# EFFICACY OF PANOBINOSTAT AN ORPHAN DRUG IN HODKIN'S LYMPHOMA

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**ABSTRACT:**

*Hodgkin's lymphoma (HL) is one of the few adult malignancies that most frequently presents with a progressive, painless enlargement of the peripheral lymph nodes. A primary osseous presentation of HL, without lymph node involvement, is extremely rare. The present review gives a basic idea about HL and the drug information of Panobinostat, many articles and case reports were reviewed about the drug and disease condition, our review also gives a conclusion if the drug use has good efficacy or not. In the therapeutic management of Hodkin's Lymphoma, along with other drugs, Panobinostat remains an important therapeutic option for refractory/relapsed Hodkin's Lymphoma patients*

**Key words:** *Hodkin's Lymphoma, Panobinostat, Plasma lactate dehydrogenase*

## 1. INTRODUCTION:

Hodgkin's disease(HL) is now known as HL, was first described by Thomas Hodgkin in 1832. HL accounts for 30% of all lymphomas and has an incidence in the UK of 2.2 per 100,000 for women and 3.3 per 100,000 for men. It is predominantly a disease of young adults, having a peak incidence between the ages of 15 and 35 years.[1] The annual number of cases of Hodgkin lymphoma is 2.7 per 100,000 per persons per year, and the disease accounts for slightly less than 1% of all cancers worldwide[2].

Cancers that begin in cells of the lymph system are referred to as malignant lymphomas. Lymphomas range from aggressive to slow growing or indolent and can be effectively .Many tests are used to diagnose, classify and stage lymphomas treated[3,4]

The cause of HL is unknown, but a number of risk factors have been identified. Epstein–Barr (glandular fever) virus has been identified in 50% of HL cases and is likely to be associated with an increase in risk of developing HL. Certain associations have been identified which suggest a genetic link with HL, for example, same-sex siblings of patients with HL have a 10 times higher risk of developing the disease. Patients with reduced immunity, for example, AIDS or those taking immune-suppressants, may have an increased risk of developing HL. The characteristic pathological finding in HL is the identification of a large, abnormal bi-nucleate lymphocyte called a Reed-Sternberg cell. HL as classified by the World Health Organization(WHO) has two distinct entities: classic HL and nodular lymphocyte- predominant Hodgkin's lymphoma(NLPHL).

Classic HL is further subdivided into four histological types:

- nodular sclerosis: this is the most common type in the UK, predominant in young adults and females, and has an excellent prognosis
- mixed cellularity: this is second most common type of classic HL and more common in males (70% male)

- lymphocyte depleted: this carries a poor prognosis and is more common in HIV-positive individuals
- lymphocyte rich: this is a rare type of classic HL

Signs and symptoms HL usually presents with painless enlargement of lymph nodes, often in the neck. About 40% of patients will present with fever, night sweats and/or weight loss. These have prognostic significance and are designated B symptoms; others include malaise, itching (25%) or pain at the site of enlarged nodes after drinking alcohol. Bone pain may result from skeletal involvement. Primary involvement of the gut, central nervous system or bone marrow is rare. If lymph nodes in the chest are involved, patients may present with breathlessness. There is often a disturbance of immune function due to a progressive loss of immunologically competent T-lymphocytes, with patients becoming particularly prone to viral and fungal infections.

Laboratory findings Laboratory findings include normochromic, normocytic anaemia, a raised erythrocyte sedimentation rate and eosinophilia. One-third of patients have a leucocytosis due to an increase in neutrophils. Advanced disease is associated with lymphopenia (lymphocytes $<0.6 \times 109$ L−1). Plasma lactate dehydrogenase (LDH) is raised in 30–40% of patients at diagnosis and has been associated with a poor prognosis. (Table:1) Investigations and staging Once the diagnosis has been made on biopsy, further investigations are needed to assess disease activity and the extent of its spread through the lymphoid system or other body sites. This is called staging and is essential for assessing prognosis, with cure rates f or localised tumours (stage I or II) being much higher than those for widespread disease (stage IV). The staging of HL is assessed by the Cotswolds modification of the Ann Arbor classification system (table1). Information about prognostic factors such as mediastinal mass and bulky disease is included in the classification system. The tests required to establish the stage include a complete history, physical examination, FBC, urea and electrolytes (U and Es), chest X-ray and computed tomography (CT). Other useful tests include erythrocyte sedimentation rate (ESR), serum LDH and liver function tests (LFTs). Positron emission tomography (PET) can be used to detect active residual disease.[1]

TABLE 1: **cotswolds modification of the ann arbor classification system for hodgkin's lymphoma**

| **COTSWOLDS MODIFICATION OF THE ANN ARBOR CLASSIFICATION SYSTEM FOR HODGKIN'S LYMPHOMA** | |
|---|---|
| **Clinical Stage** | **Defining features** |
| I | Involvement of a single lymph node region or lymphoid structure |
| II | Involvement of two or more lymphnode regions on the same side of the diaphragm |
| III | Involvement of lymph node regions or structures on both sides of the diaphragm: iii1–with or without involvement of splenic, hilar, celiac or portal nodes iii2–with involve ment of para-aortic, iliac or mesenteric nodes |
| IV | Involvement of extranodalsite(s)beyondthat designated E |

Multiple myeloma (MM) is a clonal plasma cell proliferative disorder characterized by hypercalcemia, anemia, renal dysfunction, and osteolytic bone lesions.[5] The treatment of MM is rapidly changing with the arrival of several active new agents.[6]

Standard first-line treatments for Hodgkin's lymphoma (HL) achieve long-term disease-free survival for many patients, but treatment remains challenging for the approximately 35% of patients with advanced HL who relapse.[7 ] The use of autologous stem-cell transplantation (ASCT) has improved outcomes in patients with relapsed HL; however, 40% to 50% subsequently experience progressive disease (PD).[7-9] These patients are typically managed by using various chemotherapy combinations, but responses are often short and the disease becomes increasingly chemotherapy resistant.[10,11] with median overall survival (OS) less than 3 years.[12] Deacetylases (DACs) are a family of enzymes that remove acetyl groups from lysine residues on histone and nonhistone proteins, which regulate several oncogenic pathways, including cell cycle progression, survival, angiogenesis, and immunity.[13-17] Panobinostat is a potent pan-deacetylase inhibitor (pan-DACi) with low nanomolar activity against all class I, II, and IV histone DAC enzymes.[15,17,18] In a phase I dose-escalation study, oral panobinostat demonstrated promising activity in patients with HL who had relapsed and was tolerable, with reversible thrombocytopenia as the principal dose-limiting toxicity.[19]

## 2. REVIEW OF DRUG EFICACY:

Panobinostat is available as a 10mg, light-green opaque capsule, A 15mg orange opaque capsule, and A 20mg red opaque capsule in three doses with different colours. Panobinostat is a histone deacetylase (HDAC) inhibitor that inhibits the enzymatic activity of HDACs at nanomolar concentrations. HDACs catalyze the removal of acetyl groups from the lysine residues of histones and some nonhistone proteins. Inhibition of HDAC activity results in increased acetylation of histone proteins, an epigenetic alteration that results in a relaxing of chromatin, leading to transcriptional activation. In vitro panobinostat caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Panobinostat shows more cytotoxicity towards tumor cells compared with normal cells.[20]

### A. PHARMACOKINETICS:

The oral bioavailability of panobinostat is approximately 21%, and is 90% bound to human plasma proteins and is independent of concentration. Panobinostat is metabolized in the liver via reduction, hydrolysis, oxidation, and glucuronidation. About 40% of hepatic elimination occurs via CYP3A, while CYP2D6 and CYP2C19 are minor pathways. Panobinostat has been associated with severe diarrhea, severe and fatal cardiac ischemic events, severe arrhythmias, serious hemorrhage, myelosuppression, and elevations in aminotransferases and total bilirubin. All drugs undergoing metabolism by the CYP3A and CYP2D6 pathways should be used with caution due to risk of Drug interactions.[20]

### B. EFFICACY OF THE DRUG:

In a Study the results demonstrate a promising single agent activity of panobinostat in patients with relapsed HL. Further development of panobinostat in lymphoma should take into account its unique mechanism of action. In addition to exploring the direct antitumor effect, future clinical trials might take advantage of DACi effects on the microenvironment and induction of antitumor immunity. Because panobinostat modulates several cellular mechanisms that regulate lymphoma cell survival, angiogenesis, and immunity, it has the potential of enhancing the activity of other agents when used in combination. The development of rationally designed clinical trials of panobinostat in combination with chemotherapy, monoclonal antibodies, and other small molecule inhibitors is warranted.[21] In a study performed by jing-di liu et al the treatment for relapsed or/and refractory MM patients with panobinostat combined with other agents appeared to be effective and generally well tolerated, with an ORR of 45%, especially combined with proteasome inhibitors. However, prolonged follow-up period is required to confirm the beneficial effects, more phase III clinical trials included large number of patients are warranted for further evaluation and help to establish the optimal dose and schedule.[22]

## 3. CONCLUSION:

Despite significant advances happened in the therapeutic management of Hodkin's Lymphoma, Panobinostat remains an important therapeutic option for refractory/relapsed Hodkin's Lymphoma patients. Available data from multiple clinical trials, case reports and review Articles confirms that DHAC like Panobinostat has an important role as a part of multidrug combinations.

## References:

1. Roger walker, Cate Whittlesea, Clinical pharmacy and Therapeutics, Fifth Edition,2012, page 803-805.
2. NCI Surveillance, Epidemiology, and End Results Program. Archived from the original on 17 October 2012. Retrieved 18 August 2014.
3. American Cancer Society: Cancer Facts and Figures 2017. Atlanta, Ga:American Cancer Society, 2017. Last accessed October 13, 2017.
4. Brenner H, Gondos A, Pulte D: Ongoing improvement in long-term survival of patients with Hodgkin lymphoma at all ages and recent catch-up of older patients. Blood 111 (6): 2977-83, 2008.
5. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group Updated Criteria for the Diagnosis of Multiple Myeloma. Lancet Oncol. 2014; 15:e538–548. [PubMed:25439696]
6. Rajkumar SV. Multiple myeloma: 2014 Update on diagnosis, riskstratification, and management. Am J Hematol. 2014; 89:998–1009.
7. Byrne BJ, Gockerman JP: Salvage therapy in Hodgkin's lymphoma. Oncologist 12:156-167, 2007.
8. Schmitz N, Pfistner B, Sextro M, et al: Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: A randomised trial. Lancet 359:2065-2071, 2002

9. Linch DC, Winfield D, Goldstone AH, et al: Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: Results of a BNLI randomised trial. Lancet 341:1051-1054, 1993.
10. National Comprehensive Cancer Network: The NCCN Clinical Practice Guidelines in Oncology: Hodgkin lymphoma (Version 2.20). http://www.nccn.org
11. Engert A, Eichenauer DA, Dreyling M, et al: Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 21:v168-v171, 2010 (suppl 5)
12. Horning S, Fanale M, deVos S, et al: Defining a population of Hodgkin lymphoma patients for novel therapeutics: An international effort. Ann Oncol 19:120, 2008 (suppl 4; abstr 118)
13. Xu WS, Parmigiani RB, Marks PA: Histone deacetylase inhibitors: Molecular mechanisms of action. Oncogene 26:5541-5552, 2007
14. Younes A: Beyond chemotherapy: New agents for targeted treatment of lymphoma. Nat Rev Clin Oncol 8:85-96, 2011
15. Lemoine M, Buglio D, Jona A, et al: The pan-deacetylase inhibitor panobinostat downregulates HIF-1 and VEGF and synergizes with everolimus in Hodgkin lymphoma cell lines. Blood 116, 2010 (suppl; abstr 2851)
16. Dickinson M, Johnstone RW, Prince HM: Histone deacetylase inhibitors: Potential targets responsible for their anti-cancer effect. Invest New Drugs 28:S3-S20, 2010 (suppl 1)
17. Prince HM, Bishton MJ, Johnstone RW: Panobinostat (LBH589): A potent pan-deacetylase inhibitor with promising activity against hematologic and solid tumors. Future Oncol 5:601-612, 2009
18. Atadja P: Development of the pan-DAC inhibitor panobinostat (LBH589): Successes and challenges. Cancer Lett 280:233-241, 2009
19. Dickinson M, Ritchie D, DeAngelo DJ, et al: Preliminary evidence of disease response to the pan deacetylase inhibitor panobinostat (LBH589) in refractory Hodgkin lymphoma. Br J Haematol 147:97-101, 2009.
20. Stanton L. Gerson, ... Richard J. Creger, in Hematology Pharmacology and Molecular Mechanisms of Antineoplastic Agents for Hematologic Malignancies (Seventh Edition), 2018 CHAPTER 57, pg: 849.
21. Anas Younes, Anna Sureda, Dina Ben-Yehuda et al Panobinostat in Patients With Relapsed/Refractory Hodgkin's Lymphoma After Autologous Stem-Cell Transplantation: Results of a Phase II Study vol.13, 18, 2012 pg.2197-2203.
22. Jing-di Liu, Chun-yan Sun, et al Efficacy and Safety of Panobinostat in Relapsed or/and Refractory Multiple Myeloma: Meta Analyses of Clinical Trials and Systematic Review 2016; 6: 27361