



Belinostat Therapy for Peripheral T-Cell Lymphoma

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ABSTRACT

Peripheral T-cell lymphoma (PTCL) is a type of aggressive heterogeneous non Hodgkin type of lymphoma with poor historical outcomes. The responses to conventional chemotherapy remain poor, and many rebound types of cancer growth are seen after initial therapy. The belinostat drug works by inhibiting histone deacetylase and is approved for refractory or relapsed PTCL. The metabolism of Belinostat drug is done by Cytochrome p450, which takes place in the liver. Besides this, no fixed dose combination of belinostat is available for its use as inducer or enzyme inhibitor. Belinostat is well tolerated with mild side effects, including vomiting, nausea, pyrexia, fatigue, and anemic condition in patients undergoing therapy for PTCL. Belinostat therapy is an effective and safe option to treat PTCL. This article mainly deals with pharmacology, drug therapy, efficacy, and applications of belinostat against relapsed or refractory (PTCL).

Keywords: Lymphoma, Oncology, Drug interaction, Cancer, Hematology.

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INTRODUCTION

Peripheral T-cell lymphoma (PTCL) is a type of aggressive heterogeneous non Hodgkin type of lymphoma with poor historical outcomes. Lymphoma of T-cell constitutes around 15–25% of non-Hodgkin lymphoma, while peripheral T-cell lymphoma comprises even a small percentage. About or even more than 20 different subtypes of peripheral T-cell lymphoma have been characterized, which include anaplastic large cell lymphoma (ALCL), angio immunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphoma otherwise non-specified (PTCLNOS). According to National Cancer Institute CNCD, the average survival span varies from 10 to 40 months. Primary stage treatment of peripheral T-cell lymphoma generally includes chemotherapy with anthracycline drug combination, but the forecast remains poor. At the same time, the application of conventional chemotherapy is limited, specifically in patients showing refractory or relapsed disease. Some clinical trials also show that the autologous transplantation of stem cells could improve the results in patients with PTCL. But many patients diagnosed with PTCL are not suitable candidates for transplant because of lack of stable progress before Autologous Stem Cell Transplantation can be performed.

The National Comprehensive Cancer Network (NCCN) guidelines indicate clinical trials as a suitable treatment for refractory or relapsed disease. Alternative strategies for the PTCL include chemotherapy, mixed drug combination of drugs

like romidepsin, brentuximab, bortezomib, pralatrexate, and alemtuzumab approved by food and drug administration of US and by NCCN.⁷ The result from the clinical trial study suggests belinostat, a histone deacetylase inhibitor for the treatment of refractory or relapsed peripheral T-cell lymphoma.

Food and Drug Administration (FDA) approved and granted the use of Belinostat in July 2014. Several available studies show that the histone deacetylase is overexpressed in tumor growth and also helps to trigger the growth of tumor by repression of suppressor genes of tumor, this mechanism gained the aim for the intervention of tumor, and histone deacetylase inhibition can be brought by using drug-like belinostat to suppress tumor growth. Currently, the combination of belinostat and romidepsin are approved for the treatment of PTCL.¹¹

Synthesis of Belinostat

The belinostat is synthesized by using carbonyl 3- Nitro benzaldehyde. The reaction involves the steps like conversion of (2E)-3-(3 amino phenyl) acrylic acid methyl ester by using diazotization and sulfonylation to acrylic acid methyl ester to final drug product.

Pharmacology

As belinostat is classified under the category of histone deacetylase inhibitor, it catalyzes the biochemical reaction by removing the acetyl group from the histone and non histone group of proteins. Histones are the proteins that are basic in

nature and are involved in DNA synthesis as they are involved in the process by forming histone octamer and which helps in the condensation of chromatin fibers and further forms chromosomes.¹² Change in the acetylation mechanism of histone results in abnormal growth of cells and ultimately forming abnormal tumor cells. Study data obtained after clinical trial data shows alteration in the histone deacetylase and histone acetyltransferase stimulated tumor growth. In vitro study of belinostat shows that it arrests cell cycle by bioaccumulating acetylated basic histone proteins. The cytotoxicity of belinostat is preferentially seen towards the cancerous cells compared to normal healthy cells.⁸

Pharmacokinetics

The pharmacokinetic properties of belinostat were studied in phase 1 and phase 2 clinical trials with an average dose ranging from 100–1500 mg/m².¹⁴ Drug distribution of belinostat is limited to the body tissues only. In dialysis assay, *in-vitro* studies of belinostat show about 90% of Belinostat molecules are bound to proteins. The metabolism of belinostat takes place in the liver by UGT1A1 pathway by using CYP 450. Metabolized products from belinostat amid and Belinostat acid, respectively. The half-life to eliminate belinostat is about 1-hour and about 5% of belinostat is excreted in the unchanged form via urine. Human metabolite of belinostat includes belinostat amide, belinostat methyl, belinostat glucuronide, and they are excreted in urine within a day after the administration of the drug.²¹

Safety

Belinostat is categorized as a pregnancy category D drug. The drug is also tagged by tag genotoxic drug, which targets specifically dividing cells and may lead to toxicity when fetus cell comes in contact with belinostat drug. Also, while undergoing the Belinostat therapy woman should not become pregnant. The use of belinostat is also not recommended for breastfeeding mothers. The available study of belinostat on animals also indicates that belinostat may lead to infertility, particularly in males.²³

The most common side effects of belinostat were observed in patients undergoing its therapy in patients suffering from PTCL, including vomiting, nauseous feeling, anemia, pyrexia, and fatigue. In contrast, serious side effects include multi-organ failure, increased serum creatinine level, thrombocytopenia, anemia and pneumonia.

Drug Interactions

Belinostat is metabolized in liver by using CYP 450 by UGT1A1 pathway. It is mainly a glycoprotein substrate. Belinostat should not be given in combination with Atazanavir drug; this combination increases the serum concentration of belinostat. The combination of dipyron and clozapine with Belinostat also increases the toxic effects. belinostat with anticoagulant drug warfarin shows no side effects. The dosing capacity of belinostat for better results is 950–1000 mg/m² and is administered to patients by IV 30 minutes once on days 1–5 of regular cycle of 21 days. If pain or difficulty is experienced

during administration, the infusion duration can be increased to 45–50 minutes. Before dose administration of belinostat a complete blood count should be carried out.¹⁷

Future Perspective of Belinostat Therapy

The belinostat provides an option to treat PTCL with minimal adverse effects is marked as a next generation HDAC (Hydro-oxamic acid) inhibitor.

Place in Therapy

According to NCCN guidelines, Belinostat is categorized as a 2B recommendation for its use to treat refractory or relapsed peripheral T-cell lymphoma. More work is going on scientific community is working to know more about Belinostat.¹⁷

RESULTS AND CONCLUSION

Belinostat drug is an Hydro-oxamic acid (HDAC) inhibitor and it has shown best results and largely used for treating peripheral T-cell Hodgkin lymphoma. This drug has established its unique trademark in targeting epigenetic diseases like PTCL. As per reports available from clinical trial data belinostat shows high safety and low grade 3 and 4 toxicity. It is also tolerated by the group of patients who suffer from thrombocytopenia. This proves that the belinostat is a valuable therapy for patients with refractory or relapsed PTC.

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