcriptional Activity (Arrows)



67% for single-agent compounds in clinical trials.[61] In SCID-beige orthotopic mice, short-term oral treatment with SINE compounds (KPT-251 or KPT-276) decreased the tumor burden, translating into a significant survival benefit for the SINE compound-treated mice compared with the vehicle controls (33 or 35 days vs. 23 days, respectively; $P < .005$ for both).[60] Moreover, high-resolution computed tomography imaging of mouse vertebrae revealed that the bone lesions in the SINE compound-treated mice had nearly

resolved compared with the porous bones from tumor-burdened, vehicle-treated mice.[60]

Multiple mechanisms, some of which are interlinked, are implicated in how SINE compounds selectively activate caspases-3, -7, and -9 and induce apoptosis in MM cells. First, SINE compounds activate retinoblastoma, p21, and p27 and downregulate c-Myc and its related cell cycle regulatory genes, *CDC25A* and *BRD4*, causing MM cell cycle arrest in the G_1/S phase. This allows for apoptosis induction, possibly through the c-Myc-eIF4E axis, which is believed to operate in an XPO1-dependent, positive feedback manner.[36,62,63] Second, SINE compound treatment decreases levels of cell cycle promoters, such as cyclin D1, cyclin E, and CDK2/4/6, and antiapoptotic proteins, such as Mcl-1 and Bcl-xL, presumably through control of mRNA export by eIF4E.[36,60] An increase also occurs in the nuclear localization of CDK inhibitors p21 and p27 and TSPs, including p53, IκB, FOXO3A, and FOXO1A, which promote growth arrest and apoptosis in MM.[36,60] Activation of p53 leads to downregulation of both *XPO1* and *MYC* genes,[64] contributing to a positive feedback loop. In contrast, p53-independent mechanisms of SINE-mediated anti-MM activity have also been proposed. These include inhibition of NF-κB activation through IκB and an increase of PUMA (proapoptotic p53-upregulated modulator of apoptosis) through FOXO3A.[65-67] These mechanisms might be critical in MM cells harboring mutated p53 such as those with del(17p). Furthermore, by decreasing the secretion of inflammatory cytokines, such as interleukin (IL)IL-2, IL-10, vascular endothelial growth factor (VEGF), MIPIβ from bone marrow stromal cells, and blocking RANKL-induced NFATc1 induction in osteoclast precursors,[60] SINE compounds overcome the advantage of MM cells conferred by the tumor microenvironment. The molecular pathways affected by XPO1 inhibition using SINE compounds with or without other agents are listed in Table 1.

Preclinical Data With SINE Compounds Combined With Standard Anti-MM Agents

Dexamethasone

The glucocorticoid receptor (GR) is a potential XPO1-cargo protein, and the GR agonist, dexamethasone, inhibits NF-κB activity.[80] Selinexor blocks nuclear export of phosphorylated GR, enhancing GR transcriptional activation, and thus showing synergy with dexamethasone in the dexamethasone-sensitive MM1.S cell line and potent single-agent cytotoxicity in dexamethasone-resistant MM1.R (GR^{null}) and ANBL6 cell lines.[71] Genes that are synergistically upregulated by the selinexor-dexamethasone combination include (1) early growth factor 1 (*EGR1*), a TSP that downregulates survivin; and (2) glucocorticoid-induced leucine zipper (*GILZ*), which mediates the therapeutic effects of dexamethasone in MM.[72] The selinexor-dexamethasone combination has also been shown to repress the mTOR (mammalian target of rapamycin) signaling pathway through inhibition of a small G-protein, RHEB (Ras homolog enriched in brain), a known activator of the mTOR complex (mTORC1).[73] Overall, GR activity is amplified by the combined effects of selinexor-induced GR expression and nuclear translocation of activated GR coupled with dexamethasone-mediated GR agonism.

Table 1 Potential Pathways Affected by XPO1 Inhibition in Combination With Standard Therapies for Multiple Myeloma

Compound	Critical Genes With Localization Change	Molecular and Cellular Effects	Reference
SINE compounds (selinexor/KPT-330, KPT-185, KPT-276, KPT-8602)	p53	Upregulation of $p21^{Cip1}$ G_1 cell cycle arrest	60
	APC	Downregulation of Wnt/β-catenin	27,47
	pRB	Upregulation of $p27^{Kip1}$ G_1 cell cycle arrest	36, 60
	FOXO	Downregulation of the AKT/PTEN/mTOR growth signals; increase in PUMA	36, 60, 67
	NF-κB p65, IκB	Decreased DNA binding of NF-κB; decreased transcription of target genes (eg, ACP5/TRAP, integrinB3, ITGav, DC-STAMP)	60, 65, 66
	eIF4E	Downregulation of capped-dependent translation of select oncogenes (eg, Myc, CDC25A, BRD4, Bcl-2, Bcl-6, Mcl-1, Bcl-xL)	36,62-64,68-70
With dexamethasone	GR	Increase in GR protein in the nucleus (in particular, hypophosphorylated activated form) and transcription of REDD1, BCAT2, GILZ; downregulation of mTOR	71-73
	EGR1	Downregulation of survivin	72
With PIs (carfilzomib or bortezomib)	NF-κB p65, IκB	Decrease in NF-κB transcription Increased expression and nuclear localization of IκB leading to inhibition of NF-κB transcription	65, 66
		Activation of caspase-10; association with p62 and LC3 II	74
		Reduction in Bcl-2 expression and inactivation of AKT	74
With melphalan	p53, NF-κB, FANC/BRCA	Reverses melphalan resistance in MM cells through decreased NF-κB, decreased DNA repair through FANC/BRCA	75, 76
With doxorubicin	TOP2A	Upregulation of TOP2A-mediated DNA damage and apoptosis	77, 78
With panobinostat	DDR	DDR pathway genes downregulated	79

Abbreviations: APC = adenomatous polyposis coli; DDR = DNA damage response; EGR1 = early growth response 1; eIF4E = eukaryotic initiation factor 4E; GILZ = glucocorticoid-induced leucine zipper; GR = glucocorticoid receptor; MM = multiple myeloma; PIs = proteasome inhibitors; pRb = phosphorylated retinoblastoma; PUMA = p53-upregulated modulator of apoptosis; SINE = selective inhibitor of nuclear export.

Proteasome Inhibitors

SINE compounds (KPT-185 and selinexor) work synergistically when combined with the PIs bortezomib (combinatorial index, 0.41 and 0.502, respectively) and carfilzomib (combinatorial index, 0.322 and 0.482, respectively) to reduce viability of the human H929 MM cell line.[77] Mechanistically, this combination causes (1) reduced Bcl-2 expression and inactivation of Akt; (2) intracellular activation of caspase-10 protease-dependent apoptotic activity; and (3) novel association of autophagy-associated proteins p62 and LC3 II with caspase-10.[74] In addition, the in vitro efficacy of selinexor combined with PIs against acquired PI-resistant human MM cell lines (U266PSR and 8226B25), in vivo efficacy in NOD/SCID-gamma mice challenged with PI-resistant MM tumors, and ex vivo effect on MM cells from patients with disease refractory to PIs is explained by increased nuclear localization of IκB and complex formation with NF-κB, which led to a decrease in NF-κB transcriptional activity.[65,66]

Melphalan

Selinexor and eltanexor synergistically improve, not only the response in de novo (H929, 8826, U266) cell lines with melphalan treatment, but also resensitized melphalan-resistant (8226LR5 and U266LR6) cell lines to melphalan.[75,76] This effect was also observed in vivo using NOD/SCID-γ mice with U266 xenograft tumors and ex vivo in $CD138^{+}/LC^{+}$ MM cells from patients with newly diagnosed MM and those with RRMM. This synergistic mechanism reversing melphalan resistance is due in part to increased nuclear p53, decreased NF-κB, and decreased DNA repair proteins FANC/BRAC of the Fanconi anemia/BRCA pathway.[75]

Doxorubicin

Selinexor restores the sensitivity of pegylated liposomal doxorubicin (PLD) in doxorubicin-resistant 8226Dox6 and 8226Dox40 cell lines, in human MM cells from bone marrow samples, and in xenograft mouse tumor models.[78] By preventing the nuclear export of TOP2A, selinexor synergizes with PLD to induce TOP2A-mediated DNA damage and subsequent apoptosis.

Panobinostat

The histone-deacetylase inhibitor, panobinostat, increases the effectiveness of eltanexor (median concentration at which 50% of the cells are inhibited shifted from 50 nM to 23 nM) on MM1.S cell viability.[79] Gene expression profiling revealed an increased inhibitory effect of panobinostat on deacetylation by eltanexor, which coincided with increased DNA damage.[79] Overall, the combination is thought to promote significant chromatin remodeling in the presence of a compromised DNA damage repair pathway, which destabilizes the genomic integrity of MM cells.

Clinical Trials With SINE Compounds in MM—Efficacy Data

Selinexor has been investigated in phase I and II clinical trials, as a single agent and combined with conventional MM agents such as dexamethasone, bortezomib, carfilzomib, pomalidomide, liposomal doxorubicin, and others. Although many trials are ongoing, we now have published reports available from some of these studies. The efficacy data from clinical trials with SINE compounds in patients with MM are summarized in Table 2.

SINE Compounds Plus Dexamethasone

The results from the initial phase I study involving the use of a SINE compound in patients with MM were recently reported.[81] Of the 84 heavily pretreated patients (with a median of 6 previous regimens) in that study with dose-escalation and dose-expansion stages, 57 patients received single-agent selinexor at doses ranging from 3 to 60 mg/m^2 in various schedules with 6, 8, or 10 doses per 28-day cycle. The remaining 27 patients received a combination of selinexor 45 mg/m^2 (n = 12) or 60 mg/m^2 (n = 15) with 20 mg of

Table 2 Selected Clinical Trials With SINE Compounds in Relapsed/Refractory MM

Reference, Phase, Patients Evaluable (ClinicalTrials.gov)	Patient Characteristics, Risk Factors, MPT	Treatment	ORR (PR or Better), %
Chen et al[81]; phase I; n = 84 (NCT01607892)	Median age 62 y; 44 males; MPT, 6	Sel or Sel-Dex	50% (for Sel 45 mg/m^2 BIW + 20 mg Dex; n = 12); 4% (for Sel alone; n = 57); 0% (for Sel 60 mg/m^2 BIW + 20 mg Dex; n = 15)
Vogl et al[82]; phase IIb (STORM); n = 79 (NCT02336815)	Median age 63 y; quad-refractory, n = 48; penta-refractory, n = 31; high-risk cytogenetics, n = 17/39 evaluable (44%); 37 males; MPT, 7	Sel-Dex	21% (quad-refractory; n = 48); 20% (penta-refractory; n = 31); 33% (high-risk FISH; n = 18); median OS, 9.3 mo; (not reached at 15 mo for responders; 7.2 mo for nonresponders)
Chen et al[83]; phase Ib/II (STOMP); n = 10 (NCT02343042)	Median age 58 y; 7 males; MPT, 5	Sel-Pom-Dex	60% (1 CR, 5 PR); 50% in double-refractory patients
Jakubowiak et al[84]; phase I; n = 18 (NCT02199665)	Median age 63.5 y; CFZ-refractory, n = 11; CFZ/Pom/Dex-refractory, n = 8; MPT, 4	Sel-CFZ-Dex	63%, with 25% VGPR or better (Sel 60 mg BIW + CFZ 20/27 mg/m^2 + Dex 20/10 mg)
Bahlis et al[85]; phase Ib/II (STOMP); n = 22 (NCT02343042)	Median age 65 y; PI-refractory, n = 12; 12 males; MPT, 4	Sel-Bort-Dex	77% (1 CR, 5 VGPR, 11 PR); 58% among PI-refractory
Baz et al[86]; phase I; n = 11 (NCT02186834)	Median age 59 y; MPT, 5	Sel-PLD-Dex	2 VGPR, 2 PR, 2 MR, 3 SD, 1 PD
Cornell et al[87]; phase I/II; n = 36 (NCT02649790)	Median age 66 y; 23 males; MPT, 7	Elt-Dex	13% (overall); 29% (30 mg Elt QD×5 + 20 mg Dex BIW)

Abbreviations: BIW = biweekly; Bort = bortezomib; CFZ = carfilzomib; CR = complete response; Dex = dexamethasone; Elt = eltanexor; FISH = fluorescence in situ hybridization; MPT = median number of previous therapies; MR = minimal response; ORR = overall response rate; OS = overall survival; PD = progressive disease; PI = proteasome inhibitor; PLD = pegylated liposomal doxorubicin; Pom = pomalidomide; PR = partial response; QD×5 = 5 d/wk; SD = stable disease; Sel = selinexor; VGPR = very good partial response.

dexamethasone, each given twice weekly (BIW) in 28-day cycles. The cohort on the 45 mg/m^2 selinexor plus 20 mg dexamethasone combination had an overall response rate (ORR; partial response [PR] or better) of 50%, which included 1 complete response (8%) and 5 PRs (42%), and a clinical benefit rate (CBR; minimal response [MR] or better) of 58%. In contrast, the cohort treated with single-agent selinexor had an ORR of 4% (all PRs) and a CBR of 21%. Stable disease was noted in 31% of all the patients in the study, with nearly equal distribution among all the cohorts. With the better tolerability compared with 60 mg/m^2 selinexor, that study identified a recommended phase II dose of selinexor of 45 mg/m^2 (equivalent to a flat dose of 80 mg) with 20 mg of dexamethasone, each given twice weekly.

Vogl et al[82] investigated the combination of selinexor (80 mg BIW for 6 or 8 doses per 28-day cycle) plus dexamethasone (20 mg BIW) in a phase II trial (STORM trial). Of the 79 patients, 48 had disease refractory to bortezomib, carfilzomib, lenalidomide, and pomalidomide (quad-refractory), and 31 also had disease refractory to an anti-CD38 antibody (penta-refractory). The ORR (PR or better) for all patients was 21%, including 5% of patients with very good partial responses (VGPRs). The ORR was 21% in the quad-refractory subset and 20% in the penta-refractory subset. Responses were rapid, with 22 of the 26 responders (85%) achieving at least a MR within their first cycle of treatment. Although the median duration of response among those who responded was 5 months, the median progression-free survival and median overall survival was 2.3 and 9.3 months for all patients, respectively. Of the responding patients, 65% were alive at 12 months. Furthermore, of 41 patients who had had baseline cytogenetics assessed, the ORR for the 18 patients with high-risk cytogenetics was 33%. Three of the 12 patients with a 17p abnormality responded to selinexor-dexamethasone (ORR, 25%).[82] The synergy of SINE compounds with dexamethasone is consistent with preclinical mechanistic studies.[71-73]

Cornell et al[87] reported preliminary results with the second-generation SINE compound, eltanexor, at the American Society of Hematology annual meeting in 2017. In this ongoing phase I/II dose-escalation trial, eltanexor was orally dosed daily for 5 consecutive days per week in a 28-day cycle with a starting dose of 5 mg. Dexamethasone 20 mg BIW was permitted after cycle 1 if at least a MR was not observed. Thirty-one patients had evaluable responses at the time of the study report. The ORR was 13% (10% PR, 3% VGPR), and the CBR was 45%. Among the 7 patients who received 30 mg eltanexor for 5 consecutive days per week plus 20 mg dexamethasone BIW, the ORR was 29% (all PRs), with a CBR of 71%.[87] Improved efficacy and tolerability were observed when 20 mg of dexamethasone BIW was added to the eltanexor regimen.

SINE Compounds Plus PIs

The ongoing phase Ib/II multiarm STOMP study is assessing the efficacy and safety of selinexor-dexamethasone combined with various backbone treatments, including PIs and IMiDs for patients with RRMM. The preliminary results from the on-going combination trial with bortezomib and pomalidomide were presented at the 2016 American Society of Hematology annual meeting. Bahlis et al[85] reported the findings from the arm that combined selinexor-dexamethasone with bortezomib. Twenty-two patients were enrolled, with a median of 4 previous treatment regimens (range, 1-12). Selinexor was dose escalated in once weekly (QW, starting at 80 mg and 100 mg) or BIW (starting at 60 mg or 80 mg) dosing schedules. Bortezomib (1.3 mg/m^2 subcutaneously) was administered primarily QW; 3 patients initially received bortezomib BIW, but their dosing frequency was reduced to QW within 3 weeks. Dexamethasone was given orally 40 mg QW or 20 mg BIW. The ORR was 77%, with 27% of patients achieving a VGPR or better. In the 12 patients with disease refractory to PI-based regimens before enrollment, the ORR was 58%. The ORR was 100% in those patients who either had disease not refractory to bortezomib ($n = 7$) or that was naive to PIs ($n = 3$). Ten patients continued in the study for > 4 months, with the longest response of > 9 months.[85]

Another phase I trial presented by Jakubowiak et al[84] evaluated the combination of selinexor-dexamethasone with carfilzomib (CFZ) in patients with heavily pretreated, CFZ-refractory MM.[84] Patients received oral selinexor (30-40 mg/m^2 or a 60-mg flat dose on days 1, 3, 8, 10, 15, and 17), intravenous CFZ (20-56 mg/m^2 on days 1, 2, 8, 9, 15, and 16), and dexamethasone (20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23 for cycles 1-4 and 10 mg for subsequent cycles) in 28-day cycles. Sixteen of the 18 patients enrolled were evaluable for response. All evaluable patients had had MM refractory to CFZ and 11 had had MM refractory to a CFZ-based combination as their last line of therapy. The responses were rapid, with 75% achieving at least a MR after cycle 1. The ORR included 25% VGPR or better, 63% PR or better, and 75% MR or better. Also, in those patients with MM refractory to their last line of a CFZ combination, these rates were nearly identical (ie, 18%, 64%, and 73%, respectively).[84]

SINE Compounds Plus IMiDs

The preliminary results of the combination arm of selinexor-dexamethasone with pomalidomide in patients previously treated with lenalidomide and ≥ 1 PI (another arm of the phase Ib/II STOMP trial) were reported by Chen et al.[83] Selinexor was dose escalated, starting QW at 80 mg or BIW at 60 mg, with all patients receiving pomalidomide (4 mg/d orally for days 1-21) and dexamethasone (40 mg QW in a 28-day cycle). Eleven patients were enrolled at the time of reporting, including five with MM refractory to both lenalidomide and bortezomib. Of the 10 patients with evaluable responses, 1 had a complete response and 5 had PRs (ORR, 60%), with a CBR of 90% (3 additional MRs). The ORR among the double-refractory cohort was 50%.[83]

SINE Compounds Plus PLD

Results from an ongoing phase I trial investigating the combination of selinexor-dexamethasone with doxorubicin (ClinicalTrials.gov identifier, NCT02186834) were presented at the American Society of Clinical Oncology annual meeting in 2016 by Baz et al.[86] Eleven patients, with a median of 5 previous lines of treatment, received "loading" doses of selinexor (40 mg/m^2 or 80 mg as a flat dose on days −14, −11, −7, −4, or −7 only) with dexamethasone, "induction" with PLD (20 mg/m^2), and selinexor-dexamethasone on day 1, followed by "maintenance" dosing with selinexor-dexamethasone on days 8 and 15 or 3, 8, and 10. Of the 10 evaluable responses, 2 were VGPR, 2 were PR, 2 were MR, 3 were stable disease, and 1 was PD.[86]

Management of Selinexor Adverse Events in MM

The most common adverse effects can be broadly categorized into 3 groups: (1) cytopenias, (2) constitutional/gastrointestinal, and (3) hyponatremia. Providers using selinexor should be familiar with these toxicities and management strategies. Each of these adverse events experienced in MM patients is discussed and have been summarized in Table 3.

Cytopenias

Thrombocytopenia is the most common hematologic toxicity associated with selinexor treatment, with grade ≥ 3 toxicity (platelet count < 50,000/mm^3) occurring in 40% to 60% of MM patients (Table 3), which is more common than in patients with other indications.[71,88-93] This is a dose-dependent effect, with significant differences observed between ≤ 40 mg/m^2 and ≥ 60 mg/m^2 BIW doses of selinexor.[90] The mechanism driving this thrombocytopenia has been shown to be the result of slow megakaryocyte (MK) maturation by selinexor rather than a direct cytotoxic effect on the megakaryocytes or platelets.[94] Specifically, selinexor inhibits thrombopoietin (TPO)-mediated MK maturation by way of abnormal accumulation of phosphorylated STAT3 in the MK nucleus (Figure 2).[94]

The recently reported phase II STORM study reported dose interruption, dose reduction, and drug discontinuation rates of 52%, 37%, and 18%, respectively, for adverse events in general; data specific for thrombocytopenia were not reported.[82] This implies that in nearly one half of the cases, close monitoring of platelets is sufficient for management in the absence of clinically significant bleeding. From data derived from a selected group of patients from a phase I trial of solid malignancies who developed grade 4 thrombocytopenia during selinexor treatment, Machlus et al[94] reported that drug interruptions of 8 to 16 days (ie, ~3-6 missed doses) led to improvements in platelet counts, with greater recovery after 19 to 21 days. According to the STORM study, 13% of patients (10 of 79) received TPO mimetics (romiplostim or eltrombopag).[82] Prospective data on the effects of dose interruptions, the optimal duration of the interruptions, and the efficacy and optimal dosing of TPO mimetics are lacking. Potential financial restrictions and the risks of thrombosis and myelofibrosis[95,96] should also be considered with these agents. TPO agonists require a minimum of 5 days to boost platelet production and reach maximum efficacy at ~12 days.[94,97] Platelet transfusions might be warranted if an increase in the platelet count is required more urgently. Because selinexor does not affect mature platelets,[94] no evidence has shown that selinexor has an effect on the efficacy of platelet transfusions.

Despite the relatively high incidence of grade ≥ 3 thrombocytopenia with selinexor, the results from phase I and II trials of MM have shown that bleeding events are rare; grade ≥ 3 bleeding occurred in 3% of patients.[81,82] Moreover, the induced platelet decline reaches its maximum (usually 50% of baseline levels) by ~3 to 4 weeks, with no subsequent decrease observed for ≥ 4 months with uninterrupted selinexor treatments.[94] This low but persistent platelet count has been speculated to be a result of a TPO-independent pathway that is active even when TPO-mediated MK differentiation is blocked by selinexor treatment.[94] However, caution should be used with patients receiving anticoagulants or those undergoing invasive procedures owing to the greater risk of hemorrhage with underlying significant thrombocytopenia.

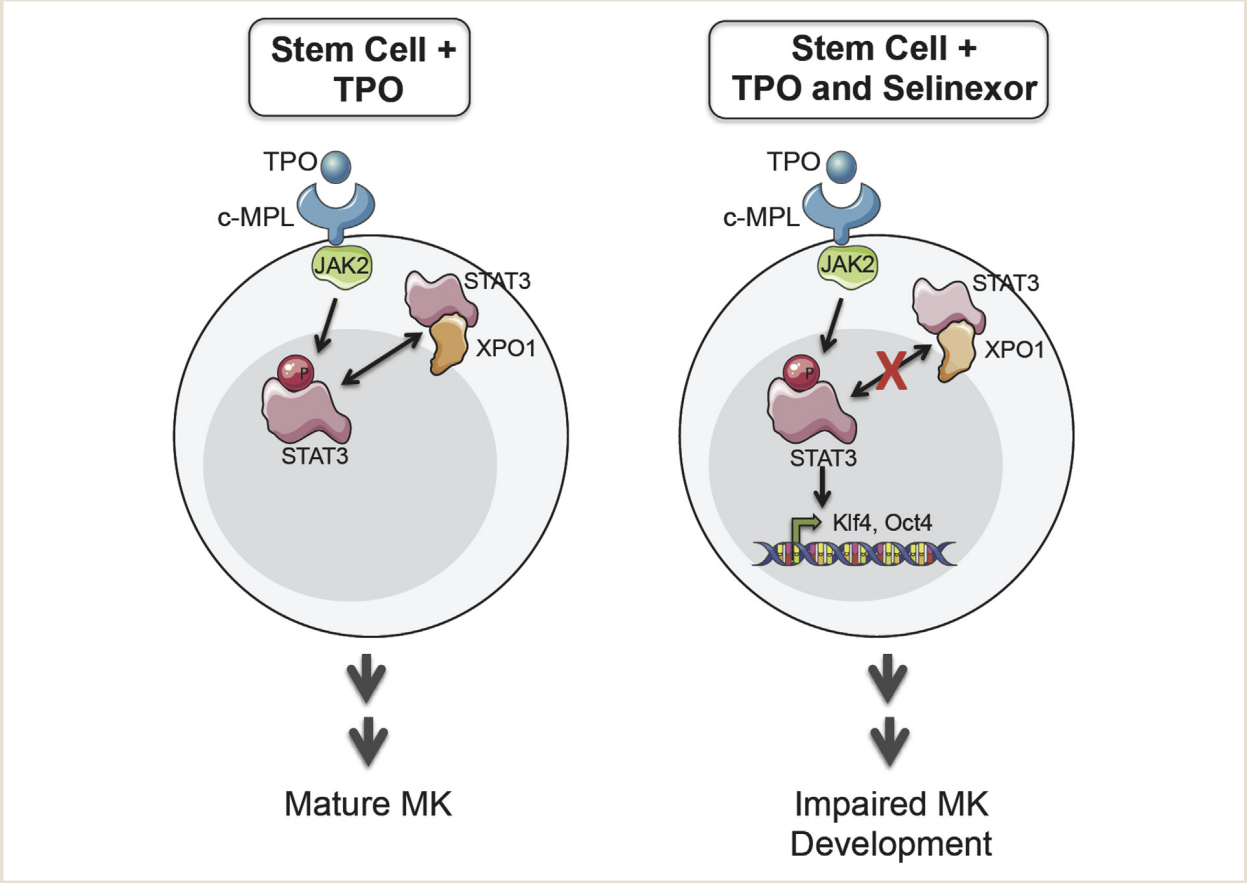
Neutropenia (grade ≥ 3) occurs in ~20% to 25% of patients receiving selinexor. To mitigate the risk of infection, the use of granulocyte colony-stimulating factors (GCSFs) should be considered. In the STORM study, 23% patients received filgrastim to increase the absolute neutrophil count.[82] No additional adverse effects have been reported with the combination of GCSFs and selinexor. Should an infection be present, it has been recommended selinexor be withheld until resolution or clinical stabilization. In cases of persistent or grade ≥ 3 neutropenia despite GCSFs, selinexor should be withheld until improvement and restarted at a lower dose level and/or frequency. Opportunistic infections in patients receiving selinexor have been uncommon, and no specific prophylactic measures have been recommended.

Table 3 Selinexor Adverse Effects (Grade ≥ 3)

Phase	Selinexor Doses; Patients, n	Safety, Percentage of ≥ Grade 3 AEs (≥ 5%)
Phase I: Sel (± Dex) in MM and WM patients[81]	3-60 mg/m^2; 84	Thrombocytopenia (45%), hyponatremia (26%), neutropenia (23%), anemia (23%), fatigue (13%), leukopenia (8%), dehydration (5%), diarrhea (5%)
	3-40 mg/m^2; 44	Thrombocytopenia (39%), hyponatremia (25%), neutropenia (23%), anemia (18%), leukopenia (7%), fatigue (5%), diarrhea (5%), dehydration (5%)
	45 mg/m^2; 25	Thrombocytopenia (60%), anemia (28%), fatigue (28%), hyponatremia (20%), neutropenia (20%), leukopenia (12%), muscle weakness (8%)
	60 mg/m^2; 15	Hyponatremia (47%), thrombocytopenia (40%), anemia (27%), neutropenia (27%), nausea (13%), fatigue (13%), anorexia (7%), vomiting (7%), diarrhea (7%), dehydration (7%), leukopenia (7%), confusion (7%)
Phase II (STORM): Sel-Dex in MM patients[82]	80 mg; 79	Thrombocytopenia (59%), anemia (28%), neutropenia (23%), hyponatremia (22%), fatigue (15%), leukopenia (15%), lymphocytopenia (11%), nausea (8%), diarrhea (5%)
	80 mg, 6 doses/cycle; 51	Thrombocytopenia (61%), anemia (33%), neutropenia (24%), hyponatremia (20%), leukopenia (16%), lymphocytopenia (14%), fatigue (8%), nausea (6%)
	80 mg, 8 doses/cycle; 28	Thrombocytopenia (57%), hyponatremia (25%), neutropenia (21%), anemia (18%), leukopenia (14%), fatigue (14%), nausea (11%), diarrhea (11%), lymphocytopenia (7%)

Abbreviations: AEs = adverse events; Dex = dexamethasone; MM = multiple myeloma; Sel = selinexor; WM = Waldenström's macroglobulinemia.

Figure 2 Proposed Schematic for Thrombocytopenia With Selinexor Use. Nuclear Export of STAT3 by Exportin 1 (XPO1) Is Essential for Maturation of Megakaryocyte (MK) From Its Precursor Hematopoietic Stem Cell (HSC), Which Takes Place in a Thrombopoietin (TPO)-activated State. Inhibition of XPO1 by Selinexor Leads to Forced Nuclear Localization of Phosphorylated STAT3 (pSTAT3), Which, in Turn, Induces Significant Expression of Downstream Targets *Klf4* and *Oct4*, Which Block HSC Differentiation and Maturation Into MK in the Presence of TPO Pathway Activation



Reprinted, with permission, from Machlus et al.[94]

Constitutional/Gastrointestinal

Selinexor results in a greater rate and severity of constitutional symptoms than those observed in many patients treated with currently approved anti-MM therapies. Constitutional adverse events include fatigue (63% for all grades, 15% for grade $\geq$ 3), anorexia (49% for all grades, 3% for grade $\geq$ 3), weight loss (33% for all grades, 1% for grade $\geq$ 3), and dysgeusia (taste alteration; 11% for all grades, 0% for grade $\geq$ 3), as reported in the phase II STORM study.[82] In addition, gastrointestinal symptoms include nausea (73% for all grades, 8% for grade $\geq$ 3), diarrhea (43% for all grades, 5% for grade $\geq$ 3), and emesis (44% for all grades, 4% for grade $\geq$ 3). Although most of these were grade $\leq$ 2, the persistence of such low-grade toxicities can affect patients' quality of life and make continuation of therapy challenging for some patients. Approximately 18% of patients require drug discontinuations as a result of some toxicity.[82] Similar rates have been reported in trials involving patients with solid tumors; the most common reasons for withdrawing consent were fatigue, nausea, and vomiting.[90]

During clinical trials, several strategies have been implemented to mitigate and manage these side effects. The routine use of dexamethasone as a part of treatment not only improved gastrointestinal symptoms but also increased overall efficacy.[81,82] Selinexor carries a moderate emetogenic risk, and it is recommended that patients receive antiemetics routinely during treatment. All patients in the phase II study received a 5-HT3 antagonist (eg, ondansetron) that was administered before the first treatment and continued daily as needed.[82] Breakthrough antiemetics should also be made available and can include phenothiazines (eg, prochlorperazine), benzodiazepines (eg, lorazepam), atypical antipsychotics (eg, olanzapine), or scopolamine. One and two additional antiemetics were required by 14% and 5% of patients, respectively.[82] Different combinations should be considered to optimize symptom relief, and monitoring for QT interval prolongation should be used depending on the agents given; selinexor has no known effect on the QT interval. Given the ability of selinexor to penetrate the blood–brain barrier, it is believed that some of these gastrointestinal toxicities might be central nervous

system mediated. A combination of centrally acting agents such as olanzapine and progesterone analogs (eg, megestrol acetate) can be used to mitigate nausea, vomiting, and anorexia.[81] Thirteen percent of the patients in the STORM study received an additional appetite stimulant beyond the therapeutic dose of dexamethasone.[82] When using progesterone analogs, one should consider the small risks of thromboembolic events and edema.

Symptoms of fatigue, anorexia (including weight loss), and dysgeusia often occur early into treatment and usually lessen in severity after the first cycle. However, these symptoms can persist throughout the duration of treatment. The first step in managing fatigue is to optimize other potential contributing factors, including hydration status, anxiety/depression, anemia, sleep hygiene, caloric intake, micronutrient deficiencies, hypothyroidism, and other comorbidities. In some cases, the use of psychostimulants (eg, methylphenidate) could be an option. The treating physician should review the patient's other medications, physical activities, and energy conservation strategies. Supportive care consultation should also be considered. The patient's nutritional status and weight should be monitored throughout treatment. The addition of dietary supplements and consultation with a nutritional specialist should be incorporated early.

In many cases, the most effective treatment is a dosing holiday (drug interruption) from selinexor. The risks and benefits of temporarily holding selinexor should be carefully considered. Patients typically display an improvement in symptoms after ~2 weeks without treatment.[81] Selinexor can then be resumed at a lower dose level and/or frequency. The first cycle is often the most challenging with regard to gastrointestinal symptoms. Thereafter, due in part to patient/drug acclimation, dose and schedule modification, and aggressive supportive care, drug tolerability often improves. Also, the constitutional and gastrointestinal side effects appear to be reduced when selinexor is given QW (as opposed to BIW) in combination with other anti-MM drugs.[83,85]

Eltanexor, the second-generation SINE compound, has demonstrated a broad therapeutic window with reduced penetration of the blood–brain barrier across species (mouse, rat, monkey) compared with selinexor.[51] After oral administration, animals treated with eltanexor showed a lower percentage of body weight loss and improved food consumption than animals similarly treated with selinexor.[98,99] This might allow for the more frequent dosing of eltanexor, enabling a longer period of exposure at higher levels than is possible with selinexor. In the ongoing phase I/II study with eltanexor, grade $\geq$ 3 constitutional symptoms were relatively less common ($\leq$ 10%)[87]; more clinical data with this SINE compound will be required to make any substantial conclusions about its side effects profile.

Hyponatremia

Grade $\geq$ 3 hyponatremia (sodium $<$ 130 mmol/mL) occurred in ~25% to 47% of patients receiving selinexor in the phase I/II trials in MM.[81,82] These rates are higher than those reported in studies involving advanced solid cancers.[88,90] The potential causes of hyponatremia include low solute intake from anorexia, hypovolemic hyponatremia from dehydration, and/or hypervolemic hyponatremia from edema. Pseudohyponatremia from elevated M-protein and/or hyperglycemia should also be ruled out. Hyperglycemia-induced hyponatremia should be considered, because the activity of corticosteroids (eg, dexamethasone) can be augmented by the effects of selinexor on the GR transport. However, in most patients treated with the combination of selinexor-dexamethasone, hyperglycemia has not been reported. A more direct effect of selinexor on sodium transport (eg, by nuclear export modulation of regulators of sodium transport) cannot be ruled out. The underlying etiology for hyponatremia should be determined by clinical assessment and measurements of urine and serum sodium and osmolality, with treatment tailored accordingly. A careful review of the patient's diet and medications, including an assessment of diuretics (particularly thiazide) and diabetic treatments, should be conducted. Other potential causes such as thyroid or adrenocortical hypofunction should also be considered. Hyponatremia due to the syndrome of inappropriate antidiuretic hormone has not been reported with selinexor treatment. Salt tablet supplements can be effective in patients with recurrent hyponatremia. In the STORM study, 6% of the patients received salt tablets.[82] Hyponatremia was reported as a serious adverse event in 2 patients in that study.[82] In most cases, hyponatremia will be asymptomatic and can be mitigated with the appropriate interventions.[81]

Conclusion

Inhibition of XPO1-mediated nuclear export of critical cargo proteins such as p53, p73, p21, IκB, FOXO3A, BRCA1, TOP2A, and GR with orally bioavailable SINE compounds represents a novel approach to target MM. Although SINE compounds have been found to have synergistic anti-MM effects when studied in combination with several agents approved for use in MM, they might also resensitize resistant MM cells to conventional agents, such as melphalan and proteasome inhibitors. The promising results from the early phase STORM and STOMP trials that demonstrated efficacy of selinexor-dexamethasone and other anti-MM agent combinations in the heavily treated, quad-, or penta-refractory MM patients have led to a larger randomized controlled trial to evaluate the addition of selinexor to the standard bortezomib-dexamethasone regimen (BOSTON trial; ClinicalTrials.gov identifier, NCT03110562).

Given that XPO1 is such a pleiotropic target, it was not surprising to observe a relatively high incidence of treatment-related adverse events, which most notably include thrombocytopenia, fatigue, nausea, and hyponatremia, and major organ toxicities or peripheral neuropathy are very uncommon. Nevertheless, with close monitoring, dose and schedule modifications (eg, QW dosing), and aggressive supportive care, the rate of drug discontinuation for tolerability has been reasonably low in the phase I/II trials. Finally, ongoing research to identify better tolerated next-generation compounds (eg, eltanexor), biomarkers that predict response and/or tolerability, and a greater understanding of the molecular mechanisms by which MM cells might evade XPO1 inhibition will be important to optimize the risk/benefit profile of this novel class of anti-MM therapeutic agents.

Disclosure

W.S., E.B., and T.J.U. are employees and shareholders of Karyopharm. D.V. reports consultancy for Karyopharm. The remaining authors have stated that they have no conflicts of interest.

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