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Newly Emerging Therapies Targeting Viral-related Lymphomas

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Abstract

Gamma-(γ)-herpes virus lymphomas comprise a heterogenous group of B-cell and T-cell neoplasms most commonly associated with Epstein Barr virus (EBV) and rarely human herpes virus-8 (HHV-8) infection. Adult T-cell leukemia/lymphoma (ATLL) is a unique disease entity caused by the human T-cell lymphotropic virus, type 1 (HTLV-I), the only retrovirus known to cause cancer in humans. Viral lymphomas behave aggressively and disproportionately affect immunocompromised individuals and those living in underdeveloped regions. These diseases are often difficult to treat with conventional approaches. Despite recent advancements using cytotoxic, lymphoma-specific, and adoptive therapies, the long-term outcome of patients with γ -herpesvirus lymphomas occurring in severely immunocompromised patients and ATLL continues to be poor. Lytic-inducing therapies targeting NF- κ B, and viral and tumor cell epigenetic mechanisms afford the advantage of exploiting the intrinsic presence of oncogenic viruses to eradicate infected tumor cells. In this review, viral-related lymphomas and newly emerging clinical approaches targeting viral latency are discussed.

Introduction

Approximately 12% of all human cancers worldwide are associated with oncogenic viruses [1]. The incidence of virus related malignancies, particularly lymphomas, varies geographically and is influenced by environmental and host co-factors. Human oncogenic viruses associated with or causing lymphoma are Epstein Barr virus (EBV), human herpes virus-8 (HHV-8), and human T-lymphotropic virus-I (HTLV-I). EBV and HHV-8 belong to the γ -herpesviridae subfamily and can induce both lymphoid and epithelial tumors. EBV is closely linked to Hodgkin lymphoma, Burkitt's lymphoma, nasal natural killer (NK) T-cell lymphoma, AIDS and post solid organ transplant lymphomas, and other rare B and T-cell lymphoproliferative disorders (Table 1) [1-7]. HHV-8, also known as the Kaposi's sarcoma associated herpesvirus, causes primary effusion lymphoma (PEL) and large B-cell lymphoma arising from multicentric Castleman's disease, usually occurring in

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immunocompromised individuals [4]. HTLV-I was the first retrovirus linked to a human cancer and is the causative agent of Adult T-cell leukemia/lymphoma (ATLL) [8,9].

During the last three decades significant research progress has been made towards understanding the role of these pathogenic viruses in cancer which are now considered not just casual passengers but rather culprits of neoplastic transformation and in some cases the driving forces of tumor growth and proliferation. Consequently, the pathophysiology of viral related lymphomas differs from virus-negative counterparts in part due to the molecular effects exerted by oncogenic viruses on host cell machinery. Lymphotropic oncoviruses become habitually latent in host malignant cells: γ -herpesviruses remain as episomal DNA structures, while HTLV-I randomly integrates as a provirus into the host genome. During latency, these proviruses retain the ability to produce a restricted number of viral proteins and non-coding RNAs which can deregulate cell cycle, promote proviral state, and evade the host's immune response [10-12]. An additional distinctive feature of EBV and HHV-8 associated lymphomas is high expression of nuclear factor kappa B (NF- κ B), which is a critical molecule for their survival [13-14] and exerts anti-apoptotic effects [15]. Tax protein encoded by HTLV-I also induces the activation of NF- κ B pathway and other intracellular signaling cascades [11-12]. In addition, the HTLV-I encoded basic leucine zipper (HBZ) gene appears to play a pathogenic role in ATLL. [11]. While expression of Tax protein is usually lost in the transformed primary ATLL cells, HBZ is persistently expressed in all ATLL tumors.

While oncogenic viruses contribute to development of multiple lymphoid neoplasms, they may also serve as unique therapeutic targets for the treatment of these malignancies. Immunocompetent individuals normally mount a potent cytotoxic T-cell (CTL) response against infected cells expressing viral epitopes. CTLs can eradicate infected tumor cells, which forms the basis of adoptive anti-EBV therapies [16]. However, oncogenic viruses generally avoid CTL surveillance by establishing latency in host cells. γ -herpesviruses express genes during the latency which can block TNF-induced proapoptotic signals generated by cell-mediated cytotoxic responses [17-19]. Latent γ -herpesviruses remain under tight transcriptional regulation by NF- κ B and histone deacetylase enzymes (HDACs) [20-22]. The HTLV-I promoter is also under the epigenetic control of HDACs [23]. Disruption of viral latency in γ -herpesvirus lymphomas using the NF- κ B and HDAC inhibitors results in lytic reactivation and cell death [20-22] and may also activate the expression of latent retroviruses such as human immunodeficiency virus (HIV) and HTLV-I [23,24]. Therefore the dual anti-neoplastic and lytic inducing roles of these drugs can be exploited in the treatment of virus-related malignancies. In this review we focus on the recent advances and newly developing therapeutic approaches targeting viral latency and the biology of virus-infected lymphomas.

γ -Herpesviruses-associated lymphomas

Most viral-associated B-cell lymphomas are associated with EBV, which has a direct causative role in some of these neoplasms [2]. EBV lymphomas show a wide geographic distribution and their incidence is influenced by environmental and host co-factors such as genetic background, age, and immune state [1,2]. The most commonly encountered EBV+

B-cell lymphomas worldwide are Burkitt lymphoma (BL), Hodgkin's lymphoma (HL), and diffuse large B-cell lymphoma (DLBCL) occurring in immunocompromised individuals [1,2]. The great majority of EBV+ BL cases occur in immunocompetent children in equatorial Africa, an area with high prevalence of malaria [1,2]. This endemic pattern is also found in the eastern region of Brazil, where most pediatric BL cases are also EBV+ [25]. EBV+ HL also occurs in immunocompetent hosts usually in the form of lymphocyte-rich and mixed-cellularity subtypes [26]. HIV-related HL is almost always associated with EBV [4]. EBV+ B-cell neoplasms occurring almost exclusively in the setting of HIV or immunocompromised states are plasmablastic lymphoma (PBL), EBV-associated primary central nervous system lymphoma (PCNSL) and PEL [1,4]. Other EBV+ lymphomas include nasal NK-T cell lymphoma and peripheral T-cell lymphomas commonly seen in Asia, DLBCL of the elderly, and rare T-cell lymphoproliferative disorders associated with chronic inflammation or EBV infection during childhood [1-3]. HHV-8 is implicated in the pathogenesis of PEL and DLBCL arising from multicentric Castleman's disease [4].

The pathophysiology of virus-related lymphomas is distinct from virus-unrelated counterparts due to unique effects exerted by the EBV and HHV-8 gene products in deregulating cell cycle control, intracellular signaling, and host immune pathways. γ -Herpesvirus lymphomas share in common the high expression of NF- κ B, an event which is a key to their survival [20]. The EBV latent membrane protein-1 (LMP-1), which transforms B-cells, constitutively signals to activate NF- κ B thus blocking pro-apoptotic signals [27,28]. Some EBV proteins upregulate cellular cyclins while HHV-8 encodes its own cyclin [29,30]. The expression of EBV genes during latency varies and depends on EBV promoter usage within specific disease subtypes. For instance, Type I latency cells such as BL only express EBV nuclear antigen-1 (EBNA-1) and small non-coding RNAs (EBERs), while Type III latency lymphoproliferative disorders express both EBNA and LMP-1 [31,32]. Type II latency tumors, such as HL, express LMP-2 in addition to EBNA [33]. LMP-2 mimics constitutive B-cell receptor signaling thus leading to NF- κ B activation [34]. EBERs are thought to target innate immune signaling by blocking RNA-dependent protein kinase (PKR), which stops protein translation after viral infection [35]. We recently demonstrated high expression of the EBV-encoded BHRF1-3 in Type III latency immunoblastic lymphoma cells, and its abrogation restored IFN-inducible T-cell attracting chemokine CXCL-11/I-TAC suggesting an immunomodulatory mechanism exerted by this microRNA (miRNA) in these tumors [36]. Specific HHV-8 non-coding miRNAs are also implicated in tumorigenesis [37]. Likewise, the HHV-8 encoded vIRF1 inhibits interferon signaling [38]. Latent HHV-8 transcripts include latency-associated nuclear antigen-1 (*LANA-1*), viral FADD-like interleukin-1- β – converting enzyme (FLICE/caspase 8)-inhibitory protein (*vFLIP*), and viral cyclin (*v-CYC*) [30]. LANA-1 is necessary for maintenance of the viral episome, and *vFLIP* is essential for PEL survival by activating the anti-apoptotic genes downstream of NF- κ B [19,30]. The lytic phase of HHV-8 results in viral replication and cell lysis, and is characterized by increased expression of early and late lytic genes such as *RTA*, *vIL-6*, and *K8.1* [39].

AIDS-related lymphomas

In the latest 2010 Joint United Nations Programme on HIV/AIDS Report, 33.3 million people were living with HIV worldwide, including 1.2 million in the U.S. HIV infected individuals are at an increased risk for developing malignancies, most commonly Kaposi's sarcoma and lymphoma. While the incidence of AIDS-related lymphomas (ARLs) has declined since the introduction of highly active antiretroviral therapy (HAART), these diseases still prevail in part due to new trends in HIV resistance [40]. Notwithstanding, non-Hodgkin lymphoma (NHL) occurs much more frequently in HIV/AIDS [40]. HL is also more common in HIV patients, and its incidence appears to be increasing despite HAART [40]. The higher incidence of malignancies seen in HIV and other immunocompromised states is in part related to the host's impaired ability to fight opportunistic oncogenic viruses.

The pathophysiology of ARLs differs from their counterparts observed in the general population. One of the most distinguishing features of ARLs as compared to the spectrum of NHLs occurring in the general population is their close association with the γ -herpesviruses. DLBCL is the most common type of NHL in HIV patients followed by BL, but unlike non-HIV cases, about one-third of these tumors are EBV+ [5]. HL, PCNSL, and oral PBL are typically associated with EBV in the setting of HIV/AIDS [2,4]. HHV-8 is associated with DLBCL arising from Castleman's disease in the HIV/AIDS setting, and is virtually found in 100% of PEL cases [4]. γ -herpesviruses play important oncogenic roles in these tumors and their intrinsic presence represent potential therapeutic target.

ARLs usually present as high-grade B-cell neoplasms with poor risk features such as high international prognostic index scores, and frequent extranodal and CNS spread [41]. A molecular feature with potential therapeutic implications in ARLs is their high proliferation rate and expression of the multidrug resistance (MDR-1) gene, which has been associated with lower remission rates [42]. The infusional chemotherapy regimens EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) and CDE (cyclophosphamide, doxorubicin and etoposide) commonly used in ARLs are thought to circumvent high MDR-1 expression and rapid tumor proliferation by prolonged drug exposure [43,44]. A recent comparative immunohistochemical analysis performed on biopsies from patients with HIV-DLBCL who participated in AMC-010 and AMC-034 studies demonstrated that EPOCH had a particular survival advantage in patients with tumors exhibiting a high proliferation index (Ki-67 >90%) while no difference was observed with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) [5]. Similarly, a previous study in non-HIV patients with DLBCL treated with EPOCH had demonstrated a significantly poorer treatment outcome in patients with Ki-67 <80% [45].

The overall outcome in lymphomas can be influenced by the molecular characteristics of these tumors. In a landmark study by Alizadeh et al., two novel subgroups of DLBCL were identified by distinct gene-expression profiles [46]. This study revealed that patients with the germinal-center B-cell-like (GCB) DLBCL subtype had a better overall survival after anthracycline-based chemotherapy as compared to the activated B-cell-like (ABC) subtype. Similarly, investigators at the National Institutes of Health (NIH) recently demonstrated 5-year progression-free survival (PFS) of 95% vs. 44% for GCB and ABC subtypes, respectively, in patients with HIV-DLBCL treated with short-course EPOCH (3-6 cycles)

and dose-dense rituximab. Overall, this regimen resulted in 5-year progression-free and overall survival (OS) of 68% and 84%, respectively [47] – a markedly improved outcome compared to historical studies using CHOP-like regimens. Other phase II studies have also demonstrated impressively high complete response (CR) and survival rates in patients with HIV-DLBCL treated with the EPOCH regimen (43,48). A direct comparison of outcome data from AMC 010 and 034 studies revealed that HIV-DLBCL patients with poor-risk features (IPI 2-3) treated with R-EPOCH had a similar outcome as low-risk (IPI 0-1) patients treated with R-CHOP [49]. In contrast, the 2-yr PFS of high-risk patients was 59% vs. 30% for R-EPOCH and R-CHOP respectively.

In a European study, 485 patients with AIDS-related NHL in the HAART era were treated with risk-adapted chemotherapy (standard CHOP or ABCVP-doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisolone). Patients were stratified according to three risk factors: prior history of AIDS, performance status 2 to 4 and CD4 lymphocyte counts $<100/\text{mm}^3$. [50]. The 5-year OS was ~50% in patients with no risk factors. Patients with intermediate risk (at least 1 factor) had similar outcomes after the use of either standard or low-dose-CHOP (5-yr OS= 28% vs. 24% respectively, $p=0.19$). Noteworthy, the overall outcome in this study was inferior compared to results observed with CDE or EPOCH regimens. The results from this and other studies justify the use of alternative regimens other than CHOP in selected high-risk groups of HIV-DLBCL patients. Consequently, EPOCH is presently regarded by many investigators as the standard of care for ARLs in the U.S.A. AMC-075 is currently testing a risk-adapted chemotherapy approach in HIV-DLBCL using rituximab(R)-CHOP in low-risk disease and R-EPOCH in high-risk disease. A recently completed trial (AMC-048) that assessed utility of modified version of the Mcgrath regimen (CODOX-M/IVAC) demonstrated that the regimen was highly tolerable and effective in HIV-BL [51].

Plasmablastic lymphoma (PBL)

PBL is classified as a distinct entity by the World Health Organization (WHO), and typically presents in the oral cavity in the setting of HIV infection, accounting for 2.6% of NHL in this population [52]. It is associated with EBV in approximately 80% of cases [4]. PBL is characterized by a diffuse proliferation of large neoplastic cells with immunoblastic morphology and an immunophenotype of terminally differentiated B-cells. Although PBL most frequently presents in the oral cavity, it is also encountered in other extranodal, particularly mucosal sites. Lymph node involvement has also been reported. Clinically, PBLs are rapidly progressive tumors associated with poor response to therapy and an average survival time of 14 months [52]. We have recently reported on the presence of two distinct subtypes of PBL identified and classified as oral and extraoral PBL and characterized by distinct pathological findings [53]. The oral PBL were strongly associated with HIV infection and commonly demonstrated plasmablastic morphology without plasmacytic differentiation. Extraoral PBL tended to occur in patients with underlying non-HIV-related immunosuppression and universally demonstrated plasmacytic differentiation. The patients with oral PBL demonstrated better overall survival compared to patients with extraoral PBL ($p=0.02$). Our findings suggested that PBL with oral and extraoral presentations represent two distinct clinicopathologic entities.

Primary Effusion Lymphoma (PEL)

PEL is a distinct and aggressive lymphoma which most commonly presents as pleural, peritoneal, or pericardial malignant effusions without a contiguous tumor mass [4]. Although less common, PEL may also develop as nodal disease or solid tumors exhibiting a similar morphology, immunophenotype and gene expression profile as classical liquid-phase PEL [4]. PEL is most commonly diagnosed in HIV+ patients, yet it may also develop in other immunosuppressed individuals [54]. Although HHV-8 is directly implicated in the oncogenesis of this lymphoma, most PEL cases are also EBV+ and the combination of the two oncoviruses may facilitate transformation. While the majority of PEL tumor cells are latently infected with HHV-8, a small subset undergoes spontaneous lytic replication. HHV-8 is unique amongst other herpes viruses because it encodes several human gene homologues and proto-oncogenes, such as v-IL6, v-cyclin, v-FLIP, and vGPCR [30].

Adult T-cell leukemia-lymphoma

Adult T-cell leukemia/lymphoma (ATLL) is an aggressive malignancy caused by HTLV-I [8,9]. This virus affects ~ 20 million people worldwide and is endemic in southwest Japan, western Africa, the Caribbean, and certain regions in South America, such as Brazil and Peru. While most HTLV-I infected individuals are asymptomatic, approximately 3% develop ATLL usually several decades after initial infection [55]. ATLL usually presents aggressively, carries a dismal prognosis, and is generally incurable with conventional chemotherapy. The acute and lymphomatous subtypes are the most common variants and have median survival of 6-10 months despite treatment [56]. The chronic leukemia and smouldering types represent the minority of the cases and usually progress to more aggressive types. A recent randomized phase III study performed in Japan demonstrated a slight survival advantage favoring the ranimustine-containing chemotherapy regimen VCAP-AMP-VECP over intensive CHOP [57]. A phase II trial sponsored by the AMC carried out in the U.S. using EPOCH followed by AZT and interferon- α (IFN α) as maintenance in aggressive ATLL showed that a significant number of subjects progressed early during their treatment, and every patient eventually relapsed [58].

At our institution we probably treat more ATLL patients than any other center in North America. The long-term clinical outcome of our patients has been dismal, and so far we have not observed any cures in this disease using conventional chemotherapy, which possibly contradicts the more optimistic clinical trial results from Japan. Some Phase II studies performed outside of Japan, including at our center, have demonstrated efficacy using the combination of AZT and IFN α in patients with untreated leukemic type ATLL. A recent meta-analysis suggests that AZT/IFN α could be as effective as chemotherapy for leukemic type ATLL in terms of survival, and some patients have remained progression-free with maintenance therapy for several years [59]. After a recent international consensus review, AZT/IFN α is now a first line option for the treatment for non-lymphomatous type ATLL [60]. Other investigational therapies showing promise in ATLL include allogeneic stem cell transplantation and monoclonal antibodies targeting T-cell receptor molecules such as Tac and CCR4 [61,62].

ATLL is challenging to study at the molecular level in part due to the lack of adequate models and its genomic complexity likely resulting from long-term HTLV-I driven T-cell proliferation and accumulation of DNA damage prior to malignant transformation. Genetically altered mice offer important models to test the role of specific viral and host genes in the development of ATLL [63]. However, these models usually express the HTLV-I oncogenic protein Tax, which exerts wide pleiotropic cellular effects through the interaction with transcription factors such as NF- κ B, CREB, SR-F and AP-1 [11,12]. Elegant studies have demonstrated the significance of Tax in driving malignant T-cell growth resulting in gene instability and transformation to ATLL [11,12]. However, Tax is not expressed in primary ATLL, yet these tumors continue to exhibit high NF- κ B activity [64]. More recently, the HTLV-I encoded HBZ gene transcribed from the minus DNA strand and consistently expressed in primary ATLL, appears to play a key role in the pathogenesis of this disease [11]. We have recently demonstrated an association between the expression of the NF- κ B/c-REL target gene interferon regulatory factor 4 (IRF-4/MUM-1) and resistance to IFN α -based therapy in ATLL [65]. We have also found that AZT may negatively affect NF- κ B function in ATLL *in vivo* [66]. However, the cytotoxic mechanisms of AZT and IFN α in ATLL as well as mechanisms of resistance to these drugs remain unclear.

Limited ATLL genome-wide molecular profiling data exists outside of Japan. In a recent NIH study of 32 leukemic ATLL samples using Affymetrix array several genes were reported to be overexpressed including the anti-apoptotic genes TCF4 and BIRC5 [67]. We had previously performed gene expression analysis in a small number of leukemic ATLL specimens and found several genes anomalously over-expressed including LYN, CSPG2 and LMO2 [68]. We have also recently completed a study of fifty ATLL specimens mainly obtained from African-descendants from the U.S., Caribbean and Brazil using a high-resolution comparative genomic hybridization (CGH) platform [69]. Previous CGH studies performed mostly on Japanese specimens had demonstrated frequent genetic lesions involving many chromosomal regions, but no specific chromosome or genetic aberrations were proven to contribute to the pathogenesis of ATLL [70,71]. Noteworthy, these studies employed less sensitive CGH arrays than currently available technologies. In our ATLL cohort we identified specific genomic alterations that were not reported previously in Japanese samples which could be important in ATLL pathogenesis [69]. The most common highly gene-specific homo- or heterozygous losses involved *CDKN2A/CDKN2B* and occurred mostly in acute-type ATLL at a higher frequency than previously reported. We also found homo- or heterozygous losses involving other tumor suppressors such as *TP53* mostly in lymphomatous-type ATLL. Our analysis is still ongoing, and our goal is to identify the specific genomic regions containing potential candidate genes which could be relevant for ATLL pathogenesis.

Targeting Latency in Viral-related Lymphomas

The prognosis of γ -herpesvirus lymphomas using standard chemotherapy is generally similar between viral and non-viral variants with the exception of specific subtypes. EBV status does not seem to impact the prognosis of BL or HL occurring in immunocompetent hosts, which are highly curable diseases with conventional chemotherapy and/or radiation. Endemic BL is highly sensitive to alkylating agents and is usually cured with

cyclophosphamide-based regimens [72]. Advanced HL is generally curable with ABVD or BEACOPP regimens [73]. However, the management of HL and BL can be problematic in the relapse setting and in individuals living in poor resource areas. Other EBV+ diseases like AIDS-related HL and NHL, and DLBCL in the elderly have poorer outcomes and are more challenging to treat with conventional approaches. NK-T cell lymphomas are relatively resistant to chemo- and radiation therapy approaches [74]. Therefore, this warrants the need for finding new therapies for these lymphomas.

Major advances have been made recently in lymphoma treatment using lymphocyte-specific therapies. The addition of the anti-CD20 specific antibody rituximab to standard CHOP chemotherapy in DLBCL has improved patients' survival [75]. A clear benefit of rituximab in the treatment of DLBCL in the HIV setting has not been well-demonstrated yet. In this special population, earlier clinical trials have demonstrated a possible increased risk of death from infection that was attributed to rituximab [44,48,76]. More recent studies using rituximab with conventional chemotherapy with HAART have demonstrated high efficacy and good safety profiles [47,77]. Rituximab is currently being widely used in post-transplant related lymphoproliferative disorders (PTLD) which are frequently EBV+ [78]. A recent advancement in the treatment of relapsed HL in immunocompetent hosts is the anti-CD30 conjugated antibody SGN-35 [79]. This agent can be effective in other CD30+ lymphomas [79], however it has not been investigated yet in ARLs. The oral HDAC inhibitor panabinstat is also showing promise in HL [80].

Few therapies directed specifically against viral lymphomas have been established. Adoptive therapies involving the passive transfer of donor-derived EBV-specific CTLs are promising in highly immunogenic tumors such as PTLD [16], but other EBV+ lymphomas have been less responsive. Newly emerging strategies are now focusing on targeting viral related lymphomas using "lytic-inducing" approaches.

AIDS-related lymphomas (ARLs)

EBV and HHV-8-associated ARLs exhibit constitutive activation of NF- κ B, which is the indirect target of new biological drugs such as the proteasome inhibitor bortezomib [81,82]. NF- κ B maintains γ -herpesvirus latency [20]. Therefore, NF- κ B inhibitors may be useful for disrupting viral latency and treating γ -herpesvirus lymphomas. AMC is currently testing the combination of bortezomib with salvage ICE (ifosfamide, carboplatin, etoposide) for treatment of relapsed/refractory γ -herpesvirus related lymphomas (AMC-053 study).

HDAC inhibitors have demonstrated activity in a wide variety of cancers, including lymphomas [83]. Several mechanisms have been proposed for the anti-tumor effects of HDAC inhibitors, including blocking histone deacetylation permitting chromatin decondensation, and expression of silenced genes or tumor suppressors.[84]. In addition to their anti-tumor properties, HDAC inhibitors can also disrupt γ -herpesvirus latency resulting in lytic activation leading to tumor cell death [21,22]. These drugs can also alter HIV latency and thus theoretically help eliminate HIV-infected reservoirs with antiretroviral therapy (ART) [24,85]. Valproic acid (VPA), an older generation HDAC inhibitor, has been shown to activate latent HIV and reduced number of infected CD4 cells by ~75% in patients taking antiretrovirals [85]. Vorinostat, a proto-type of the newer class of HDAC inhibitors can also

activate HIV from latency suggesting this drug can help eliminate latently-infected cell reservoirs [24]. The selective induction of HIV in patients treated with HAART might allow the immune response to clear HIV infection [85]. In preclinical studies, vorinostat was highly synergistic with anthracyclines and etoposide [86,87], which form the backbone of the EPOCH regimen commonly used in ARLs. Therefore, the dual role of HDAC inhibitors (antitumor and viral inducer) may be exploited in the setting of both HIV and γ -herpesvirus-related malignancies. Based on these biological concepts, AMC is currently testing vorinostat in combination with risk-adapted chemotherapy under a phase I/randomized II study design for HIV-DLBCL (AMC-075).

The use of antivirals with anti-herpetic activity such as azidothymidine (AZT) and gancyclovir (GCV) is also appealing for treating γ -herpesvirus tumors. These drugs are preferentially phosphorylated by viral kinases thus potentiating their own cytostatic or anti-tumor effects [88]. The HDAC inhibitor arginine butyrate can sensitize EBV+ lymphoma cells to GCV [89]. In a recent clinical study, the combination of arginine butyrate and GCV resulted in objective clinical responses in patients with refractory EBV+ lymphoid diseases [90]. AZT and GCV have shown efficacy in EBV+ AIDS-related PCNSL [91,92]. We have demonstrated that AZT but not GCV can inhibit NF- κ B activity inducing EBV lytic gene expression and apoptosis in primary EBV+ BL cells [93]. As compared to other anti-herpetic drugs, AZT, a thymidine analogue, appears to be a superior substrate for EBV and HHV-8 thymidine kinases (TKs) [88]. The cytotoxic drugs doxorubicin and methotrexate (MTX) can also induce EBV lytic expression [94,95]. AZT and MTX work synergistically and their combination is clinically active in ARLs [96]. MTX inhibits thymidylate synthase thus blocking de novo synthesis of dTMP increasing the likelihood of AZT incorporation into DNA [96]. Based on these clinical studies and concepts, at our institution we often use the combination of AZT-MTX for γ -herpesvirus ARLs. We have recently reported the results of upfront treatment with AZT-MTX-based chemotherapy in 9 EBV+ NHLs (PBL (n=4), BL (n=3), DLBCL (n=1), or solid PEL variant (n=1) [97]. All but one subject with BL were HIV+. Seven of 9 patients (78%) achieved a CR (sustained for 18-65 months) with overall and progression-free survival rates at 3 years of 78% and 58%, respectively in our updated analysis. Notably 3 of 4 patients who had oral PBL, a disease with relatively poor prognosis, remained in remission for 18-20 months. Therefore, a high-dose AZT-based approach appears to be promising in EBV+ lymphomas. Currently, at our institution we have an ongoing phase II clinical trial testing the combination of high-dose AZT-MTX with hydroxyurea and doxorubicin for relapsed EBV+ lymphomas.

Primary effusion lymphoma (PEL)

Patients with PEL do poorly with conventional chemotherapy. PELs express NF- κ B, and its pharmacologic inhibition leads to HHV-8 re-activation and cell apoptosis [19,98]. In a recent report, an HIV-negative patient with PEL treated with bortezomib in combination with liposomal doxorubicin and rituximab achieved a clinical remission [99]. Therefore targeting PEL with lytic-inducing agents is a novel and exciting treatment approach.

We recently established a culture naïve PEL xenograph model in SCID mice [100]. UM-PEL-1 was co-infected with both HHV-8 and EBV, and manifested as both peritoneal

disease and solid masses infiltrating multiple organs. We demonstrated that bortezomib and doxorubicin both induced HHV-8 lytic gene expression prior to cell death and increased survival in SCID mice inoculated with UM-PEL-1 cells. The combination of these drugs further increased SCID mice survival. The cell killing mechanism of bortezomib in UM-PEL-1 appeared to be independent of NF- κ B and the unfolded protein response. Since then, we have successfully established two new *in vivo* PEL models from HIV subjects. One of these tumors (UM-PEL-2) is HHV-8+ only, and the other (UM-PEL-3) is coinfecting with HHV-8 and EBV from a chemotherapy resistant subject (unpublished data). We are currently testing novel combinations of lytic-inducing agents in our models.

Adult T-cell Leukemia/lymphoma

Conventional chemotherapy or AZT/IFN α treatment can transiently suppress but not really cure ATLL. In our recent study we demonstrated that gene expression profiling before and immediately after AZT/IFN α treatment can identify an IFN-response gene expression signature that correlated with clinical response to this therapy [68]. However, these approaches fail to eradicate malignant ATLL clones as patients inevitably relapse and die of their disease. In the recent AMC-sponsored study using EPOCH chemotherapy in ATLL subjects, Mansouri et al. demonstrated that disease progression correlated with an increase in HTLV-I proviral load [58]. Recent studies have demonstrated that raltegravir, an integrase inhibitor approved for the treatment of HIV, inhibits HTLV-I infection *in vitro* [101]. ATLL tumors display a high expression of NF- κ B [11,12,64]. Based on these principles a phase I/II trial utilizing the combination of EPOCH with bortezomib and raltegravir for the treatment of ATLL is currently ongoing at the Washington University and multiple U.S. sites.

Previous studies demonstrated that treatment with VPA resulted in HTLV-I proviral load reduction in chronically infected subjects with HTLV-I associated myelopathy/tropical spastic paresis (HAM/TSP) [102]. Consequently, we are currently conducting a prospective trial examining the efficacy of combination of AZT/IFN α regimen with VPA that is given during the maintenance treatment phase. Histone acetylation can result in HTLV-I promoter activation and viral transcription [23] thus potentially facilitating elimination of persistent ATLL clones by CTL cells. In patients treated on the study we observed a serial decrease in clonal ATLL disease followed by molecular clearance in one subject after VPA treatment (Ramos JC, unpublished data). In past studies, we had failed in our long-term responders to observe this effect after AZT/IFN α alone [65]. Based on our preliminary observations, targeting intact HTLV-I provirus in ATLL cells by HDAC inhibitors may represent an exciting approach which could help advance the cure for ATLL.

Conclusions

Viral-associated lymphomas occur more frequently in special populations. These diseases are usually more aggressive and difficult to treat in immunocompromised patients and individuals living in underdeveloped areas. Recent advancements using chemotherapy in combination with lymphoma-specific therapies have improved the cure rates for aggressive B-cell neoplasms like DLBCL, BL and HL. However, some viral related lymphomas such as

EBV + AIDS-related lymphomas, PEL, PBL, nasal NK-T cell lymphoma, and HTLV-I related adult T-cell leukemia/lymphoma continue to cause significant morbidity and mortality. Therapies targeting viral latency offer the advantage of exploiting the intrinsic presence of oncogenic viruses to kill infected tumor cells. This concept is now emerging in clinical trial settings and promise to advance the knowledge and treatment of viral-related malignancies.

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Table 1

Viral associated lymphomas

Lymphoma subtype (WHO 2008)	Virus	% Infection	References
<i>Hodgkin lymphoma</i>	EBV		
-General world population (varies with age and region)		40-50	1,2
- AIDS-related		80-100	4
<i>Burkitt lymphoma</i>	EBV		
-Endemic		>95	1,2
-Sporadic		10-90 [*]	2
-AIDS-related		30-40	1
<i>Diffuse large B-cell lymphoma or DLBCL not otherwise specified (NOS):</i>	EBV		
-AIDS-related cases		30	5
-Primary DLBCL of the central nervous system (CNS):			
-AIDS-related cases		79-100	2
<i>Large B-cell lymphoma arising in HHV8-associated multicentric Castlemann disease</i>	HHV-8	100	4
<i>Early post-transplant lymphoproliferative disorders</i>	EBV	70-80	6,7
<i>Plasmablastic lymphoma (AIDS related)</i>	EBV	80	4
<i>Primary effusion lymphoma</i>	HHV-8 EBV	100 80	4
<i>Extra nodal NK-T cell lymphoma, nasal type</i>	EBV	~100	2
<i>Adult T-cell Leukemia/Lymphoma</i>	HTLV-1	100	8,9

* Sporadic Burkitt lymphoma: EBV infection varies widely in non-endemic regions, with a significantly low incidence in North America and Western Europe, and much higher rates in some Latin America areas. **Note:** Other rare EBV-associated B-cell and T-cell lymphoproliferative disorders include: DLBCL of the elderly, peripheral T-cell lymphomas not otherwise specified (NOS), systemic EBV+ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection), hydroa vacciniforme-like lymphoma, DLBCL associated with chronic inflammation (most often chronic pyothorax), and lymphomatoid granulomatosis [3].