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Review Article

Immunotherapy in Hodgkin Lymphoma

Timothy Allen[1] and Ghazaleh Shoja E Razavi[2]*

[1]*Global Allied Pharmaceutical, Center for Excellence in Research & Development, USA*

[2]*Department of Clinical Development-Oncology and Respiratory, Global Allied Pharmaceutical, Center for Excellence in Research & Development, USA*

***Corresponding Author:** Ghazaleh Shoja E Razavi, Department of Clinical Development-Oncology and Respiratory, Global Allied Pharmaceutical, USA.

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Absrtact

Hodgkin's lymphoma is a lymphocyte cancer, with a 9,190 new cases per year in the U.S. It is sub-divided into two main categories: the Classical Hodgkin Lymphoma "CHL" and the Nodular lymphocyte predominant Hodgkin lymphoma "NLPHL". The main cause of Hodgkin lymphoma is not yet clear, but there are some risk factors like Epstein-Barr virus "EBV" infectious mononucleosis, HIV infection and genetic susceptibility. The aim of this review is to discuss the Immunotherapies available for Hodgkin lymphoma, as the treatment has developed over the past years decreasing its incidence and increasing the five year survival to 85.3%. Brentuximab Vedotin is the only immunotherapeutic drug which is FDA approved immunotherapy for the Hodgkin lymphoma, and there are several other drugs which are still under clinical trial.

Keywords: *Hodgkin's lymphoma; Immunotherapy; Immunosupression; Kinase; Cytokine; Multiclonal antibodies, Interferons*

Epidemiology

According to SEER, in 2014, 9,190 new cases (4,120 in women and 5,070 in men) of Hodgkin lymphoma were estimated and in the same year, 1,180 deaths (510 women and 670 men) were also estimated in the United States. The annual rate of new cases was 2.7 per 100,000 men and women and the death rate was 0.4 per 100,000 men and women. In the year 2011, it was estimated that there were about 185793 people living with Hodgkin Lymphoma in the United States. The five year survival rate of patients is 85.3% after the diagnosis of Hodgkin lymphoma. It represents 0.6% of all the cancers in the United States [1]. There is a bimodal age related incidence for Hodgkin's lymphoma with two peaks, first in the third decade of life (15 to 34 years) and the other peak appears in the fifth decade (after the age of 55). There is an increased incidence of Hodgkin lymphoma in the HIV infected patients [2]. There is 1.3:1 predominance of male over female [3].

Hodgkin lymphomas are mainly sub classified into two categories: Classic Hodgkin disease and Nodular lymphocyte predominant Hodgkin disease (NLPHL). Its complete classification is mentioned in Table-1. The Classic Hodgkin disease is reported as about 95% of overall cases of Hodgkin lymphoma and NLPHL comprises about 5% cases of Hodgkin lymphoma [4].

The exact cause of Hodgkin lymphoma is not yet clear, but some researchers stated that the Epstein–Barr virus causes some DNA mutations in B lymphocytes, which leads to the growth of Reed–Sternberg cells and these are the cancerous cells in the Hodgkin lymphoma [4]. The most common sign and symptoms of Hodgkin lymphoma are fatigue, fever, night sweats, weight loss, and painless enlargement of spleen and lymph nodes [5]. Familial incidence and genetic susceptibility, Epstein–Barr virus infection/mononucleosis, gender and HIV infection are the main risk factors of Hodgkin lymphoma [6].

The most common genetic alterations in Hodgkin lymphoma can be categorized into four important categories, which include: gene amplifications, chromosome translocations, chromosomal instability, and subtle DNA sequence changes including microsatellite instability [7].

Types	Subtypes
Classic Hodgkin disease	Nodular sclerosis Hodgkin disease
	Mixed cellularity Hodgkin disease
	Lymphocyte-depleted Hodgkin disease
	Lymphocyte-rich Hodgkin disease
NLPHL	NA

***Table 1**: Classification of Hodgkin Lymphoma [4].*

Immunotherapeutics in Hodgkin Lymphoma

Monoclonal Antibody (MAB) Immunotherapy

Brentuximab Vedotin [8]: An antibody–drug conjugate (ADC) directed against the tumor necrosis factor (TNF) receptor CD30 with potential antineoplastic activity. Brentuximab vedotin is generated by conjugating the humanized anti-CD30 MAB, SGN-30 to the cytotoxic agent monomethylauristatin E (MMAE) via a valine-citrulline peptide linker. Upon administration and internalization by CD30-positive tumor cells, Brentuximab vedotin undergoes enzymatic cleavage, releasing MMAE into the cytosol; MMAE binds to tubulin and inhibits tubulin polymerization, which may result in G2/M phase arrest and tumor cell apoptosis. Transiently activated during lymphocyte activation, CD30 (tumor necrosis factor receptor super family, member 8 (TNFRSF8)) may be constitutively expressed in hematologic malignancies, including Hodgkin lymphoma and some T-cell non-Hodgkin lymphomas. The linkage system in Brentuximab vedotin is highly stable in plasma, resulting in cytotoxic specificity for CD30-positive cells.

It is approved for the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients, who are not candidates for ASCT. The treatment with Brentuximab vedotin produces peripheral neuropathy. So, the dose of Brentuximab vedotin should be changed or it should be discontinued. The infusion-related reactions have occurred with Brentuximab vedotin. So, in these cases, Brentuximab vedotin should be permanently discontinued. Stevens–Johnson syndrome and Tumor lysis syndrome has been reported with Brentuximab vedotin. Therefore, Brentuximab vedotin should be discontinued in these cases. Brentuximab vedotin can cause fetal harm. So, it should not give to the pregnant women. The most common adverse effects are rash, vomiting, fatigue, neutropenia, pyrexia, cough, diarrhoea, peripheral sensory neuropathy, anemia, thrombocytopenia, nausea, and upper respiratory tract infection.

There are few other MABs that are not currently approved by FDA for Hodgkin lymphoma and are under clinical trials in phase I, II and III as in the Table-2 below:

Rituximab: It is a human monoclonal antibody which works against CD20 antigen. It initiates a host cytotoxic immune response against CD20-positive cells.

Alemtuzumab: It is a DNA derived monoclonal antibody, which works against cell surface glycoprotein CD52. It binds to CD52 and initiates host immune response, which may result in the lysis of CD52 and cells.

TNX-650: It is a monoclonal antibody with anti-neoplastic activity, which works against IL-13. It binds to and blocks the IL-13, which may result in the inhibition of the cell proliferation in the Hodgkin lymphoma.

AMG 655: A fully human monoclonal agonist antibody directed against the extracellular domain of human tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor 2 (TR-2) with potential antineoplastic activity. Conatumumab mimics the activity of native TRAIL, binding to and activating TR-2, thereby activating caspase cascades and inducing tumor cell apoptosis. TR-2 is expressed by a variety of solid tumors and cancers of hematopoietic origin.

Daclizumab: A recombinant monoclonal antibody interleukin-2 receptor antagonist. Daclizumab binds specifically to the alpha subunit of the human interleukin-2 (IL-2) receptor expressed on the surface of activated lymphocytes in vivo, thereby inhibiting IL-2 binding and IL-2-mediated lymphocyte activation, a critical cellular immune response pathway.

Yttrium Y 90 anti-CD45 Monoclonal Antibody BC8: A radio-immunoconjugate containing the murine IgG1 anti-CD45 monoclonal antibody (MoAb) BC8 labelled with yttrium 90 (Y90), with potential immunotherapeutic activity. Yttrium Y 90 anti-CD45 monoclonal antibody BC8 binds to CD45 antigen, a receptor protein-tyrosine phosphatase expressed on the surface of both normal and malignant hematopoietic cells. After binding and internalization by CD45-expressing tumor cells, this agent may deliver a cytotoxic dose of beta radiation.

Iodine I 131 Monoclonal Antibody BC8: A radio-immunoconjugate, consisting of BC8, a murine IgG1 anti-CD45 monoclonal antibody labelled with iodine 131 (I-131), with radio immunotherapeutic properties. Using monoclonal antibody, BC8 as a carrier for I-131 results in the targeted destruction of cells expressing CD45. CD45 is a tyrosine phosphatase, expressed virtually on all leukocytes, including myeloid and lymphoid precursors in bone marrow and matures lymphocytes in lymph nodes; it is also expressed on most myeloid and lymphoid leukemic cells, but not on mature erythrocytes or platelets.

Ipilimumab: A monoclonal antibody directed against cytotoxic T-lymphocyte-associated antigen-4 (CTLA4), an antigen that is expressed on activated T-cells and exhibits affinity for B7 co-stimulatory molecules. By binding CTLA4, ipilimumab enhances T-cell activation and blocks B7-1 and B7-2 T-cell co-stimulatory pathways.

Drug	Clinical Trial Identifier Number	Phase	Study Design	Target
Rituximab	NCT00504504	Phase II	Open label, Safety/Efficacy Study	CD20 antigen
Alemtuzumab	NCT00129753	Phase II	Non-Randomized, Open label, Safety/Efficacy Study	CD52 glycoprotein
TNX-650	NCT00441818	Phase I, II	Non-Randomized, Open label, Safety/Efficacy Study	IL-13
Yttrium Y 90 anti-CD45 monoclonal antibody BC8	NCT01921387	Phase I, II	Open label, Safety/Efficacy Study	CD45 antigen
AMG 655	NCT00791011	Phase I	Non-Randomized, Open label, Safety/Efficacy Study	TRAIL-2 (TR-2)
Daclizumab	NCT01468311	Phase I	Open label, Safety Study	IL-2
Iodine I 131 monoclonal antibody BC8	NCT00860171	Phase I	Open label, Safety Study	CD45
Ipilimumab	NCT01822509	Phase I	Open label, Safety Study	B7-1 and B7-2

Table 2: *Non-FDA approved MAB drugs [9-16].*

Mammalian Target of Rapamycin (mToR) Immunotherapy

There are no drugs that are currently approved by FDA for Hodgkin lymphoma. However, many drugs are under clinical trials in phase I, II and III as in the Table-3 below:

Drug	Clinical Trial Identifier Number	Phase	Study design	Target
Everolimus	NCT01075321	Phase I, II	Open label, Safety/Efficacy Study	mTOR
Temsirolimus	NCT00838955	Phase II	Open label, Safety/Efficacy Study	mTOR
Sirolimus	NCT00105001	Phase II	Randomized, Open label, Efficacy Study	mTOR

Table 3*: Non-FDA approved mTOR drugs [17-19].*

Kinase Inhibitors Immunotherapy

There is no kinase inhibitor that is currently approved by FDA for Hodgkin lymphoma. However, few kinase inhibitors are under clinical trials in phase I, II and III as in the Table-4 below:

Drug	Clinical trial Identifier Number	Phase	Study Design	Target
PLX3397	NCT01217229	Phase II	Non-Randomized, Open label	KIT, CSF1R, FLT3
Dasatinib	NCT01609816	Phase I, II	Open label, Safety/Efficacy Study	Bcr-Abl kinase

Table 4: *Non-FDA approved kinase inhibitor drugs [20,21].*

Proteasome Inhibitors

Bortezomib is proteosome inhibitor that is under clinical trial

Drug	Clinical Trial Identifier Number	Phase	Study Design	Target
Bortezomib	NCT00967369	Phase I,II2	Randomized, Open label, Safety/ Efficacy Study	NF-kaapaB, Proteasome inhibitor, 26 proteasome

Table 5: *Non-FDA approved proteasome inhibitor drugs [22].*

Miscellaneous

Few other drugs that are under various phases of clinical trials are mentioned below:

Idelalisib: An orally bio available, small molecule inhibitor of the delta isoform of the 110 kDa catalytic subunit of class I phosphoinositide-3 kinase (PI3K) with potential immunomodulating and antineoplastic activities. Idelalisib inhibits the production of the second messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3), preventing the activation of the PI3K signaling pathway and inhibiting tumor cell proliferation, motility and survival. Unlike other isoforms of PI3K, PI3K-delta is expressed primarily in hematopoietic lineages. The targeted inhibition of PI3K-delta is designed to preserve PI3K signaling in normal, non-neoplastic cells.

Natural Killer Cells: A population of activated, immortalized, interleukin-2 (IL-2)-dependent, cytotoxic natural killer (NK) cells with potential antitumor activity. Natural killer cells ZRx101 are derived from NK-92 cells, having been modified to target tumor-associated antigens (TAAs) up regulated in certain types of cancer. The NK-92 cell line was originally isolated from a patient with large granular lymphocytic (LGL) leukaemia/lymphoma.

Alisertib: It is a second-generation, orally bio available, selective small molecule inhibitor of the serine/threonine protein kinase Aurora A kinase with potential antineoplastic activity. Alisertib binds to and inhibits Aurora A kinase, which may result in disruption of the assembly of the mitotic spindle apparatus, disruption of chromosome segregation, and inhibition of cell proliferation. Aurora A kinase localizes to the spindle poles and to spindle microtubules during mitosis and is thought to regulate spindle assembly. Aberrant expression of Aurora kinases was noted in a wide variety of cancers.

IL-15: A fusion protein complex composed of a mutated form of the cytokine interleukin (IL) -15 (IL-15N72D) and a soluble, dimeric IL-15 receptor alpha (IL-15Ra) Fc fusion protein (IL-15Ra-Fc) (IL-15N72D/IL-15Ra-Fc), with potential antineoplastic activity. Upon administration, super-agonist interleukin-15:interleukin-15 receptor alpha Su/Fc fusion complex ALT-803 binds to the IL-2/IL-15 receptor beta-common gamma chain (IL-2Rbetagamma) receptor on NK and CD8+ T lymphocytes, which activates and increases the levels of NK cells and memory CD8+ (CD44high) T-cells. The memory T-cells enhances the secretion of the cytokine interferon-gamma (IFN-g), which further, potentiates the immune response against tumor cells. This may increase tumor cell killing and decrease tumor cell proliferation. IL-15 regulates CD8+ T and NK cell development, activation and proliferation. By coupling IL-15 to IL15Ra-Fc, this agent has a prolonged drug half-life and shows an increased ability to bind IL-2R beta gamma, which enhances its immune stimulatory activity as compared to IL-15 alone.

Drug	Clinical Trial Identifier Number	Phase	Study Design	Target
Idelalisib	NCT01393106	Phase I	Open label, Safety/Efficacy Study	PIP3
Natural killer cells	NCT01287104	Phase I, II	Non-Randomized, Open label, Safety/Efficacy Study	Cancer cells
Alisertib	NCT01567709	Phase I	Open label, Safety/Efficacy Study	Aurora A kinase
IL-15	NCT01572493	Phase I	Open label, Safety Study	Cancer cells

Table 6: *Non-FDA approved drugs [23-26].*

Stem Cell Transplantations [4]

Generally, there are two basic types of transplantation, which include Autologous (the cells come from the patient itself) and Allogeneic (the cells come from a matched related or unrelated donor). Both these methods are used for the treatment of Hodgkin lymphoma.

Autologous Stem Cell Transplantations: It utilizes the own stem cells of the patient, isolated from the bone marrow or the blood, and is put to freeze. After intensive chemotherapy and/or radiation therapy, these cells are re-infused into the patient.

Allogeneic Stem Cell Transplantations: In this type of transplantation, the stem cells are obtained from another person, whose HLA type closely resembles to that of the patient. The most successful donors are often a close relative, or more specifically a brother or sister. If the HLA of close relatives does not match, stem cells can be obtained from a matched unrelated donor (MUD). However, use of such stem cells might lead to several complications. Umbilical cord stem cells can also be used. These types of stem cells are used for the treatment of Hodgkin lymphoma.

Conclusion

The Hodgkin lymphoma is much less common than non-Hodgkin lymphoma. The incidence of this cancer has actually been declining in recent years, in contrast to the increase in non-Hodgkin's lymphoma. Brentuximabvedotin is the only FDA approved drug for the treatment of Hodgkin lymphoma. There are several drugs, which are under clinical trials for the treatment of Hodgkin lymphoma. Various targeted therapies are also under clinical trials. The researchers are still challenged in exploring innate and adaptive immune systems. The recent activities have increased our understanding of the tumor microenvironment, various immunotherapeutic modalities or combination therapy (like chemotherapy with immunotherapy) in various clinical trials. The complete perspective of immunotherapy treatment has not been realized and/or utilized. Proper preclinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating cancer patients.

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