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BELINOSTAT: A HISTONE DEACETYLASE INHIBITOR FOR THE TREATMENT OF PATIENTS WITH RELAPSED OR REFRACTORY PERIPHERAL T-CELL LYMPHOMA

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ABSTRACT: Histone deacetylase inhibitors (HDACIs) are a group of agents that have exhibited antitumor activity *in vivo* and *in vitro*, directing to clinical trials estimating their efficacy in multiple cancer types. Belinostat is under global development with Spectrum Pharmaceuticals, currently approved by the U.S. Food and Drug Administration with indications for relapsed or refractory peripheral T-cell lymphoma on July 2014 and is under regulatory review in the Europe. Belinostat has been investigated as a single agent and in groups with further chemotherapies and biological agents, in the management of solid tumors and lymphoma. The main side effects are pyrexia, pneumonia, anemia, thrombocytopenia, neutropenia and fatigue, which are manageable. Belinostat is also being investigated in patients with bladder cancer, prostate cancer, solid tumor, mantle cell lymphoma, refractory advanced thymic epithelial tumors, pancreatic cancer and ovarian cancer. This article reviews the obtainable information on Belinostat with respect to its clinical pharmacology, mechanism of action, pharmacodynamics, pharmacokinetics, metabolism, preclinical studies and clinical trials.

INTRODUCTION: Lymphoma is a cancer of the lymphocytes (white blood cells) that comprise the lymphatic system. Lymphoma has mainly two forms, namely Hodgkin lymphoma and non-Hodgkin lymphoma [1]. Lymphomas of additional grown-up T-cells are known as 'peripheral T-cell lymphomas [2]. Peripheral T-cell lymphomas (PTCLs) include a varied group of unusual and aggressive syndromes in which the patient's T cells to be converted into cancerous cells. In Western countries, T-cell lymphomas report for between 10-15 percent of all non-Hodgkin lymphomas (NHLs) [3-5].

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Peripheral T-cell lymphomas are classified by the World Health Organization (WHO) into many categories which are mentioned in **Table 1.**

TABLE 1: CLASSIFICATION OF PERIPHERAL T-CELL LYMPHOMAS [45]

S. no.	Extranodal	Nodal
1	Mycosis fungoides	Angioimmunoblastic
2	Cutaneous anaplastic large cell	Peripheral T-cell, unspecified
3	Extranodal NK/T-cell	Anaplastic large T/null cell
4	Enteropathy type	Uncertain
5	Hepatosplenic	Blastic NK-cell
6	Subcutaneous panniculitis-like	

The occurrence of the additional general peripheral T-cell lymphomas, as originating in a great international cram, is shown in **Table 2**. Aberrant gene transcription is one of the main features of cancer. Regulation of gene transcription is managed by relations of a lot of progressions containing DNA methylation, histone tail

modification and RNA-associated silencing [6-8]. The acetylation and deacetylation properties of histone tails are attained by completing the action of acetylating enzymes, histone acetyl transferases and deacetylating enzymes histone deacetylases (HDACs) [6]. Histone deacetylases (HDACs) were primarily recognized as the target of trapoxin (natural product), which is responsible for separation of cancer cells and was employed as an affinity ligand to insert the target HDAC1 from the cell lysate [9] are responsible to catalyze the subtraction of acetyl fractions from lysine residues of histone proteins, dense chromatin and thus suppresses the transcription of connected genes. Deregulation in the look of HDACs has been associated with the growth of cancers [10]. The HDACs has two families, first is the Zn^{+2}-based HDAC family contained of category I (HDACs 1, 2, 3 and 8), category II a/b (HDACs 4, 5, 6, 7, 9 and 10), and category IV (HDAC 11) and second is Zn^{+2}-independent NAD-dependent category III SIRT enzymes. HDACs do not show their action independently, but somewhat in performance with multi-protein complexes [8, 11].

TABLE 2: RELATIVE FREQUENCY OF PERIPHERAL T-CELL LYMPHOMA (EXCLUDING ANAPLASTIC LARGE CELL) IN EIGHT COUNTRIES [5]

S. no.	City (Country)	PTCL/all NHL	Percent PTCL
1	Omaha (USA)	6/200	3
2	Vancouver (Canada)	3/200	1.5
3	Cape Town (South Africa)	16/18	8.5
4	London (UK)	11/119	9.2
5	Locarno (Switzerland)	5/79	6.3
6	Lyon (France)	10/192	5.2
7	Wurzburg (Germany)	9/203	4.4
8	Hong Kong (China)	36/197	18.3

1. History: Histone deacetylase inhibitors (HDACIs) are a group of agents that have exhibited antitumor action *in vivo* and *in vitro*, most important in clinical trials estimating their efficacy in various cancer types. HDAC inhibitors can induce apoptosis, cell cycle arrest and cellular differentiation, as well as inhibit angiogenesis. Various HDAC inhibitors have previously claimed a number of anti-tumor activities in both pre-clinical and clinical situations. A number of HDAC inhibitors are approved by the U.S. Food and Drug Administration to treat different types of cancer, such as romidepsin to peripheral T-cell lymphoma, vorinostat for cutaneous T-cell lymphoma [12-15]. More than a few chemical groups of HDIs have been developed. These consist of the short-chain fatty acids such as sodium butyrate, phenylbutyrate, pivanex, and valproic acid. Novel and extra selective groups consist of hydroxamic acids such as vorinostat, panobinostat, and dacinostat, Benzamides groups counting entinostat and mocetinostat, and the bicyclic depsipeptide such as romidepsin [16]. The structure of some HDAC inhibitors are given in **Fig. 1**.

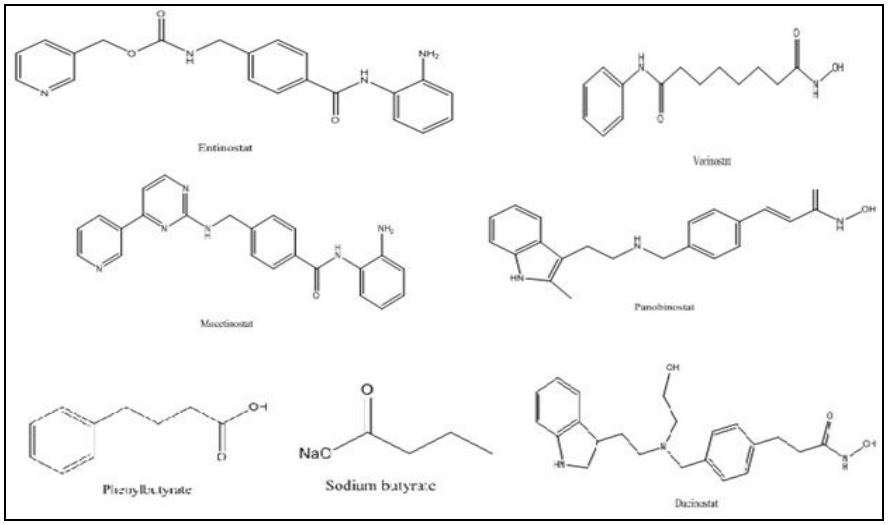

FIG. 1: STRUCTURE OF SOME HDAC INHIBITORS

On February 2010, Spectrum Pharmaceuticals and TopoTarget entered into a research and development agreement for belinostat providing exclusive development and marketing rights of Spectrum Pharmaceuticals North America, India and a choice for China in substitute for a truthful cash payment of $30 million, potential highlight payments of up to $320 million. Spectrum and TopoTarget will evenly sponsor improvement activities, whereby clinical trial prices will be 70% accepted by Spectrum and 30% by TopoTarget for novel trials to be started.

Spectrum Pharmaceuticals has presented a New Drug Application (NDA) with the FDA in 2011 because Belinostat shows the best potential in category HDAC inhibitor for both hematological and solid tumors [17].

Belinostat, a new intravenous, once daily component of the hydroxamate category of HDAC was developed by Spectrum Pharmaceuticals for the treatment of relapsed or refractory peripheral T-cell lymphoma [18]. On the basis of presented request, Recently in July 2014, belinostat was the histone deacetylase inhibitor to be approved in the USA for the treatment of mature patients with relapsed or refractory peripheral T-cell lymphoma, who did not obtain enhanced after handling with extra drugs or whose cancer came backside after management with other drugs. Belinostat gets European orphan drug designation for the treatment of malignant thymomas On July 17, 2013. Belinostat (PXD101) has a low molecular weight and a hydroxamic acid inhibitor of category I and II HDACs [19-22].

The purpose of this article is to review the offered information on Belinostat with respect to preclinical studies, clinical pharmacology, mechanism of action, pharmacodynamic and pharmacokinetic properties, results of various clinical trials, clinical efficacy for relapsed or refractory peripheral T-cell lymphoma, adverse-effect profile and dosage and administration. Data from studies using Belinostat in combination with other chemotherapeutic agents are also reported.

2. Molecule: Belinostat is a white to off-white crystalline solid with a molecular weight of 318.30 g/mol and molecular formula of $C_{15}H_{14}N_2O_4S$.

The structure of Belinostat is given in Figure 2. The chemical structure name is (2E)-N-hydroxy-3-[3-(phenylsulfamoyl) phenyl] prop – 2 - enamide. Belinostat has sparingly soluble in aqueous solutions, polyethylene glycol and freely soluble in ethanol. It has pKa values of 7.87 and 8.71 (in potentiometer), 7.86 and 8.59 (in UV). Belinostat is an originally developed HDAC inhibitor by using structural design stand on identifying natural HDAC inhibitor. Belinostat is a sulfonamide derivative and its molecule has a zinc-chelating hydroxamic acid group and like potency as additional HDAC inhibitors in its related category, such as vorinostat and trichostatin A. Belinostat is stored at room temperature 20-25^{0}c and excursions permitted to15^{0}C–30^{0}C [23-27]. Some of the main features of belinostat are given in **Table 3**.

TABLE 3: SOME MAIN FEATURES AND PROPERTIES OF BELINOSTAT

Features and Properties of Belinostat	
Alternative names	Beleodaq, PXD101
Category	Histone deacetylase inhibitors, hydroxamic acid derivatives
Mechanism of action	Inhibit hydroxamic acid of class I and II HDAC enzymes, produce cell cycle arrest or apoptosis
Route of administration	Intravenous infusion
Dose	1,000 mg/m^2
Pharmaceutical form	Injection
Pharmacokinetics	Rapid dose proportional absorption after IV administration, total mean clearance 1240 ml/min, half-life1. 1 hour, extensively bound to plasma proteins 92.9% to 95.8 %, metabolized in the liver. Approximately40% of the drug is excreted in renal and 2% in the urine.
Side effects	Pyrexia, pneumonia, infection and anemia, thrombocytopenia, multi-organ failure
Chemical name	(2E)-N-hydroxy-3-[3-(phenylsulfamoyl)phenyl]prop-2-enamide
Molecular weight	318.30 g/mol
Molecular formula	$C_{15}H_{14}N_2O_4S$
Solubility	Sparingly soluble in aqueous solutions, polyethylene glycol and freely soluble in ethanol
Color and phase	White to off-white crystalline solid

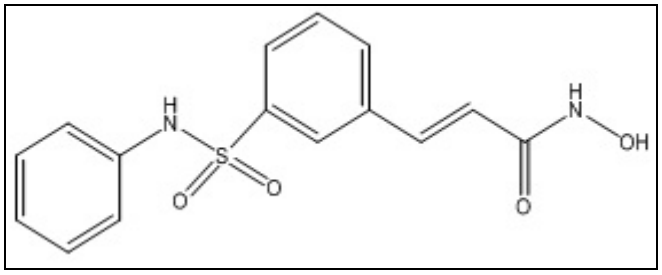

FIG. 2: STRUCTURE OF BELINOSTAT

2.1 Mechanism of Action: Belinostat acts by inhibiting potential of hydroxamic acid of class I and II histone deacetylase (HDAC) enzymes, which adjust acetylation intensities of histone and non-histone proteins. [28, 29] Acetylated histones and other proteins are accumulated by Belinostat by producing cell cycle arrest or apoptosis of various transformed cells *in vitro* [30]. HDACs can control the appearance of tumor suppressor genes and actions of transcriptional factors occupied in cancer instigation and progression through adjustment of DNA or the structural constituents of chromatin. So HDACIs are recognized to provoke cell death in malignant cells in the course of multiple mechanisms, counting up regulation of death receptors and initiation of cell cycle arrest [31, 32].

2.2 Preclinical studies: A preclinical study by Michael and Joanne reported that *in vitro and in vivo*, belinostat suppresses bladder cancer cell growth by using 5637, T24, J82, and RT4 urothelial cell lines (human urinary bladder carcinoma cell lines). All urothelial cell lines at 1–5 μM belinostat for 48 h generated a dose-dependent embarrassment of proliferation, by showing the most potent inhibitory result on 5637 cells. Minimum inhibitory result evaluated on RT4 cells [29]. Qian *et al.* reported anticancer activity of belinostat on prostate cancer.

In vitro, proliferation evaluations showed that belinostat potently reduced or inhibited the enlargement of prostate cancer cell lines (IC_{50} < 1.0 LM) and produced a cytotoxic effect to these cells by inducing G2/M arrest and increased the percentage of cells with subG1 DNA content. Belinostat also enhanced the appearance of p21 and reduced the appearance of potentially oncogenic proteins. Orthotopic prostate cancer tumor method showed that tumor growth (up to 43%) was inhibited by Belinostat [33].

Luca Paoluzzi *et al.* reported the effect of belinostat in Mantle Cell Lymphoma. *In vitro*, belinostat demonstrated concentration-dependent cytotoxic response against a group of MCL cell lines, namely HBL-2, Jeko-1, and Granta-519. Belinostat and bortezomib also stimulated strong mitochondrial membrane depolarization and apoptosis but no noteworthy apoptosis were monitored in peripheral blood mononuclear cells [32].

Dmitriy *et al.* performed *in vivo* and *in vitro* study for belinostat in pancreatic cancer. The cytotoxic effect of belinostst was performed on tumor cell lines, namely T3M4, AsPC-1 and Panc-1. In vitro and in vivo study, belinostat showed significant growth inhibition of PDAC cells by inducing apoptosis in a dose-dependent manner. Belinostat increased the apoptotic action of gemcitabine. Treatment with belinostat was responsible to increase the appearance of the cell cycle regulator such as $p21^{Cip1/Waf1}$ in Panc-1, and of acH4 in all cell lines investigated. The fall in xenograft cancer was related to embarrassment of cell proliferation [34].

Peter *et al.* performed long-term complete remission with belinostat in refractory peripheral T-cell lymphoma patients. Belinostat was administered at a dose of 1000 mg/m^2 for days 1 to 5 in a 21 day cycle. Belinostat treatment was abided and governs for 28 cycles.

Hematologic side effects were soft with no any toxicity additional CTC grade 2. However, after cycle 2 the patient developed nonhematologic toxicity (> 2 grade) [28]. *In vivo* study, Belinostat has showed action against both ovarian and colon cancer xenograft models with lacking significant toxicity in these murine cancer models. Belinostat exhibited additive to synergistic action when merged with standard cytotoxic agents, for example carboplatin and paclitaxel in ovarian cancer models [35].

2.3 Clinical trials: CLN-19 BELIEF study was a multicentre, single group and open label project in 129 R/R PTCL patients. On dose administration of Belinostat to the patients, the result was found that ORR in all PTCL patients was found to be 26%. 28% ORR was found in PTCL patients with platelet counts above 100,000/μL and 45.5% ORR

produced in that patients, those suffering with the PTCL subtype angioimmunoblastic T-cell lymphoma. In this study, the median duration of response was found to be 8.3 months and the longest median duration of response was 29.4 months. Belinostat was given to the patient as an intravenous infusion on a daily-for-5-days schedule [36].

The primary Phase I trial of belinostat was accomplished in patients with advanced solid tumors. In this trial, Belinostat showed the most frequent adverse events such as fatigue, nausea, vomiting and phlebitis but no grade 4 toxicities were watched. In Phase II trials, An MTD of 1000 mg/m^2/day was decided for progression [37].

A Multicenter Phase II Study of Belinostat was organized by National cancer institute on December 2007 for the treatment of thymus cancer and this had been completed on June 2014. This was Open Label, multicentre and single group job in 18 years of age or older patients with an advanced thymic tumor (ATT) that has evaluated after dealing with platinum-containing chemotherapy. Patients received 1000 mg/m^2/day as a 30 minute intravenous (IV) infusion every day for 5 days each 3 weeks (day 1-5 of the 3 week treatment cycle). After completion of 12 cycles of treatment, the cycles will be provided for 5 days every 4 weeks [38].

In the Phase II study, when Belinostat was administered to the patients by intravenously at 1gm/m^2 on days 1 to 5 of a 21-day cycle. 25 patients showed thymoma and 16 patients produced thymic carcinoma out of 41 patients. Two patients accomplished partial response. 13 patients achieved progressive disease and 25 accomplished stable disease. Treatment was well stranded with nausea, vomiting and fatigue [39].

Another Phase II study was performed with advanced multiple myeloma patients who take delivery of single belinostat for >2 cycles, there were 6 SD and 6 PD indicating that Belinostat therapy showed the effect in the stabilization of advanced and progressive disease. When belinostat administered with the combination of dexamethasone led to single MR as well as the lengthy interval of stable sickness, even in patients who have taken delivery of many dexamethasone courses of therapies [40].

Key clinical trials of Belinostat are given in **Table 4.**

TABLE 4: KEY CLINICAL TRIALS OF BELINOSTAT

S.no.	Study phase	Trial Identifiers	Company	Report	Status
1	I	NCT 00413075	CuraGen Corp.	Oral, PXD101 (Belinostat) in the treatment of advanced solid tumors	Completed
2	I	NCT 00336804	U. Chicago/NCI	Oral, combination with azaditidine in AML, ALL, APL, MDS and CML	Completed
3	II	NCT 00274651	CuraGen Corp.	Oral, Belinostat in CTCL, PTCL, non-Hodgkins lymphoma	Completed
4	I	NCT 00411476	MD Anderson/CuraGen Corp.	Oral, Belinostat in QD or BID in advanced solid tumors	Completed
5	I	NCT 00413322	CuraGen/TopoTarget A/S	Combination with 5-FU in advanced solid tumors and advanced colorectal cancer	Completed
6	I	NCT 00348985	U. Colo./NCI	Combination with bortezomib (PS-341) in advanced solid tumors and lymphoma, i.v. day 1–5 30 min infusion	Completed
7	I/II	NCT 00421889	CuraGen/TopoTarget A/S	Belinostat combination with carboplatin or paclitaxel in advanced solid tumors—ovarian, epithelial ovarian and fallopian tube cancers	Completed
8	I	NCT 00351975	U. Chicago/NCI	Combination with azacitidine (5-aza) in advanced hematological malignancies, CML, leukemia, MDS or MPD	Ongoing
9	I	NCT 00334789	CA Cancer Consortium/NCI	Combination with isotretinoin in metastatic or unresectable solid tumors	Ongoing
10	II	NCT 00357162	Mayo Clinic/NCI	MDS (i.v. days 1–5 30 min infusion)	Completed

11	II	NCT 00357032	CA Cancer Consortium/NCI	Relapsed or refractory AML or older patients with newly diagnosed AML (i.v. days 1–5 30 min infusion)	Completed
12	I/II	NCT 00321594	Cancer Therapeutics Research Group/NCI	Belinostat in liver cancer, unresectable HCC	Completed
13	II	NCT 00303953	SWOG/NCI	Belinostat in relapsed or refractory aggressive B-cell non-Hodgkins lymphoma	Completed
14	II	NCT 00365053	CA Cancer Consortium/NCI	Malignant mesothelioma	Completed
15	I	NCT 00301756		Platinum-resistant epithelial ovarian cancer and micro papillary/borderline (LMP) ovarian tumors	Ongoing
16	I	NCT 00354185	U. Wisconso/NCI	Combination with 17-AAG in metastatic or unrespectable tumors or lymphoma	Terminated
17	II	NCT00589290	NCI	To treat tumors of the thymus at an advanced stage	Completed
18	I	NCT00926640	Maryland/NCI	Combination With Cisplatin and Etoposide in Adults With Small Cell Lung Carcinoma and Other Advanced Cancers	Ongoing

2.4 Pharmacokinetics profile: Belinostat may enclose pitiable solubility and bioavailability problems [41, 42]. 30-35% an oral bioavailability was found in dogs [43]. In plasma, total mean clearance was found to be 1240 ml/min with a half-life (eliminated) of 1.1 hours, respectively. At steady state, the mean apparent volume of distribution of belinostat is coming close to total body water because it has limited distribution in body tissue. The plasma protein binding of belinostat is 92.9% to 95.8 % *in vitro* plasma study, and it is not concentration dependent [27]. Clearance was obtained rapidly, i.e. 425 mL/min/m^2 with a half life ($t_{1/2}$) of 1.0 h in rhesus monkeys [41]. Belinostat is metabolized in the liver.

Firstly, UGT1A1 is responsible for the metabolism of belinostat and tough UGT1A1 blockers are supposed to enhance exposure to it. Belinostat amide and belinostat acid are formed by CYP2A6, CYP2C9, and CYP3A4 enzymes in hepatic metabolism [27]. Approximately 40% of the belinostat dose is renally excreted; there are insufficient data to recommend a belinostat dose in patients with creatinine clearance ≤ 39 ml/min [44]. Belinostat is eliminated mostly during metabolism with a smaller amount of 2% of the dose recovered as unchanged in urine. After dose administration of belinostat, every one main metabolite such as methyl belinostat, belinostat amide, belinostat acid, belinostat glucuronide, and 3-ASBA are commonly excreted in urine within the first 24 hours. Belinostat glucuronide and 3-ASBA characterized the maximum parts of the belinostat dose excreted in urine, i.e 4.61% and 30.5%, respectively [27].

2.5 Side effects: The most common side effects of belinostat were nausea, fatigue, pyrexia, anemia, and vomiting. Thrombocytopenia, the incidence of grade > 3 or 4 toxicity is around 16% and 7% of patients. The serious adverse reactions were pyrexia, pneumonia, infection and anemia, increased level of creatinine, thrombocytopenia, and multi-organ failure [27, 44].

2.6 Drug interaction: Firstly UGT1A1 is responsible for the metabolism of belinostat. Steer clear of associated administration of Belenostat with strong inhibitors of UGT1A1such as indinavir and atazanavir. When belinostat and warfarin coadministered to each other, clinically significant raise in plasma exposure is not found of either R-warfarin or S-warfarin.

The metabolic activities of CYP2C8 and CYP2C9 are inhibited by belinostat and its metabolites namely belinostat amide, belinostat glucuronide and methyl belinostat. 3-ASBA and belinostat acid (metabolites) is responsible for the inhibition of CYP2C8 *in vitro* study. Belinostat is improbable to inhibit glycoprotein (P-gp) [27].

2.7 Dose and administration: Belinostat has to be administered as 1,000 mg/m^2 by intravenous infusion once daily over 30 minutes on days 1-5 every 3 weeks [27].

2.8 Storage Condition: Belinostat should be stored at room temperature 20-25^{0}C and excursions permitted to15 ^{0}C–30 ^{0}C [27].

2.9 Special populations with special care:

2.9.1 Pregnancy: Belinostat is a genotoxic medicine and dividing cells are targeted aggressively by it. So it can produce teratogenicity or embryo-fetal lethality. It is contraindicated during pregnancy because it causes embryo-fetal harm. So the pregnant woman should not be given Belinostat [27].

2.9.2. Nursing mothers: It is not identified till now whether Belinostat undertake excretion via human milk or not. Because several medicines are excreted in human milk and because of the probable for adverse reactions in nursing infants from Belinostat, a choice should be prepared whether to break off nursing or to stop the drug, taking into details the significance of the drug to the mother [27].

2.9.3 Pediatric Use: Belinostat's safety and effectiveness in pediatric patients less than 18 years have not been yet found [27].

2.9.4 Geriatric Use: 62 patients 65 years and older, and 13 patients 75 years and older were exposed to Belinostat in single arm clinical studies of Belinostat. Patients 65 years and older had a higher incidence rate than patients 75 years and older, while no significant diversities in response rate were watched.

Clinically significant variations in serious adverse reactions were not monitored in patients based on age [27].

Current Status: Intravenous Belinostat received its first global approval on July 2014 for the treatment of relapsed or refractory peripheral T-cell lymphoma in the USA.

CONCLUSION: In the field of research, improvement of anticancer drugs can control the signs of the disease resourcefully. HDAC, inhibitors characterize a promising novel set of anticancer agents. Belinostat has a recent novel marketed drug which has shown a significant activity and efficacy in heavily pretreated relapsed or refractory peripheral T-cell lymphoma patients. Pyrexia, pneumonia, thrombocytopenia and anemia are the most frequent adverse events related to this drug. Thus, it was concluded that, refractory peripheral T-cell lymphoma can be controlled by taking effective therapy.

CONFLICT OF INTEREST: The authors confirm that this article content has no conflict of interest.

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