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Review article

HIV and HTLV1 Associated Lymphoma and Immunotherapy

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Abstract

People with HIV infections are at increased risk for lymphoma. It is a disease in which malignant cells form in the lymphatic system of patients who have acquired immunodeficiency syndrome. The use of highly active anti-retroviral therapy (HAART) to treat HIV has helped patients to better tolerate treatments such as chemo and immunotherapy. Targeted immunotherapies are the evolving therapies where drugs that block the growth and spread of the cancer by interfering with specific molecules that are involved in carcinogenesis. It is a treatment alternative to chemotherapy and radiation in already immuno compromised HIV patients. In this paper, we will discuss the current trends in various immunotherapies and their target molecules involved in the proliferation of the disease.

Keywords: Human Immunodeficiency Virus (HIV); Acquired Immunodeficiency Syndrome (AIDS); Immunotherapy; Immunosuppression; Kinase Inhibitors; Cytokines; Monoclonal Antibodies; Interferons

Introduction/Epidemiology

The Human immunodeficiency virus (HIV) is a causative agent of Acquired Immunodeficiency Syndrome (AIDS). The HIV infected patients are at the increased risk of developing various types of cancer as compared to the general population of the similar age and gender. Around two third of AIDS-related lymphoma (ARL) cases are classified as diffuse large B-cell type, with Burkitt's lymphoma (BL) comprising 25%. Human T-cell Lymphotropic virus type 1 (HTLV-1) is a retrovirus responsible for the development of Adult T-cell Leukemia/lymphoma (ATL), an aggressive lymphoproliferative disorder. There are several unusually proliferative entities, occurring more frequently in the setting of HIV infection: plasmablastic and peripheral T-cell lymphomas, primary effusion, Castleman disease, and an entity with resemblance to PTLDs [1].

Etiology/Predisposing Factors

The HIV decreases the numbers of T-cell lymphocytes, known as CD4 cells. Untreated HIV infection decreases the number of T-cells, which leads to the production of more B-cells. The Epstein–Barr virus (EBV) and the human herpesvirus type 8 (HHV-8) are the other viruses, which increase the risk of developing lymphoma [2].

HIV associated lymphomas are part of a continuum beginning with polyclonal proliferation of B cells and culminating with the outgrowth of a transformed B-cell clone. Polyclonal proliferation of B cells occurs as the initial step because of inadequate B-cell control from T cells depleted or rendered dysfunctional by HIV infection and subsequent host immunodeficiency. Continuously proliferating B cells would provide a population of B cells at increased risk for accumulation of additional as yet undefined genetic events that would ultimately lead to the malignant transformation and outgrowth of B-cell clones. For those HIV-associated lymphomas that have been observed clinically, polyclonal lymphomas would represent events occurring during the early and middle stages of this model, and monoclonal lymphomas the final stage [3].

More recent studies have provided further evidence to support this model. Grulich and colleagues identified B-cell stimulation and prolonged immunodeficiency as risk factors for lymphoma development in HIV-infected individuals [3].

The signs and symptoms of HIV–AIDS related lymphoma include painless swelling in the neck, chest, underarm and groin due to enlarged lymph nodes, night sweats, fever, weight loss, and a feeling of fullness below the ribs [4].

Pathophysiology/Molecular Basis

There are various genetic abnormalities in HIV associated lymphoma, and they are categorized in Table3. The pathological heterogeneity of AIDS- related NHL reflects the heterogeneity of their associated molecular lesions. In AIDs-related BL, the molecular lesions involve inactivation of p53 gene, activation of c-MYC and infection with EBV [5]. The chemokine and cytokine dysregulation, such as IL-6 and IL-10 are associated with HHV-8 and EBV-associated lymphomas and probably play an important role in the lymphomagenesis [6].

All these factors have been associated with the abnormalities of various upstream proteins as well as A20, BCL-10 and CARD11 and leads to the activation of NF-B and IB kinase [7,8]. MYC is a pleiotropic transcription factor, which is involved in various cellular processes. MYC translocations is a recurrent genetic alteration in BL and diffuse large B-cell lymphoma (DLBCL) BL can be distinguished from DLBCL by the high level MYC and germinal center B-cell genes expression, and the low level of expression of NF-B target genes and MHC Class I genes [9,10].

Histologic Subtype	EBV+	KSHV/ HHV-8+	Common recurring chromosomal abnormalities
Diffuse large B-cell lymphoma Centroblastic Immunoblastic	30% 80-90%	0 0	MYC (10%); BCL-6 (20% of Centroblastic DLBCL); TP53
Plasmablastic lymphoma	>50%	80%	None
Primary effusion lymphoma	100%	100%	None
BL	30-50%	0%	MYC (100%); TP53 (50-60%)
Primary CNS lymphoma	100%	0%	BCL6 (30-40%)
Hodgkin lymphoma	80-100%	0%	None
KSHV Kaposi sarcoma herpes virus			

Table 1. Viral and genetic abnormalities in HIV associated lymphoma [11]

The first pathway involves AIDS–BL and it is characterized by mild immunodeficiency of the host and several genetic lesions of the tumor, including disruption of p53, activation of c-MYC and although less frequently, infection by EBV. Normally, EBV-infected AIDS–BL fails to express the viral transforming antigens, EBV nuclear proteins-2 (EBNA-2), and latent membrane protein-1 (LMP1). There are two different pathways, which involve the IBL and AIDS–Centroblastic (CB). While the majority of these lymphomas carry EBV infection, only IBL cases express the viral antigen LMP1.The KSHV/HHV8-associated lymphomas are related to the last pathway in the molecular genetics. These lymphomas constantly harbor infection by KSHV/HHV8 and frequently also by the EBV. All other genetic lesions, commonly detected among the AIDS–Non-Hodgkin Lymphoma (NHL) are constantly negative.

The model for the histogenesis of AIDS–NHL is derived from the expression profile of CD138/syndecan-1 (syn-1) and BCL-6, throughout the physiological B-cell maturation. The B-cells inside the GC exhibit the BCL-6$^+$/syn-1$^-$ phenotype, while the B-cells that have excited the GC and have undergone further maturation towards the plasma cell stage, exhibit the BCL-6$^-$/syn-1$^+$ phenotype. AIDS–NHL displaying the BCL-6$^+$/syn-1$^-$ phenotype, i.e. AIDS-BL and AIDS-CB, which usually display large non-cleaved cell morphology, are postulated to originate from GC B cells. On the other hand, AIDS–NHL displaying the BCL-6-/syn-1$^+$ phenotype, i.e. AIDS–IBL and KSHV/HHV8-associated lymphomas are postulated to derive from post-GC, pre-terminally differentiated
B-cells [12-18].

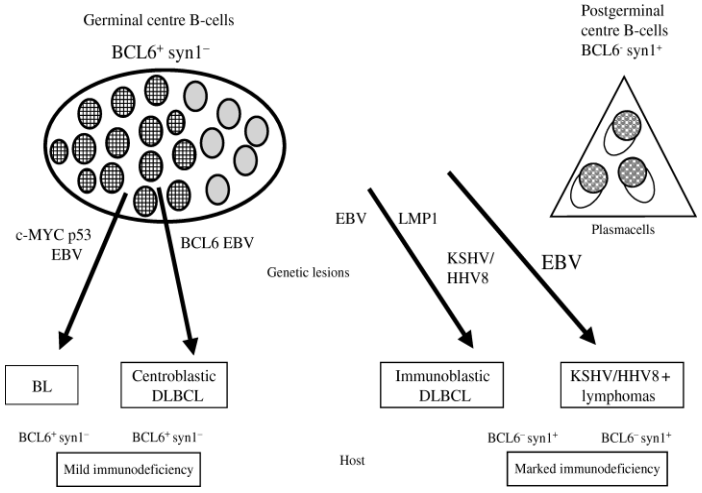

Figure 1. AIDS-related NHL histogenesis model and associated molecular pathways [19].
Syn-1: CD138/syndecan-1

Immunotherapy

A. Stem Cell Transplantations:

Generally, there are two basic types of stem cell transplantation, which include Autologous (the cells come from the pa-

tient itself) and Allogeneic stem cell transplantation (the cells come from a matched related or unrelated donor); they utilize different sources of blood-forming stem cells [20].

1. Autologous Stem Cell Transplantations:

Autologous Stem Cell Transplantations (ASCT) 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.

2. 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 stem cell transplantations are always done with high dose of chemotherapy and sometimes with radiation therapy. The high dose chemotherapy (HDC) with the ASCT (HDC-ASCT) remains the standard of care in the HIV negative patients with relapsed Hodgkin lymphoma, which is based on improved EFS and PFS compared to traditional salvage chemotherapy [21,22]. In the combination anti-retroviral therapy (cART) period, HDC-ASCT has been shown to be a successful and feasible strategy in the refractory or relapsed HIV-HL as well but with significant potential toxicity (Table 2) [22-28].

Patients	cART	%HL	Complete response	Overall survival	Disease-free survival	Treatment-related mortality
14	Yes	43%	71%	36% (32 m)	29% (26 m)	0%
20	Yes	10%	90%	85% (32 m)	85% (32 m)	5%
14	Yes	21%	73%	65% (30 m)	65% (30 m)	0%
20	Yes	25%	53%	74% (6 m)	49% (6 m)	5%
68	Yes	26%	NR	61% (32 m)	56% (32 m)	4%
50 (27*)	Yes	38%	48% (89%*)	50% (44 m) (75% (44 m)*)	49% (44 m) (74% (44 m)*)	0%
53	Yes	34%	NR	62% (30 m)	61% (30 m)	NR

NR: not reported.

*Indicates the outcomes for only patients who taken HDC-ASCT.

Table 2. Studies of HDC-ASCT in relapsed HIV-associated lymphomas [23-29].

B. Proteasome Inhibitor Immunotherapy:

There is no proteasome inhibitor that is currently approved by FDA for HIV. However, only proteasome inhibitor that is under clinical trials in phase I-III is in Table 3 below:

1. Bortezomib: It is a proteasome inhibitor drug with anti-neoplastic activity, which inhibits 26 proteasome. It also inhibits nuclear factor (NF)-kappaB, which interferes with tumor development and angiogenesis.

Drug	Clinical trial identifier number	Phase	Study design	Target
Bortezomib	NCT00598169	Phase I, II	Non-Randomized, Safety/Efficacy Study, Open Label	KIT, CSF1R, FLT3

Table 3. Non-FDA Approved proteasome inhibitor drugs [30].

C. Monoclonal Antibodies (MABs): There are no MABs that are currently approved by FDA for HIV. However, few are under clinical trials in phase I-III as in Table 4 below:

1. Ibritumomab Y-90:

A radioimmunotherapeutic agent consisting of a murine monoclonal anti-CD20 antibody (ibritumomab) linked by the chelatortiuxetan to the radioisotope yttrium-90 (Y 90). Yttrium Y 90 ibritumomabtiuxetan binds to and specifically delivers beta radiation to CD20-expressing tumor cells, thereby minimizing the systemic effects of radiation.

2. SAR566658:

An immunoconjugate consisting of a humanized monoclonal antibody against the tumor-associated sialoglycotope CA6 (huDS6) conjugated to the cytotoxic maytansinoid DM4, with potential antineoplastic activity. The anti-CA6 monoclonal antibody moiety of SAR566658 targets and binds to the cell surface antigen CA6. Upon antibody/antigen binding and internalization, the immunoconjugate releases DM4, which binds to tubulin and disrupts microtubule assembly/disassembly dynamics, resulting in inhibition of cell division and cell growth of CA6-expressing tumor cells. The CA6 epitope is found on a variety of solid tumors, including breast, ovarian, cervical, lung, and pancreatic tumors.

3. Rituximab:

A recombinant chimeric murine/human antibody directed against the CD20 antigen, a hydrophobic transmembrane protein located on normal pre-B and mature B-lymphocytes. Following binding, rituximab triggers a host cytotoxic immune response against CD20-positive cells.

4. Brentuximab Vedotin:

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 monoclonal antibody SGN-30 to the cytotoxic agent monomethyl auristatin 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 then 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 superfamily, member 8; TNFRSF8) may be constitutively expressed in hematologic malignancies, including Hodgkin lymphoma and some T-cell NHLs. The linkage system in Brentuximab vedotin is highly stable in plasma, resulting in cytotoxic specificity for CD30-positive cells.

5. Ofatumumab:
A fully human, high-affinity IgG1 monoclonal antibody directed against the B cell CD20 cell surface antigen with potential antineoplastic activity. Ofatumumab binds specifically to CD20 on the surfaces of B cells, triggering complement-dependent cell lysis (CDCL) and antibody-dependent cell-mediated cytotoxicity (ADCC) of B cells overexpressing CD20. The CD20 antigen, found on over 90% of B cells, B cell lymphomas and other B cells of lymphoid tumors of B cell origin, is a non-glycosylated cell surface phosphoprotein that acts as a calcium ion channel; it is exclusively expressed on B cells during most stages of B cell development.

Drug	Clinical trial identifier number	Phase	Study design	Target
Ibritumomab	NCT00761384	Phase I, II	Non-Randomized, Safety/Efficacy Study, Open Label	CD20
SAR566658	NCT01084252	Phase I, II	Safety Study, Open Label	CA6
Rituximab	NCT01193842	Phase I, II	Randomized, Safety/Efficacy Study, Open Label	CD20 antigen
BrentuximabVedotin	NCT01771107	Phase I,II	Safety/Efficacy Study, Open Label	Tubulin polymerization
Ofatumumab	NCT01286272	Phase II	Randomized, Efficacy Study, Open Label	CD20

Table 4. Non-FDA approved MABs [31-35].

D. Mammalian Target of Rapamycin Immunotherapy: There is no Mammalian Target of Rapamycin (mTOR) inhibitor that is currently approved by FDA for HIV. Few drugs that are under clinical trials in phase I-III are listed in Table 5 below:

1. Temsirolimus:
An ester analog of rapamycin, Temsirolimus binds to and inhibits the mTOR, resulting in decreased expression of mRNAs necessary for cell cycle progression and arresting cells in the G1 phase of the cell cycle. mTOR is a serine/threonine kinase, which plays a role in the phosphoinositide 3-kinase(PI3K)/AKT pathway that is upregulated in some tumors.

2. Sirolimus:
A natural macrocyclic lactone produced by the bacterium *Streptomyces hygroscopicus*, with immunosuppressant properties. In cells, sirolimus binds to the immunophilin FK Binding Protein-12 (FKBP-12) to generate an immunosuppressive complex that binds to and inhibits the activation of the mTOR, a key regulatory kinase. This results in the inhibition of T lymphocyte activation and proliferation, that occurs in response to antigenic and cytokine (IL-2, IL-4 and IL-15) stimulation and inhibition of antibody production.

3. Everolimus:
A derivative of the natural macrocyclic lactone sirolimus with immunosuppressant and anti-angiogenic properties. In cells, everolimus binds to the immunophilin FKBP-12 to generate an immunosuppressive complex that binds to and inhibits the activation of the mTOR, a key regulatory kinase. Inhibition of mTOR activation results in the inhibition of T lymphocyte activation and proliferation associated with antigen and cytokine (IL-2, IL-4, and IL-15) stimulation and the inhibition of antibody production.

Drug	Clinical trial identifier number	Phase	Study design	Target
Temsirolimus	NCT01076543	Phase I, II	Safety/Efficacy Study, Open Label	mTOR
Sirolimus	NCT01203722	Phase I, II	Non-Randomized, Safety/Efficacy Study, Open Label	mTOR
Everolimus	NCT01334502	Phase I	Open Label	mTOR

Table 5. Non-FDA Approved mTOR drugs [36-38].

E. Kinase Inhibitors Drugs: Few drugs that are under clinical trials in phase I-III are listed in Table 6 below:

1. Pazopanib:
A small molecule inhibitor of multiple protein tyrosine kinases with potential antineoplastic activity. Pazopanib selectively inhibits VEGF-1, -2 and -3, c-kit and PDGF-R, which may result in inhibition of angiogenesis in tumors in which these receptors are upregulated.

2. Ibrutinib:
An orally bioavailable, small-molecule inhibitor of Bruton's tyrosine kinase (BTK) with potential antineoplastic activity. Upon oral administration, ibrutinib binds to and irreversibly inhibits BTK activity, thereby preventing both B-cell activation and B-cell-mediated signaling. This leads to an inhibition of the growth of malignant B cells that overexpress BTK. BTK, a mem-

ber of the SRC-related BTK/Tec family of cytoplasmic tyrosine kinases, is required for B cell receptor signaling, plays a key role in B-cell maturation, and is overexpressed in a number of B-cell malignancies. The expression of BTK in tumor cells is also associated with increased proliferation and survival.

Drug	Clinical trial identifier number	Phase	Study design	Target
Pazopanib	NCT01339871	Phase I	Safety/Efficacy Study, Open Label	VEGF-1,-2,-3, c-kit, PDGFR
Ibrutinib	NCT02109224	Phase I	Safety Study, Open Label	BTK activity

Table 6. Non-FDA Approved kinase inhibitor drugs [39-40].

F. Miscellaneous: Few other drugs that are under clinical trials in phase I-III are listed in Table 7 below:

1. A-dmDT390-bisFv (UCHT1):
A bivalent recombinant fusion protein immunotoxin derived from the anti-CD3 monoclonal antibody UCHT1 with potential antineoplastic activity. Anti-CD3 immunotoxin A-dmDT390-bisFv (UCHT1) consists of 1–390 amino acid residues of chain A diphtheria toxin (DT) joined via a spacer to the Fv fragment of UCHT1, which is connected to a second UCHT1 Fv fragment via a disulfide bond (hence the "bisFv" designation); the addition of the second Fv fragment overcomes the steric hindrance of immunotoxin binding due to the large N-terminal DT domain. Once inside target T cells, the DT moiety catalyzes the transfer of the ADP-ribose moiety of NAD to diphthamide, a posttranslationally modified histidine residue found in elongation factor 2 (EF-2), inactivats EF-2, disrupts polypeptide chain elongation, and ensues cell death. CD3 is a complex of five cell-surface polypeptides associated with the T cell receptor (TCR) complex.

Drug	Clinical trial identifier number	Phase	Study design	Target
A-dmDT390-bisFv(UCHT1)	NCT00611208	Phase II	Open Label	Cancer cells

Table 7. Non-FDA Approved miscellaneous drugs [41].

Conclusion

Rituximab is the only FDA approved immunotherapeutics for the treatment of Hodgkin lymphoma. There are some adoptive T-cell therapies, monoclonal antibodies, proteasome inhibitors and anti-viral agents, which are effective in the treatment of HIV and HTLV-1 associated lymphoma. There are various targeted therapies with several immunotherapeutics, but they are under clinical trials. The researchers are still challenged to explore the innate and adaptive immune systems. The recent activities have increased our understanding of the tumor microenvironment, various immunotherapeutic modalities, or combination therapies (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.

Abbreviations

HIV= Human Immunodeficiency Virus, HTLV= Human T-cell Lymphotropic virus, AIDS= Acquired Immunodeficiency Syndrome, ATL= Adult T-cell Leukemia/lymphoma, BL= Burkitt's lymphoma, EBV= Epstein–Barr virus, HHV-8=Human Herpes Virus type 8, IL=Interleukin, TCR= T cell receptor, mTOR= Mammalian Target of Rapamycin, TKI=Tyrosine Kinase Inhibitor.

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