Review

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

Ujjawal H. Gandhi,[1] William Senapedis,[2] Erkan Baloglu,[2] Thaddeus J. Unger,[2] Ajai Chari,[3] Dan Vogl,[4] Robert F. Cornell[1]

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

[1]Division of Hematology and Oncology, Vanderbilt University Medical Center, Nashville, TN
[2]Karyopharm Therapeutics, Inc, Newton, MA
[3]Division of Hematology and Oncology, Mount Sinai Hospital, New York, NY
[4]Division of Hematology and Oncology, University of Pennsylvania, Philadelphia, PA

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Address for correspondence: Robert F. Cornell, MD, MS, Division of Hematology and Oncology, Vanderbilt University Medical Center, 777 Preston Research Building, Nashville, TN
E-mail contact: robert.f.cornell@vanderbilt.edu

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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