**Therapeutic Brief**

The potential of XPO1 inhibitor as a game changer in the relapsed/refractory setting of hematologic malignancies

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**Abstract:**

XPO1 is a transporter receptor protein that transports leucine-rich proteins from the nucleus into the cytoplasm through the nuclear pore complex. In hematologic malignancies, XPO1 is often overexpressed, leading to abnormal regulation of cell growth and apoptosis or abnormal cell cycle. Therefore, XPO1 inhibitors can be used as targeted drugs to block the transport of overexpressed XPO1, thus achieving the effect of treating malignant tumors of the blood system. We summarized the application of XPO1 inhibitor in clinical studies according to different hematologic malignancies, and reviewed its efficacy and toxicity.

**Key words:**

XPO1 inhibitor; hematologic malignancies; selinexor; targeted therapy

**Introduction**

The nucleus is an organelle that coats the genetic material with a double membrane, separating the transcription in the nucleus from the translation process in the cytoplasm. In order to achieve adequate cellular function, this spatial division of eukaryotic cells requires selective and efficient bidirectional transport of specific proteins and mRNAs through the nuclear pore complex (NPC) of the nuclear membrane. Macromolecule (>40 kDa) cargo passing NPCs requires specific transporter receptor proteins. The mammalian nuclear adhesin family is the main family of transporter receptor proteins, consisting of 20 members, including nuclear adhesin protein α (KPNA)1-6, nuclear adhesin protein β (KPNB)1, and exportin 1 (XPO1). Nuclear adhesins use the energy in the RanGTPase complex to insert or export them into or out of the nucleus, depending on the presence of precise transport signals, nuclear localization signals (NLS) or nuclear export signals (NES) in cargo proteins.

XPO1 is the main transporter receptor protein, through which leucine-rich protein enters the cytoplasm from the nucleus via NPCs. In the nucleus, XPO1 binds to NES-containing cargo and forms a ternary complex with RanGTP, passing through NPCs and entering the cytoplasm. The XPO1-Cargo protein, driven by GTP hydrolysis, contains almost all tumor suppressor proteins (TSPs; such as p53, Rb, BRCA1/2, APC, Survivin), cell cycle regulatory proteins (such as p21, p27, Galactin-3), glucocorticoid receptor (GR), and chemotherapy targets (such as DNA topoisomerase) [1-2]。

XPO1 mutations and/or overexpression have been reported in almost all malignancies and have been associated with enhanced extranuclear cargo transport, resulting in apoptotic inactivation, disrupted cell cycle regulation, abnormal cell growth signaling, impaired glucocorticoid signaling, and chemotherapy resistance. For example, repeated mutations in the highly conserved region of XPO1 contribute to the development of chronic lymphocytic leukemia (CLL), while overexpression of XPO1 is associated with solid tumors and hematologic malignancies [3-5]. XPO1 inhibitors in the treatment of malignant tumors, therefore, are of great clinical value. These inhibitors combine with XPO1 in a reversible way through covalent binding Cys528 residues in the tank, inactivating its nuclear transport function [6]. Studies have also found that XPO1 inhibitors preferentially destroy the 3D nuclear tissue of telomeres in tumor cells [7], which may be another way for XPO1 inhibitors to play a role. The selective inhibitor of nuclear export (SINE) compounds under study include KPT-185, KPT-251, KPT-276, KPT-335 (Verdinexor), KPT-8602 (Eltanexor) and KPT-330 (Selinexor). Selinexor has been approved on an accelerated basis by the US FDA in combination with dexamethasone for the treatment of relapsed/refractory multiple myeloma (MM) after four lines of treatment [8]. As the second generation of oral XPO1 inhibitor, eltanexor significantly reduces the permeability of brain tissue compared with selinexor, thereby reducing the side effects such as central nervous system-mediated anorexia and weight loss, and may have a better safety profile and wider therapeutic window [9]. In the following, the clinical progress of XPO1 inhibitors in different hematologic malignancies will be reviewed in detail.

**Application of** **XPO1 inhibitors in multiple myeloma**

In view of the considerable effect of XPO1 inhibitor in preclinical application, a number of subsequent clinical studies have been carried out, and the use of XPO1 inhibitors in MM patients have also shown a good response. Selinexor has a certain activity in patients with extremely refractory MM, and combined use of selinexor has shown that it makes some drugs that were previously insensitive to MM become sensitive again, showing a good characteristic of inducing re-sensitivity [10]. In addition, the second-generation XPO1 inhibitor, eltanexor, has gradually entered into clinical studies, and has shown considerable anti-tumor activity in patients with relapsed/refractory MM treated with end-line therapy [11].

**Selinexor plus dexamethasone**

There are many combinations of drugs, among which there are many studies on the combination of selinexor and dexamethasone. A phase I study [12] found that the overall response rate (ORR) of 84 RRMM and Waldenstrom macroglobulinemia patients treated with selinexor and dexamethasone was 10%, including 1 complete response (CR) and 7 partial response (PR). Median response time was 1 month (1-3 months) and median duration of response was 5 months (2-11 months). Minimal response (MR) was observed in an additional 13 patients (15%), with a clinical benefit rate (CBR) of 25%. Currently, there are mainly three categories of MM drugs on the market in China: proteasome inhibitors (PIs), IMiDs, and CD38 monoclonal antibody. Studies have shown that the median survival time of MM patients with refractory to all above drugs is only 1.3-3.5 months, with a very poor prognosis. In a multicenter phase II study [13], 122 patients of RRMM who failed the above three categories of myeloma drugs received selinexor and dexamethasone, among whom 32 (26%) had partial or better response, including two (2%) with stringent CR (sCR), 6 (5%) with very good partial response (VGPR) and 24 (20%) PR. Median progression-free survival (PFS) and overall survival (OS) were 3.7 and 8.6 months, respectively, significantly improving the prognosis of those end-line treated MM patients.

**XPO1 inhibitor plus proteasome inhibitors and dexamethasone**

Preclinical studies have shown that XPO1 inhibitor has synergistic effect with proteasome inhibitor and can induce MM to be re-sensitive to proteasome inhibitor. In a phase I study [14], 18 RRMM patients were treated with selinexor, ixazomib and low-dose dexamethasone (SId). Of the 14 evaluable patients, 2 had VGPR, 1 PR, 7 had stable disease (SD), and 4 had progressive disease (PD), with the longest response duration of 14 months. Another study [15] treated 21 RRMM patients with selinexor combined with carfilzomib and dexamethasone. The results showed that MR was 71%, PR was 48%, and VGPR was 14%. In addition, in the study where 42 patients treated with bortezomib (SVd) [16], overall response was achieved in 25 (63%) of the 40 evaluable patients, including 3 CR, 9 VGPR, and 13 PR, with a median PFS of 9 months. The data from these studies confirmed the synergistic effect observed between selinexor and proteasome inhibitors and obtained a better therapeutic effect, which provided a new therapeutic approach for RRMM patients.

**XPO1 inhibitor plus immunomodulatory drugs (IMids) and dexamethasone**

A number of previous studies and meta-analyses have shown that lenalidomide (the second generation of IMids) has a good synergistic effect with a variety of MM drugs, so the combined drug strategy based on lenalidomide is often recommended in RRMM patients. Darrell J White et al [17] used selinexor in combination with lenalidomide and dexamethasone (SRd) in 8 newly diagnosed patients with multiple myeloma. Of the 7 patients assessed for efficacy, 6 were effective (ORR 86%). In a previous study [18],18 RRMM patients received selinexor, lenalidomide and dexamethasone. Results of the 15 patients with evaluable efficacy, ORR was 73%, and ORR was 91% in the lenalidomide-sensitive group (n=11). Another study [19] used combination of selinexor, pomalidomide (the third generation of IMids) and dexamethasone (SPd) in 48 patients with RRMM. The ORR was 58% (7 cases of VGPR, 11 cases of PR) and the median PFS was 12.2 months in patients who were first treated with pomalidomide (N=31). Among the 13 patients refractory to lenalidomide/pomalidomide, the ORR was 31% (4 patients with PR) and the median PFS was 4.2 months. The above studies indicated that for patients with RRMM, the all-oral regimen SPd could achieve a lasting effect, and it had better remission rate and longer PFS in MM patients who were sensitive to IMids.

**XPO1 inhibitor plus other classifications of drugs and dexamethasone**

Currently, the treatment of MM has entered the era of monoclonal antibody, and the combined daratumumab based regimen has achieved good results in RRMM patients. A phase Ib study [20] used a combination of selinexor, daratumumab, and dexamethasone (SDd) in 25 RRMM patients previously exposed to proteasome inhibitors and IMids. Among the 19 daratumumab sensitive patients, the ORR was 74% (5 VGPR, 9 PR, 2 MR, 2 SD, 1 PD). In the 2 cases of daratumumab refractory MM, there were 1 case of PD and 1 case of SD. This study confirmed that SDd has great clinical application value in patients refractory to PIs/IMiDs. In addition, studies [21] have combined liposome doxorubicin with selinexor and dexamethasone in the treatment of RRMM. Among the 27 patients enrolled, ORR was 15%, and clinical benefit rate (MR or better) was 26%, suggesting that adding anthracyclines to the combination of XPO1 inhibitor and dexamethasone does not seem to further enhance the efficacy.

Therefore, the above studies indicated that the combination drug strategy based on XPO1 inhibitor brought new treatment options for RRMM patients and significantly improved the prognosis of patients with pan-drug resistant MM. Currently, clinical trials of XPO1 inhibitor is being carried out in newly diagnosed MM patients.

**The toxicity profiles of XPO1 inhibitor**

Common adverse reactions in patients treated with XPO1 inhibitors are: gastrointestinal tract reaction (anorexia, nausea, vomiting, diarrhea, constipation), hematology adverse reactions (thrombocytopenia, anemia, neutropenia and lymphopenia), mental status changes, fatigue, dizziness, insomnia, pneumonia, liver function abnormalities, and electrolyte disorder. Gastrointestinal adverse reactions can be alleviated by prophylactic megestrol acetate and ondansetron, and symptoms can be alleviated by reducing dosage or discontinuation of medication in patients with more severe adverse reactions. The second generation of oral XPO1 inhibitor, eltanexor, has significantly lower permeability of brain tissue than selinexor, and is therefore superior to selinexor in central nervous system-mediated side effects, such as anorexia and weight loss.

**Clinical trials of XPO1 inhibitor in the treatment of acute myeloid leukemia (AML)**

**XPO1 inhibitor monotherapy in AML**

XPO1 inhibitor monotherapy showed some anti-leukemia activity in AML patients. A dose-escalation study [22] included 95 patients with recurrent or refractory AML. Of the 81 evaluable patients, 11 (14%) achieved objective remission (OR), including 5 patients with CR and 2 patients with CR and incomplete peripheral blood cell count recovery (CRi). Median PFS (5.1 versus 1.3 months) and OS (9.7 versus 2.7 months) showed significant improvements compared to non-responders. The results of this study indicate that selinexor is safe and effective as monotherapy for patients with recurrent or refractory AML.

**XPO1 inhibitor based combination therapy in AML**

Combined use of XPO1 inhibitor showed better disease control than monotherapy. A study [23] combined selinexor with decitabine in 25 patients with refractory/relapsed AML (n=20) or previously untreated older adults (> 60 years old) (n = 5). Ten patients responded to treatment (40%), and of the five elderly, four responded to treatment. PFS and OS for patients with response were 11.8 and 12.9 months, respectively, compared with 4.4 and 5.9 months, respectively, for non-responders. This study demonstrated that the combination of selinexor and decitabine resulted in higher ORR, and this combination significantly improved therapeutic response, especially in newly diagnosed elderly patients. In the study of combination of selinexor and sorafenib, a significant apoptosis-inducing effect was also found, and patients with resistance to FLT3 inhibitor also had a better CR rate (45%) [24]. There are many studies on selinexor combined with cytarabine and other drugs. In a study, 20 patients with newly diagnosed or recurrent/refractory AML were treated with selinexor combined with high dose cytarabine and mitoxantrone [25]. There were 10 cases (50%) of CR, 3 cases (15%) of CRi, 1 case (5%) of PR, 6 cases (30%) of PD, and 70% of ORR. Sweet, K et al [47] treated 21 high-risk AML patients with selinexor in combination with daunorubicin and cytarabine (7 + 3 regimen). Of the 19 evaluable patients, 10 (53%) achieved CR/CRi. There was no dose-restricted toxicity (DLT) during induction. This study confirmed a synergistic effect between selinexor and daunorubicin, and 80 mg of selinexor can be safely used in combination with a 7+3 induction regimen to treat patients with AML. Timothy S et al [26] applied 7 + 3 regimen combined with selinexor in elderly patients over 60 years old, and all patients taking selinexor achieved clinical response. Another study [27] used selinexor in combination with CLAG regimen to treat 40 patients with recurrent or refractory AML, and the results showed that 18 patients (45%) achieved CR or CRi, with a median remission period of 9.1 months, median PFS and OS of 6.1 and 7.8 months, respectively. The above study confirmed that the selinexor-based combination therapy in the treatment of patients with recurrent AML provided an effective and reasonable alternative for bridging transplantation.

**Use of XPO1 inhibitor in non-Hodgkin Lymphoma (NHL)**

In a preclinical study, Muqbil, I et al [28] combined Selinexor with dexamethasone in an animal model of NHL, and observed reduced expression of caspase-3 and significant reduction of XPO1 in the combined treatment group. In addition, studies have found that [29] selinexor can enable ibrutinib-resistant mantle cell lymphoma (MCL) to overcome drug resistance, which provides a new therapeutic approach for patients with ibrutinib-resistant MCL.

In clinical studies, XPO1 inhibitors have demonstrated long-lasting and effective antitumor activity. A phase I study [30] included 79 NHL patients, 47 of whom were in the dose escalation group, who received selinexor of 3-80mg/m2 for 3 or 4 weeks. Thirty-two patients in the extended cohort received either 35 mg/m2 or 60 mg/m2 Selinexor. Of the 70 evaluable patients, 22 (31%) received OR, including 4 CR and 18 PR. SD was obtained in 21 cases (30%) and disease control rate (DCR) was 61%. These results suggest that oral administration of selinexor 35mg/m2 is a safe treatment and has considerable anticancer activity in patients with relapsed/refractory NHL. A phase 2b study conducted in DLBCL included 110 patients [31] treated with 60 mg selinexor, administered twice a week, on a 28-day cycle. In the initial interim analysis of 32 patients, ORR was 34.4%(5 CR and 6 PR). The median duration of response (DOR) was 8.4 months, of which some CR lasted longer than 24 months, showing a profound and lasting response. Another study used the same medication regimen to treat 129 relapsed/refractory DLBCL patients who had previously received 2-5 lines of therapy, and got an ORR of 27.6% (14 CR, 21 PR). These results suggest the potential of selinexor as a new therapy for DLBCL. Currently, the US FDA has included the application of selinexor for treating patients with relapsed/refractory DLBCL who have received at least 2 lines of treatment before into accelerated approval. In addition, an isolated CNS relapse has been reported [32] in a patient with DLBCL, who was then given selinexor twice a week (day 1 and day 3) for oral administration of 60 mg/day. After 5 months of selinexor treatment, the patient's symptoms disappeared, and the MRI scan showed that the brain tumor had completely disappeared. This report demonstrates the permeability of selinexor to the central nervous system and its significant efficacy in the treatment of central nervous system DLBCL.

**Conclusions**

As a new targeted drug, XPO1 inhibitor has shown good anti-tumor activity in a variety of hematologic malignancies. Increasing clinical studies on XPO1 inhibitors are being carried out gradually. Selinexor, the first-generation XPO1 inhibitor, has been approved for use in RRMM and is about to be approved for treatment in relapsed/refractory DLBCL. The emergence of the second generation of XPO1 inhibitors provides a wider therapeutic window, and its lower central nervous system permeability supports a continuous medication approach, which will further improve the efficacy and safety of treatment. In conclusion, the advent of XPO1 inhibitors has brought new therapeutic options and may be a potential game changer for relapsed/refractory hematologic malignancies.

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