bjh review

Viral lymphomagenesis: from pathophysiology to the rationale for novel therapies

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Summary

The association between viruses and lymphomas has long been recognized; however, the pathophysiological phenomena behind this relationship are unclear, and have been the object of intense research. Although our understanding of such mechanisms is slowly improving, much is still left to learn. With the recent advances in cancer biology, a diversity of biological pathways and novel targets and agents have been described in patients with haematological malignancies and successfully put into clinical practice. Clear examples are rituximab and brentuximab vedotin in patients with B cell lymphomas and Hodgkin lymphoma respectively. The main purpose of this review is not only to succinctly summarize what we know regarding the pathogenesis and pathophysiology of virally induced lymphomas and to describe the current practices in terms of diagnosis of treatment of such lymphomas, but also to provide a scientific rationale for the use of novel therapies that are likely to improve the outcomes of patients with these conditions.

Keywords: lymphoma, Epstein-Barr virus, human herpesvirus 8, human T-lymphotrophic virus type 1, lymphomagenesis.

Lymphomas are a largely heterogeneous group of haematological malignancies that are characterized by the uncontrolled growth of clonal lymphocytes. Given the variability inherent to lymphomas, their aetiology is, understandably, heterogeneous as well (Morton *et al*, 2008). A series of diverse risk factors have been described, such as infections, autoimmune diseases, environmental and genetic factors and exposure to chemical or other toxins (Grulich & Vajdic, 2005; Alexander *et al*, 2007). The association between viruses and lymphomas has been long recognized; however, the pathophysiological phenomena behind this relationship remain unclear.

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With the recent advances in cancer biology, a diversity of biological targets and their respective targeted agents have been described and put into clinical practice. One of the most notable advances was the development of rituximab (Rituxan®), a chimeric monoclonal antibody directed against CD20. The addition of rituximab to chemotherapy has substantially increased the response and survival rates in patients with B cell lymphomas (Feugier *et al*, 2005; Marcus *et al*, 2005; Pfreundschuh *et al*, 2011). More recently, the development of an anti-CD30 antibody–drug conjugate (ADC), brentuximab vedotin (Adcetris®) has demonstrated exceptional clinical activity in patients with Hodgkin lymphoma (HL) and anaplastic large cell lymphoma (Younes *et al*, 2010).

The main purpose of this review is not only to summarize what we know regarding the pathophysiology of virally induced lymphomas and to describe the current practices in terms of diagnosis and treatment of such lymphomas, but also to provide a scientific rationale for the use of novel therapies. We will focus on Epstein-Barr virus (EBV), human herpesvirus 8 (HHV8) and human T cell lymphotrophic virus type 1 (HTLV-1) and their relationships with Burkitt lymphoma (BL), post-transplant lymphoproliferative disorder (PTLD), EBV+ diffuse large B cell lymphoma (DLBCL) of the elderly, extranodal natural killer/T cell lymphoma (ENKTL), primary effusion lymphoma (PEL) and adult T cell leukaemia/lymphoma (ATLL).

In all these lymphomas, there is presence of viral genome within the nucleus of the malignant cells supporting a direct aetiological role. Although human immunodeficiency virus (HIV) infection has been associated with the development of a series of lymphomas, such as DLBCL, BL and HL, there has not been convincing data to support an infection of the malignant cell by HIV, with exception of a handful of T cell lymphomas (Herndier *et al*, 1992; Shiramizu *et al*, 1994). For this reason, HIV lymphomagenesis is beyond the scope of this review.

Epstein barr virus

EBV is a *gamma*-herpesvirus first identified *via* electron microscopy by Epstein and Barr over 50 years ago. The discovery of EBV has been recently reviewed (Epstein, 2012).

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Overall, EBV infects 90–95% of people worldwide. The virus gains entry into humans typically at a young age and persists throughout the person's lifetime. Humans serve as the only known reservoir for EBV and transmission occurs from host to host *via* saliva.

EBV lymphomagenesis (Fig 1)

Infection occurs first within orophrayngeal epithelial cells (Sixbey *et al*, 1984), where the IgA:EBV complex docks at the IgA receptor and gains cellular entry. Circulating B cells that come in proximity to infected epithelial cells then become infected via viral attachment to CD21 followed by entry into the nucleus (Nemerow *et al*, 1985). Here, the viral genome circularizes and begins to express EBV nuclear antigen leader protein (EBNA-LP) and EBNA-2. Approximately 24–48 h later, additional EBNAs and latent membrane proteins (LMPs) are produced, leading to cell growth and transformation, and suppression of apoptosis through increase in BCL2 expression. Full expression of all EBV proteins transforms the naïve B cell into an activated lymphoblast. Circulating cytotoxic T-lymphocytes (CTLs) recognize EBNA-3A, 3B, 3C and LMP2, eradicating most activated lymphoblasts. In order to survive, the virus adapts and decreases viral protein expression, avoiding immunosurveillance. Further increase in LMP2 drives EBV into latency (Thompson & Kurzrock, 2004). EBV-infected lymphoblasts continue to differentiate within the germinal centre into memory B cells, the reservoir of EBV infection (Gratama *et al*, 1988; Karajannis *et al*, 1997). Throughout the course of latent infection, EBV expresses nuclear antigens, membrane proteins, small non-coding RNAs and cell transcripts that further contribute to viral genomic maintenance and evasion of host immunosurveillance.

The mechanism by which EBV infects T cells is unknown secondary to T cell surface expression of CD21. In T cell lymphoma cases like ENKTL, where EBV expression is 100% (Li *et al*, 2013), there is little to no detectable expression of CD21 on the T cell surface (Braun *et al*, 1998). Other potential mechanisms for EBV infection of T cells include cellular entry when coupled to IgG as well as direct cell-to-cell contact of T cells with infected B cells (Imai *et al*, 1998). CTLs are activated by the host immune system following initial EBV B cell infection, lymphoblast transformation, and EBV-derived proteins expression. CTLs then target infected B cells for elimination. The direct cell-to-cell contact and subsequent lysis releases virus, which may infect CTLs and natural killer (NK)-cells nearby.

Once infected, lymphomagenesis is dependent on expression of EBV gene products that may inhibit apoptosis and/or promote proliferation via *MYC* activation or through inhibition of tumour suppressor genes (Hemann *et al*, 2005). There are three different latency patterns in EBV-related malignant disorders and EBV-derived cell lines, recognized as latency patterns I, II and III. More profound immunosuppression and reliance on EBV for tumour development are associated with higher latency states (Knecht *et al*, 2001; Vereide & Sugden, 2011). Tumours with latency pattern I, such as endemic BL, are seen in relatively immunocompetent individuals and only partially rely on virally-mediated inhibition of apoptosis while lymphomas with latency pattern III, like PTLD, are seen in immunosuppressed patients and require EBV for inhibition of apoptosis and to drive tumour proliferation. EBV-related proteins expressed in various diseases according to the latency patterns are shown in Table I.

Within the latency patterns, several key gene products have been described as crucial to lymphoma development. In

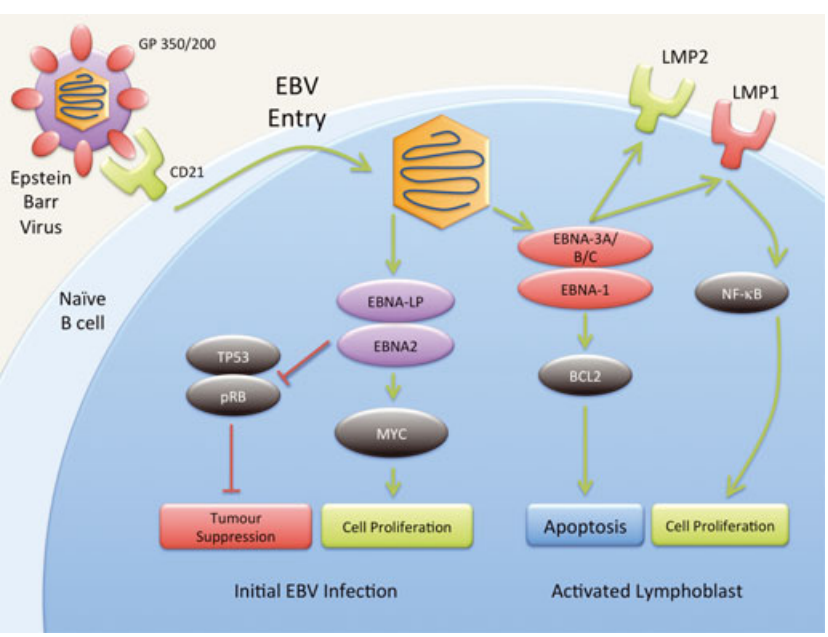

Fig 1. Schematic representation of the lymphomagenetic role of the Epstein-Barr virus. EBV, Epstein-Barr virus.

latency pattern I, EBV gene expression is primarily in the form of EBNA1 and LMP2A. EBNA1 expression leads to up regulation of microRNA, which impairs B cell differentiation (Leucci *et al*, 2010). Meanwhile, LMP2A augments MYC-induced proliferation (Fish *et al*, 2013) and protects B cells with MYC overexpression from apoptosis (Bultema *et al*, 2009). In latency pattern II, LMP1 serves as the dominant oncoprotein and is essential for *in vitro* and *in vivo* lymphomagenesis (Kaye *et al*, 1993). LMP1 induces B cell proliferation through tumour necrosis factor receptor signalling (Mosialos *et al*, 1995) and nuclear factor kappa B (NF-κB) activation (Huen *et al*, 1995). More importantly for B cell immortalization, LMP1 acts as a viral mimic of CD40 thereby constitutively activating B cells in the absence of T cell signalling (Kilger *et al*, 1998). EBNA2, seen in latency pattern III, also increases MYC expression (Egle *et al*, 2004) and decreases apoptosis (Fischer *et al*, 2007) through down-regulation of the BCL2 family protein BIM (BCL2L11) (Clybouw *et al*, 2005).

Burkitt lymphoma

BL is an aggressive B cell lymphoma and one of the fastest growing human tumours. The first cases, described by Burkitt in 1957, referred to young children presenting with rapidly expanding tumours of the jaw (Harford, 2012). Epidemiologically, BL can be characterized as endemic (seen in equatorial Africa), sporadic (seen throughout the world) and immunodeficiency-associated (seen in HIV infection) (Leoncini *et al*, 2008). EBV can be detected in almost 100% of patients with the endemic variant but only in 5–10% of sporadic and 30–40% of immunodeficiency-associated cases. Approximately 70% of all the cases of BL in the world are diagnosed in Sub-Saharan Africa (Harford, 2012). Typically, BL presents with a rapidly expanding mass accompanied by systemic symptoms, such as fever, night sweats and unintentional weight loss. The cell turnover is such that patients frequently develop tumour lysis syndrome (TLS) while undergoing therapy and a portion of patients can experience spontaneous TLS even before therapy is initiated. TLS is potentially lethal due to electrolyte abnormalities and acute kidney injury and should be managed proactively with intravenous fluids, allopurinol prophylaxis and rasburicase therapy. TLS classification and therapeutic recommendations have been published (Cairo & Bishop, 2004).

Pathologically, tumours present with a monotonous involvement of the lymph node by medium sized lymphocytes in a classic 'starry-sky' pattern (Leoncini *et al*, 2008). The malignant cells are strongly positive for monotypic surface IgM, CD19 and CD20 and co-expresses CD10 and BCL6 but not CD5 or BCL2. The proliferation rate is approximately 100%. A defining feature of BL in a translocation between the *MYC* gene and either the *IGH* gene [t(8:14)], seen in 80% of the cases, or the genes for the *kappa* or *lambda* light chains [t(2;8) and t(8;22) respectively]. BL should be differentiated from immunoblastic DLBCL, double-hit lymphoma and aggressive B cell lymphoma with intermediate features between DLBCL and BL.

Data on prognostic factors are rather scant although sporadic and immunodeficiency-associated BL appear to have worse outcomes than endemic BL (Ferry, 2006). A recent population-based study identified older age, black race and advanced clinical stage as adverse prognostic factors for survival in a cohort of over 2000 patients from the US (Castillo *et al*, 2013). In HIV+ patients, studies have not satisfactorily proved that the addition of antiretroviral therapy (ART) has improved the outcomes of patients with BL (Lim *et al*, 2005a). The therapy is based on intensive combination chemotherapy regimens in combination with the anti-CD20 monoclonal antibody, rituximab. Two US population-based studies have demonstrated an improved outcome in patients that correlates with the introduction of rituximab (Castillo *et al*, 2013; Costa *et al*, 2013). These studies also showed that patients older than 60 years are less likely to derive benefit from current therapies, probably due to toxicity but also chemoresistance.

Novel therapies: immunoconjugates. Given the expression of CD19 by the malignant cells in BL, there are ongoing clinical trials evaluating anti-CD19 therapy. SGN-19A is an ADC linking a humanized anti-CD19 monoclonal antibody and

Table I. EBV-related proteins expressed in various diseases according to the latency patterns.

	EBV-associated proteins			
Latency pattern	*EBNA1/ LMP2A*	*LMP1/ LMP2B*	*EBNA2/3A/ 3B/ 3C/LP*	Lymphoma
I	+	−	−	Burkitt lymphoma
II	+	+	−	Hodgkin lymphoma, extranodal NK/T cell lymphoma, primary effusion lymphoma
III	+	+	+	PTLD, AIDS-related lymphoma, EBV+ DLBCL of the elderly

DLBCL, diffuse large B cell lymphoma; EBNA, EBV nuclear antigen; EBV, Epstein-Barr virus; LMP, latent membrane protein; NK, natural killer; PTLD, post-transplant lymphoproliferative disorder.

auristatin, a potent anti-tubule chemotherapy agent. A preclinical study showed internalization and trafficking of SGN-19A through the endosomal-lysosomal pathway with potent *in vitro* cytotoxic activity against BL cell lines (Law *et al*, 2011). Additionally, in mouse xenograft models, SGN-19A induced tumour regression and prolonged survival in treated mice at levels below its maximum tolerated dose. A phase I safety prospective clinical trial is ongoing in patients with relapsed lymphomas, including BL (NCT01786135). This open-label, dose escalation study aims to accrue 120 patients 12 years of age or older who have not undergone allogeneic haematopoietic stem cell transplantation (HSCT).

Blinatumomab is a bi-specific T cell engager (BiTe) monoclonal antibody with two variable regions, one targeting CD3 and one targeting CD19, which induces an effector and cytotoxic $CD3^+$ T cell response against the $CD19^+$ malignant B cells (Bassan, 2012). Preclinically, blinatumomab has been shown to induce 50% killing of B cell lines at doses as small as 10^1 pg/ml while rituximab induced 20% cell killing at doses of 10^3 pg/ml. Blinatumomab has already shown efficacy in patients with relapsed/refractory acute lymphoblastic leukaemia (ALL), a disease as aggressive as BL (Topp *et al*, 2012). In this study on 21 patients with persistent or relapsed minimal residual disease (MRD)+ B cell ALL, blinatumomab induced MRD responses in 80% of the patients within four cycles of therapy. Additionally, the haematological relapse-free survival (RFS) was 33 months; historically, the haematological RFS in this population is 2·5 months (Raff *et al*, 2007). A phase I safety study has completed accrual of 76 patients 18 years of age or older with relapsed lymphoma (NCT00274742).

BL cells also express CD22, a transmembrane glycoprotein that plays a role in cellular adhesion and regulation of B cell homing and activation, and is internalized when bound to antibody (Carnahan *et al*, 2003). The immunoconjugate inotuzumab ozogamicin combines a humanized anti-CD22 monoclonal antibody with calicheamicin, a potent antitumour antibiotic that binds DNA and causes double-strand breaks resulting in apoptosis (DiJoseph *et al*, 2004). Preclinical studies showed that inotuzumab ozogamicin caused regression of tumours and prolonged survival in Burkitt-bearing mice. Two prospective phase I studies evaluating inotuzumab ozogamicin either alone (Advani *et al*, 2010) or in combination with rituximab (Fayad *et al*, 2013) in patients with relapsed/refractory B cell lymphoma have been published; however, no BL patients appeared to have been included.

Post-transplant lymphoproliferative disorders

PTLD are lymphoid or plasmacytic proliferations seen in recipients of solid organs, and bone marrow transplantation or HSCT undergoing immunosuppression. The frequency of PTLD varies according to the allograft, as follows: renal (<1%), allogeneic HSCT (*c.* 1%), hepatic and cardiac (1–2%) and heart-lung, lung and intestinal (5%) (Swerdlow *et al*, 2008). The majority of PTLD is EBV-induced (*c.* 70%) and more likely to occur within a year after transplant. The remaining 30%, not associated with EBV, are more likely to be of T cell origin and occur later after transplant (*c.* 5 years). The clinical presentation includes constitutional symptoms, fever, lymphadenopathy and organ-specific dysfunction.

Pathologically, PTLD can be categorized as polymorphic, monomorphic and HL-type (Swerdlow *et al*, 2008). Polymorphic PTLD are composed of immunoblasts, plasma cells, occasional Reed Sternberg (RS)-like cells and small and medium-sized lymphocytes, and it is most common in children. The malignant cells express CD20 and the RS-like cells CD30. EBER by *in situ* hybridization is detected in most cases. Monomorphic and HL-type PTLD meet criteria for specific B cell and T cell lymphomas seen in immunocompetent patients, such as HL, DLBCL, BL or peripheral T cell lymphoma (PTCL).

A recent multi-centre retrospective study in 80 patients with PTLD showed an improvement in outcome in patients receiving rituximab as part of their therapy with a 3-year survival of 73% vs. 33% in patients who did not receive rituximab (Evens *et al*, 2010). In this study, central nervous system (CNS) involvement, bone marrow involvement and hypoalbuminaemia were associated with worse outcomes. The initial treatment in most cases entails stopping immunosuppresants, which has been associated with durable responses in 5–30% of the patients. There is no standard therapy for PTLD, and current approaches include rituximab, rituximab-containing chemotherapy regimens, surgery and/or radiation therapy.

Novel therapies: cellular therapy and antiviral agents. The first successful trials for the treatment of EBV+ lymphomas incorporated the use of adoptive cellular immunotherapy either through donor lymphocyte infusions or by administration of EBV-specific cytotoxic T-lymphocytes (CTLs) generated from EBV-transformed lymphoblastoid cell lines (Heslop *et al*, 2010; Doubrovina *et al*, 2012). EBV-specific CTLs have been utilized in cases of PTLD with response rates of 80% and as prophylaxis in patients at high risk for PTLD with response rates of 100%. Thus far, EBV-specific CTLs are most successful in PTLD following HSCT but are considerably less effective post-solid organ transplantation (SOT), probably because of lack of persistence (Comoli *et al*, 2002; Haque *et al*, 2002; Savoldo *et al*, 2006). Other issues with the widespread use of EBV-specific CTLs are the 2–3-month preparation time and the specialized facilities required for generation. In order to create an 'off-the-shelf' product, one previous phase II study created a bank of partially human leucocyte antigen (HLA)-matched allogeneic EBV-specific CTLs for rapid administration to patients with PTLD secondary to haematopoietic and SOT. Response rates of 52% at 6 months post-infusion are encouraging for future

applications (Haque *et al*, 2007). More recently, trials that administer third-party allogeneic and autologous CTLs directed against LMP1 and 2 (NCT01956084, NCT00368082, NCT01636388) as well as LMP1/2, BARF and EBNA1, so called GRALE T cells, (NCT01555892) in patients with refractory EBV+ lymphomas, have been opened.

Chimeric antigen receptor (CAR) modified T cells show durable activity in refractory B cell malignancies (Porter *et al*, 2011; Kochenderfer *et al*, 2013) and may provide an answer to the *in vivo* expansion drawback of EBV-specific CTLs. One current clinical trial examines autologous EBV-specific CAR T cells with a CD30 target in patients unfit for standard lymphoma therapies or with relapsed or refractory lymphoma (NCT01192464). Potential future clinical trials may exploit EBV gene expression in latency pattern II and III as targets for CAR T cells.

Antiviral agents have been less successful because of the relative quiescent nature of the virus outside of the lytic phase. Increased viral activity results in elevated thymidine kinase levels and allows antivirals to exert their effects through inhibition of viral DNA replication. Arginine butyrate has been previously shown to up-regulate thymidine kinase activity and activate the virus, thereby increasing the susceptibility to antiviral medications. The results of a phase I/II trial of arginine butyrate with ganciclovir in 15 patients with refractory EBV+ lymphoid malignancies have been published (Perrine *et al*, 2007). From the six PTLD patients included in this study, two experienced complete response (CR) and three achieved partial response (PR), for an overall response rate (ORR) of 83%. The most common adverse events associated with therapy were nausea and headache. A study combining bortezomib and ganciclovir for EBV+ lymphomas has recently been terminated (NCT00093704).

EBV+ DLBCL of the elderly

EBV+ DLBCL of the elderly is a rare lymphoma recently included as a provisional entity in the World Health Organization (WHO) classification (Nakamura *et al*, 2008). Diagnostic criteria include presence of EBV+ DLBCL in patients over 50 years of age with no underlying immunodeficiency. The overall incidence of EBV+ DLBCL of the elderly is variable; studies from Asia and Central/South America report an incidence of 5–14% (Oyama *et al*, 2007; Park *et al*, 2007; Beltran *et al*, 2011a; Hofscheier *et al*, 2011). European and North American studies have noted lower incidences of 1–3%, suggesting some genetic or environmental predisposition (Gibson & Hsi, 2009; Hoeller *et al*, 2010; Hofscheier *et al*, 2011). EBV+ DLCL of the elderly is typically seen in individuals in their early 70s (Oyama *et al*, 2007; Park *et al*, 2007; Beltran *et al*, 2011a). On presentation, half of the patients present with advanced clinical stage and have more aggressive disease based on worse performance status, increased frequency of B symptoms, and elevated lactate dehydrogenase (LDH).

Two pathological subtypes of EBV+ DLBCL of the elderly have been described. The monomorphic subtype has centroblastic or immunoblastic morphology, with frequent mitoses, and usually associated with necrosis. The polymorphic subtype shows large neoplastic cells with immunoblastic morphology admixed with variable amounts of small lymphocytes and histiocytes (Ok *et al*, 2013). Most cases depict large RS-like cells that can compromise the predominant cellular population. Cells stain for CD45 and B cell markers CD19, CD20, CD79s and PAX5. Typically, a non-germinal centre phenotype is seen (CD10−, BCL6−, MUM1+) (Park *et al*, 2007; Beltran *et al*, 2011a). CD30 expression has been documented in 50–90% of RS-like cells (Hoeller *et al*, 2010; Beltran *et al*, 2011a; Montes-Moreno *et al*, 2012). Cellular proliferation is high with Ki-67 expression in 70–80% of the cells. Greater than 90% of cases are positive for EBV LMP1 and 15–30% express EBNA-2 suggesting an EBV latency type III. EBV can be detected by *in situ* hybridization techniques for EBV-encoded RNA (EBER). Although no clear cut-off point for positivity has been established, previous studies have defined EBER positivity as presence in >20–50% of tumour cells (Oyama *et al*, 2007; Park *et al*, 2007; Beltran *et al*, 2011a). The diagnosis of EBV+ DLBCL involves the exclusion of non-malignant processes, such as chronic EBV infection or medications like methotrexate. The differential diagnosis includes PTLD, plasmablastic lymphoma (PBL), primary effusion lymphoma (PEL), DLBCL associated with chronic inflammation and EBV+ HL, among others (Ok *et al*, 2013).

Based on large randomized studies, the combination of rituximab and chemotherapy has become the standard of care for patients with DLBCL (Feugier *et al*, 2005; Pfreundschuh *et al*, 2011). However, these trials did not take into account EBV status. No randomized studies have been done specifically in EBV+ DLBCL patients. Most retrospective data, however, have reported the use of non-rituximab-containing regimens, with complete remission rates ranging between 30% and 60%, which appear lower than in EBV-negative DLBCL (Oyama *et al*, 2007; Park *et al*, 2007; Beltran *et al*, 2011a). Data on the addition of rituximab to anthracycline-containing regimens is considerably more sparse although CR rates appear higher at 60–70% (Hoeller *et al*, 2010; Beltran *et al*, 2011a; Marques *et al*, 2012).

Novel therapies: proteasome inhibitors and anti-CD30 ADC. EBV+ DLBCL of the elderly is associated with increased activity of the canonical and non-canonical NF-κB pathways (Montes-Moreno *et al*, 2012). NF-κB activation, demonstrated by nuclear staining of p150/p50 and p105/p52, was seen in 79% and 74% of the malignant cells respectively. This frequency was significantly higher than in EBV-negative DLBCL controls. The proteasome inhibitor bortezomib (Velcade®) blocks NF-κB activation and has been shown to induce caspases 8- and 9-mediated apoptosis in EBV-transformed cells *in vitro* and *in vivo* (Zou *et al*, 2007).

Bortezomib reduced the levels of the p50 component of the canonical pathway and also the p52 component of the non-canonical pathway, which is induced by LMP1. Interestingly, bortezomib seemed to be more effective at cell killing in EBV+ B cells with type III latency pattern than those with type I latency. Finally, bortezomib prolonged the survival of mice inoculated with EBV-transformed cells.

Given the expression of CD30 in the RS-like cells prevalent in EBV+ DLBCL, brentuximab vedotin is a potential future treatment option. Results from a recent retrospective study showed not only that the expression of CD30 was higher in EBV+ than EBV-negative DLBCL but CD30 expression was associated with lower 5-year overall survival (OS) rates (Young *et al*, 2013). A clinical trial evaluating the efficacy of the combination of brentuximab vedotin and rituximab for the frontline therapy in patients with $CD30^+$ and/or EBV+ lymphoma is ongoing (NCT01805037).

Extranodal NK/T cell lymphoma

ENKTL was classified as a distinct entity in 1997 (Harris *et al*, 1999), and recognized by its aggressive nature, involvement of the upper airway, and positivity for neural cell adhesion molecule (NCAM, CD56) (Kern *et al*, 1992). ENKTL is most common in Asia, Central America and South America, where it accounts for up to 10% of all lymphomas (Ai *et al*, 2012). ENKTL has a male predominance with a median age at diagnosis in the early 50s (Cheung *et al*, 2002; Wu *et al*, 2008). Patients with ENKTL present with nasal congestion, fever, purulent or bloody nasal discharge and headache secondary to a destructive mass typically seen in the nasal cavity. ENKTL, however, can present elsewhere in the upper aerodigestive tract (UADT). ENKTL may also present outside of the UADT, such as skin, testes, and gastrointestinal tract. UADT ENKTL tends to remain locoregional while non-UADT tends to present and disseminate to distant areas (Kwong, 2011).

Histologically, there is diffuse involvement of a variety of small to large abnormal lymphoid cells with irregular nuclei and open chromatin (Kwong *et al*, 1997). Admixed within malignant cells is an inflammatory background of small lymphocytes, eosinophils, histiocytes and plasma cells. Within the tumour mass, there is necrosis with malignant cells showing angiocentricity. Over 90% of cases are surface CD3-negative but positive for CD2 and cytoplasmic CD3 (Kwong *et al*, 1997). The NK marker CD56 is expressed in 80% of cases. ENKTL has also a high degree of CD30 expression (70% of cases) (Pongpruttipan *et al*, 2011). Approximately 50–70% of cases express LMP1 and 40% of cases LMP2A, reflecting an EBV latency type II (Chiang *et al*, 1997; Pongpruttipan *et al*, 2011; Kanemitsu *et al*, 2012). EBER can be detected using *in situ* hybridization techniques (Chiang *et al*, 1997). While most ENKTL are of NK origin (>80%), at least 10% of cases are derived from T cells. The differential diagnosis includes PTCL, not otherwise specified (PTCL-NOS), chronic active EBV infection and aggressive NK-cell leukaemia (ANKL). ENKTL is distinguished from ANKL by the degree of bone marrow or peripheral blood involvement (Takahashi *et al*, 2011).

Although the International Prognostic Index (IPI) score appears to be prognostic in ENKTL (Cheung *et al*, 2002; Lee *et al*, 2006; Wu *et al*, 2008), approximately 50% of patients have an IPI score ≤1 (Chim *et al*, 2004). A retrospective review of 262 patients with low IPI scores identified B symptoms, stage III/IV, elevated LDH and regional nodal involvement as adverse factors (Lee *et al*, 2006). In a subset analysis within the International Peripheral T Cell Lymphoma Project, non-nasal ENKTL had a worse outcome than nasal ENKTL (Au *et al*, 2009). Haemophagocytic syndrome carries a dismal prognosis, as survival can be measured in days to weeks (Kwong, 2011). In patients with stage I disease, radiotherapy alone or chemoradiation is recommended. In patients with stage II disease, concurrent chemoradiation with regimens such as DeVIC (dexamethasone, etoposide, ifosfamide and carboplatin), VIPD (etoposide, ifosfamide, cisplatin and dexamethasone) or GELOX (gemcitabine, L-asparaginase and oxaliplatin) is recommended. In advanced disease, studies have explored the use of L-asparaginase-containing protocols. A phase II study treated patients with SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) and showed a CR and 5-year OS rate of 56% and 50% respectively (Yamaguchi *et al*, 2011). In the relapsed setting, L-asparaginase-containing regimens, such as SMILE and AspaMetDex (L-asparaginase, methotrexate and dexamethasone), have been associated with a CR rate of 50–60% and a median OS of approximately 1 year (Yamaguchi *et al*, 2008; Jaccard *et al*, 2011).

Novel therapies: proteasome inhibitors and anti-CD30 ADC. Possibly contributing to the aggressive nature of ENKTL is the up-regulation of the NF-κB pathway. However, unlike EBV+ DLBCL, where the canonical and non-canonical pathways are activated, only the non-canonical pathway seems to be activated in ENKTL. In a study using samples from 23 patients with previously untreated ENKTL patients, 65% of the samples showed p52 nuclear staining but none of the cases showed nuclear staining for p65 or p50 (Liu *et al*, 2009). Additionally, p52+ patients experienced significantly lower response rates and worse survival than p52-negative patients. In an *in vitro* study, low concentrations of bortezomib were effective at inhibiting the growth of ENKTL cell lines and primary cells, with evidence of apoptosis within 6 h of exposure (Shen *et al*, 2007). Bortezomib has been added to CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) in a phase I trial in 13 patients with advanced stage PTCL and ENKTL and found to be well tolerated with a 62% CR rate (Lee *et al*, 2008). One of the three patients with ENKTL experienced CR (33%). More recently, a phase II study evaluated bortezomib-CHOP in 43 patients with PTCL and ENKTL (Kim *et al*, 2012a). The CR rate in

ENKTL patients ($n = 10$) was 30%, which appears lower than the CR rate seen in patients treated with SMILE (56%), although with less toxicity.

CD30 is expressed by the malignant cells in many cases of ENKTL (Kanavaros *et al*, 2000; Pongpruttipan *et al*, 2011), which raises the possibility of brentuximab vedotin as a therapeutic option. Additionally, CD30 expression determined by >50% membranous staining might be related with a worse prognosis in ENKTL (Hong *et al*, 2012). In this retrospective study in untreated patients, $CD30^+$ ENKLT patients had inferior event-free survival and OS than CD30-negative ENKTL patients. There are currently two ongoing studies evaluating brentuximab vedotin in patients with untreated and relapsed $CD30^+$ lymphoma, including ENKTL (NCT01805037 and NCT01703949 respectively).

Human herpesvirus 8

Human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus, is a *gamma*-herpesvirus identified in 1994 in patients with Kaposi sarcoma (Chang *et al*, 1994). Multiple subtypes of HHV-8 have been identified, each with different geographic predilections (Dukers & Rezza, 2003). Transmission of the virus occurs *via* blood products and sexual contact, and is hypothesized to be transmissible *via* saliva though this has not been fully established. Vertical transmission, however, is not commonly seen. HHV-8 has been associated with the development of primary effusion lymphoma (PEL), a rare lymphoma typically seen in patients infected with HIV.

HHV8 lymphomagenesis (Fig 2)

The actual mechanism of HHV-8 oncogenesis is an active field of study, and a number of cell signalling factors and cell cycle determinants have been implicated. FLICE-inhibitory protein (v-FLIP) K13 has been demonstrated to activate both classical and alternative NF-κB pathways and has also been proposed to block Fas-activated caspase activation (Chugh *et al*, 2005). v-FLIP has also been shown to down-regulate CD19 and drive expression of the proliferative cytokine RANTES/CCL5 (Punj *et al*, 2012). These changes collectively result in constitutive cell cycle activation and anti-apoptotic mechanisms that drive uninhibited PEL-cell growth. Production of CCL5 may also contribute to the paracrine-driven growth of cells adjacent to the transformed lymphocytes (Matta & Chaudhary, 2004; Punj *et al*, 2012). Signal Transducer and Activator of Transcription-3 (STAT3) has been found to be constitutively active in PEL cells, resulting in de-regulated survivin expression (Aoki *et al*, 2003). Survivin is an inhibitor of apoptosis protein (IAP) known to play a central role in tumourigenesis in multiple cancers, and its expression has been shown to de-regulate many cell signalling pathways including the PI3k/AKT, mTOR, MAP kinase, EGFR and VEGF pathways (Kanwar *et al*, 2013). Members of the latency-associated nuclear antigen (LANA) family are believed to play multiple roles in PEL tumourigenesis. LANA1 facilitates the propagation of HHV-8 episomes to PEL daughter cells *via* chromosomal tethering (Ballestas *et al*, 1999) as well as inhibition of p53 (TP53) resulting in impaired tumour suppression (Friborg *et al*, 1999). LANA2 has been shown to regulate survivin expression (Marcos-Villar *et al*, 2009). v-Cyclin is a cyclin D homolog that is up-regulated in HHV-8-infected cells. It has been shown to drive persistent cyclin-dependent kinase (CDK) activation and thus activate cell cycle progression independent of inhibition by $p16^{Ink4a}$ (CDKN2A), $p21^{Cip1}$ (CDKN1A) and $p27^{Kip1}$ (CDKN1B) (Swanton *et al*, 1997). KSbcl-2 is a viral BCL2 homolog with sequence homology to BHRF1 (EBV) and ORF16 (*Herpesvirus saimiri*) that has been proposed to confer constitutive cell cycle activation in HHV-8 as well (Cheng *et al*, 1997).

Primary effusion lymphoma

PEL is a rare non-Hodgkin lymphoma subtype that occurs most frequently in HIV+ patients (Cesarman *et al*, 1995) but has also been reported in post-transplant patients and the elderly (Jones *et al*, 1998; Dotti *et al*, 1999; Klepfish *et al*, 2001). PEL has been reported to account for 1–4% of HIV-associated lymphomas (Mbulaiteye *et al*, 2002; Simonelli *et al*, 2003; Chen *et al*, 2007). WHO criteria require HHV-8 infection for diagnosis of PEL (Said & Cesarman, 2008). PEL most commonly presents with symptoms of fluid accumulation in one or more body cavities. Patients usually present with B symptoms and signs corresponding to the body cavity involved (i.e. cardiac tamponade, shortness of breath, abdominal distention or scrotal swelling). PEL was initially believed to be a liquid-phase tumour, but more recent reports have demonstrated lymphomas with similar characteristics and HHV-8 viral proteins in solid organs, which have been termed extra-cavitary or solid PEL (Kim *et al*, 2012b).

The malignant cell population in PEL is of B-lymphocyte lineage with immunoblastic or plasmablastic appearance. The cells typically express CD45, CD30, CD38 and CD138, but are commonly negative for CD19, CD20, or CD79a. The nuclei of the malignant cells should stain positive for HHV-8-associated latent proteins. BL and DLBCL may present as a lymphomatous effusion in HIV-negative and HIV+ patients, but can be distinguished by the absence of HHV-8 makers, which is not associated with PEL (Chen *et al*, 2007). Both BL and DLBCL malignant cells are also $CD20^+$. However, there seems to be a subset of PEL cases that expresses CD20 (Castillo *et al*, 2012).

Prognosis in PEL is generally poor, with median survival times of 6–9 months (Simonelli *et al*, 2003; Boulanger *et al*, 2005; Castillo *et al*, 2012). Data on prognostic factors are scant. A study including 28 HIV+ patients identified a poor performance status and no ART prior to PEL diagnosis as

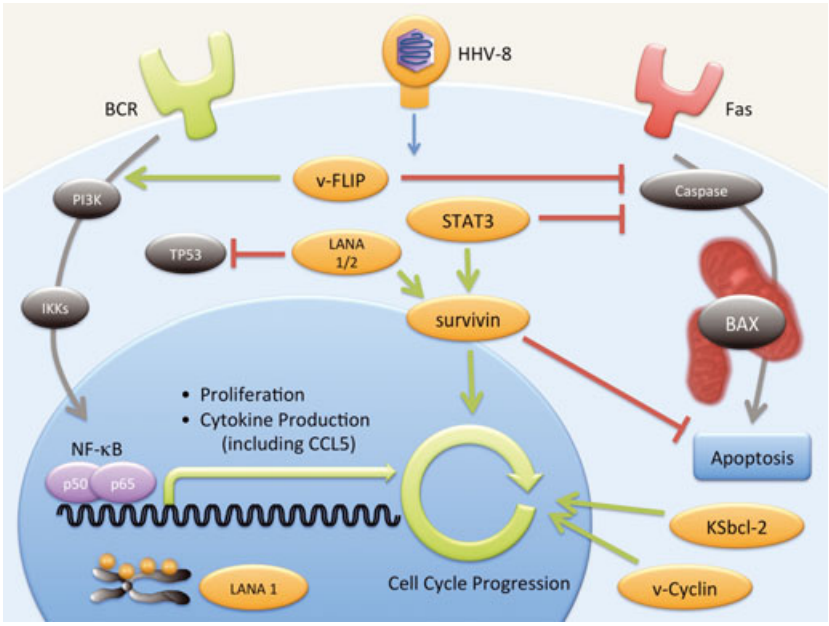

Fig 2. Schematic representation of the lymphomagenetic role of the human Herpesvirus 8. HHV-8, Herpesvirus 8; BCR, B cell receptor; PI3K, phosphatidylinositide 3-kinase; IKKs, IκB kinases.

adverse factors (Boulanger *et al*, 2005). A recent systematic review of the literature showed that outcomes were worse in patients with a higher number of body cavities involved (Castillo *et al*, 2012). There have been no prospective studies to validate one chemotherapy regimen over another in patients with PEL. Furthermore, most retrospective studies are small and heterogeneous. One study reported complete remission in 42% of patients with PEL who both had and had not received previous ART, using CHOP. Another retrospective series reported a 50% CR rate with a 39% 1-year OS rate in patients who received chemotherapy of any type concurrently with ART (Boulanger *et al*, 2005). Current guidelines recommend the use of regimens such as CHOP, infusional etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (EPOCH) or cyclophosphamide, doxorubicin and etoposide (CDE) .

Novel therapies: proteasome inhibitors, monoclonal antibodies and histone deacetylase inhibitors. There are mounting data supporting the killing ability of bortezomib in PEL cells and tumour xenografts. In an *in vitro* study, bortezomib at low concentrations inhibited the constitutive activation of NF-κB and also inhibited the growth and induced apoptosis in PEL cell lines (An *et al*, 2004). More recently, the efficacy of bortezomib has been studied in a xenograft model (Matta & Chaudhary, 2005). Primary PEL cells obtained from a PEL patient were injected in non-obese diabetic severe combined immunodeficiency (NOD/SCID) mice, which developed peritoneal swelling and died from disease 15 d after injection. In this experiment, bortezomib induced higher levels of apoptosis at earlier time points that doxorubicin. *In vivo*, bortezomib prolonged the survival on PEL-bearing mice and was superior to doxorubicin. The clinical use of bortezomib in PEL is limited to case reports (Boulanger *et al*, 2008; Siddiqi & Joyce, 2008).

A recent systematic review showed that 69% and 33% of PEL cases express CD30 and CD20 respectively (Castillo *et al*, 2012). CD30 expression was also observed in PEL cell lines as well as eight out of nine primary PEL specimens (Bhatt *et al*, 2013a). *In vitro*, brentuximab vedotin blocks proliferation, induces G2/M cell cycle arrest and triggers apoptosis in PEL cells. *In vivo*, brentuximab vedotin prolonged the median survival of PEL-bearing mice. There are few cases reported in the literature on the use of rituximab in $CD20^+$ PEL with early evidence of success (Perez & Rudoy, 2001; Takao *et al*, 2004; Lim *et al*, 2005b). The combination of brentuximab vedotin and rituximab in EBV+ and/or $CD30^+$ lymphomas, including PEL, is under investigation (NCT01805037).

The potential for use of histone deacetylase (HDAC) inhibitors has been studied in PEL cell lines. Treatment of cultured cells with HDAC inhibitors [sodium butyrate (NaB) or trichostatin A (TSA)] was shown to release LANA from the ORF50 promoter, which was found to stimulate HHV8 lytic reactivation in latently-infected cells (Lu *et al*, 2006). It has also been demonstrated that early apoptosis and late-phase cell death could be induced in PEL cell lines in a dose-dependent manner by the HDAC inhibitors romidepsin, vorinostat, or TSA (Niedermeier *et al*, 2006). More recently, an *ex vivo* model of PEL has been modelled in NOD/SCID mice. This model was used to demonstrate the benefit of combination therapy with the proteasome inhibitor

bortezomib and vorinostat. Treatment resulted in significant activation of HHV-8 lytic replication and massive apoptosis, as well as prolonged survival of the PEL-bearing mice (Bhatt *et al*, 2013b).

Human T-lymphotrophic virus type 1

The human T-lymphotropic virus type-1 (HTLV-1) is a retrovirus, endemic in Southwestern Japan, the Middle East, North Africa, the Caribbean and South America. HTLV-1 was identified as the first human retrovirus in Japan in 1977 (Poiesz *et al*, 1981). HTLV-1 is the pathogenic agent associated with the development of adult T cell lymphoma/leukaemia (ATLL), among other diseases.

HTLV-1 lymphomagenesis (Fig 3)

Transmission of HTLV-1 can occur in three ways including mother-to-child *via* breast-feeding (vertical), sexual contact or parenteral, such as contact with blood or intravenous drug use. One of the key mediators of HTLV-1 oncogenesis is the protein Tax (Transcriptional Activator of pX region), which is encoded in the pX region of the viral genome (Azran *et al*, 2004). Tax can activate NF-κB, cAMP response element-binding protein (CREB), and serum response factor (SRF) pathways to promote viral transcription (Munoz & Israel, 1995). Apoptosis and DNA repair factors, such as Bcl-xl (BCL2L1), BAX and PCNA can also be affected by Tax (Azran *et al*, 2004). During the latter stages of oncogenesis, the signalling pathways initiated by Tax become maintained independently and eventually Tax expression becomes suppressed through genetic mutations or epigenetic repression (Giam & Jeang, 2007). Another protein implicated in HTLV-1 oncogenesis is Rex, which is also encoded in the pX region (Nakano & Watanabe, 2012). Rex modulates viral gene expression at the post-transcriptional level by binding and transporting unspliced and singly spliced viral RNAs from the nucleus to the cytoplasm. These viral RNAs encode the structural proteins env, gag and pol. The protein HTLV-1 bZip factor or HBZ is also involved in HTLV-1 oncogenesis (Matsuoka & Jeang, 2011). By inhibiting the activator protein 1 signalling pathway, HBZ inhibits $CD4^+$ T cell responses to infected cells promoting viral gene transcription.

Adult T cell leukaemia/lymphoma

Adult T cell lymphoma/leukaemia (ATLL) is a malignancy of mature T-lymphocytes linked with HTLV-1 infection (Ohshima *et al*, 2008). The incidence and geographical distribution of ATLL is closely related with HTLV-1 endemic areas of the world including South Japan, the Caribbean basin, South America, the Middle East and Africa (Ohshima *et al*, 2008). A small proportion (1–4%) of individuals infected with HTLV-1, however, would develop ATLL after a latency period of approximately 30–50 years. ATLL can be divided into four subtypes: two aggressive subtypes, acute (leukaemic) and lymphomatous, and two indolent subtypes, chronic and smouldering (Ohshima *et al*, 2008). In the acute leukaemia type, lymphadenopathy and hepatosplenomegaly can be seen, and bone marrow is usually involved. Lytic bone lesions and visceral lesions involving the skin, gastrointestinal tract and lungs can also be seen. The lymphomatous subtype shares

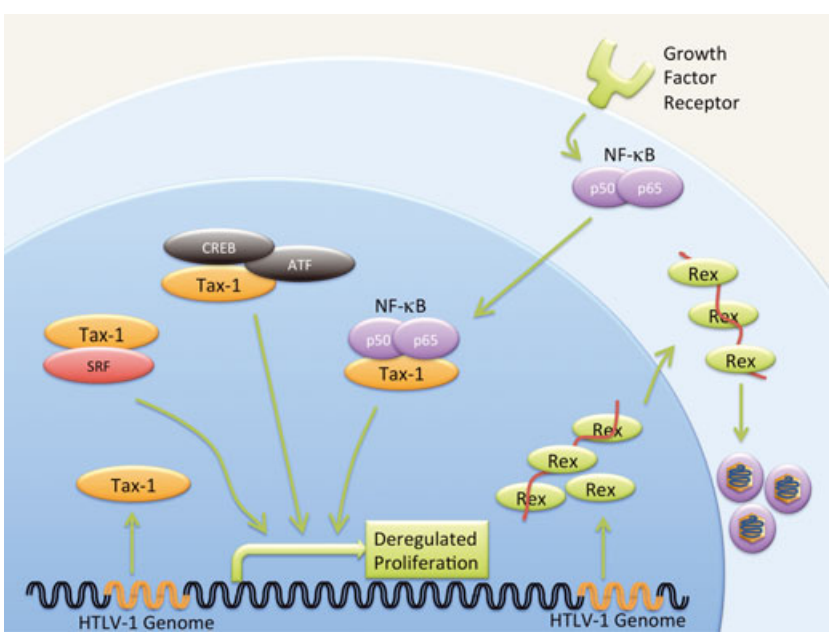

Fig 3. Schematic representation of the lymphomagenetic role of the human T-lymphotrophic virus type 1. SRF, serum response factor; CREB, c-AMP response element-binding factor.

many clinical characteristics with the acute subtype, but lymphadenopathy appears more prominent with absence of peripheral blood involvement. Most patients will present with positive serological tests for HTLV-1. In patients with a negative serological test but with a high suspicion for ATLL, polymerase chain reaction (PCR) testing can demonstrate HTLV-1 proviral integration (Tsukasaki *et al*, 2009).

Under microscopy, leukaemic ATLL cells can present with atypically multilobulated nucleus, which are often referred to as flower or clover cells (Ohshima *et al*, 2008). The malignant cells characteristically express CD2, CD4, CD5, CD25 and HLA-DR. Recent studies have reported an increased expression of FOXP3, a transcription factor implicated in T cell regulation, activation and differentiation, and a master control gene for the development and function of regulatory T cells (Roncador *et al*, 2005), although this relationship has been challenged (Toulza *et al*, 2009). Through PCR techniques, ATLL cells can show *TRA/TRB* gene rearrangements.

Prognosis for the aggressive forms of ATLL tends to be poor with a 5-year OS of 14% (Vose *et al*, 2008). Although the IPI score can be of value in patients with aggressive ATLL (Suzumiya *et al*, 2009; Beltran *et al*, 2011b), a large Japanese study has described a prognostic index for patients with aggressive ATLL subtypes (ATL-PI) (Katsuya *et al*, 2012). The only randomized study in patients with aggressive ATLL compared the outcomes between CHOP every 2 weeks *versus* VCAP (vincristine, cyclophosphamide, doxorubicin and prednisone), AMP (doxorubicin, ranimustine and prednisone), and VECP (vindesine, etoposide, carboplatin and prednisone) (Tsukasaki *et al*, 2007). In this Japanese study, VCAP-AMP-VECP was associated with higher CR rates but the 3-year OS was not statistically different. Additionally, toxicity was lower with CHOP. Other regimens that have been recommended are CHOEP (bolus CHOP and etoposide), infusional EPOCH and hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine), although the experience with these regimens is limited to case reports (Alduaij *et al*, 2010) or consensus opinions. A meta-analysis has evaluated the combination of zidovudine and interferon (AZT/IFN) in patients with ATLL (Bazarbachi *et al*, 2010). In that study, only acute ATLL patients derived benefit from this combination. However, a recent study has suggested that AZT/IFN can be of value in both aggressive ATLL subtypes when administered sequentially or concurrently with chemotherapy (Hodson *et al*, 2011). In all aggressive subtypes, CNS prophylaxis should be considered as well as allogeneic HSCT in eligible candidates.

Novel therapies: anti-CXCR4 therapy, hypomethylating agents and HDAC inhibitors. Recently, pre-clinical studies have shown that ATLL cells respond to stimulation with human stromal cell-derived factor 1-*alpha*, also known as CXCL12 (Nagasawa *et al*, 1996). CXCL12 binds and signals exclusively through the chemokine receptor CXCR4, which acts as a chemoattractant for lymphocytes, and plays a role in stem cell localization. Hence, CXCR4 might be involved in ATLL cell migration and infiltration. Additionally, the CXCR4 antagonist AMD3100 was shown to inhibit ATLL infiltration into the liver and lungs in SCID mice (Kawaguchi *et al*, 2009), providing the rationale for the use of CXCR4 inhibitors in ATLL. A recent phase II study showed that mogalizumab (KW-0761), a fucosylated humanized anti-CXCR4 monoclonal antibody, was associated with an ORR of 50% and a CR rate of 30% in patients with relapsed/refractory ATLL with acceptable toxicity (Ishida *et al*, 2012). In such patients, the expected ORR was 5%. Based on these results, a randomized phase II study is underway in Japan in which intensified chemotherapy will be evaluated with and without mogalizumab (NCT01173887).

DNA hypermethylation seems to play a pathophysiological role on ATLL. A series of studies have shown that important genes, such as *KLF4*, which encodes a cell cycle regulator, and *EGR3*, encoding a transcriptional factor for the expression of Fas ligand, are located near hypermethylated regions and silenced in ATLL cells, among others (Yasunaga *et al*, 2004). The *PDLIM2* gene, which plays a suppressive role for HTLV-1 Tax-mediated tumourigenesis, was also found hypermethylated and silenced in ATLL cells (Yan *et al*, 2009a, b). A recent preclinical study has shown that the hypomethylating agent azacitidine (Vidaza®) induced growth inhibition of ATLL cell lines and restored the transcript expression of *CDKN2A*, a cell cycle regulator silenced in ATLL cells (Uenogawa *et al*, 2011).

HDACs might play a role in ATLL lymphomagenesis by promoting the decrease in transcription of affected genes. By inhibiting this process, HDAC inhibitors would lead to the reactivation of transcriptionally repressed genes ultimately causing cell cycle arrest and apoptosis of ATLL cells (Zimmerman *et al*, 2011). Specific targets for HDAC inhibitors include Histone H3 in both MT-2 and C8166 cell lines. By targeting this cell line-specific Histone H3 in animal models, an orally bioavailable HDAC inhibitor (AR-42) was shown to prolong survival of ATLL-engrafted mice compared to controls. Other preclinical studies have shown promise in other HDAC inhibitors, such as vorinostat, romidepsin and panobinostat (Tsukasaki & Tobinai, 2012).

Conclusion

Based on our review, the response and survival rates in patients with virally-induced lymphomas, when treated with standard chemotherapeutic approaches, appear lower than in individuals whose lymphomas are not driven by a viral infection. As an example, the outcomes of patients with ENKTL, PEL and ATLL remain dismal, and in a large proportion of cases, patients would not survive for more than a year after diagnosis. One could hypothesize, and in many cases demonstrate, that there are specific biological mechanisms that enhance proliferation, blunt apoptosis and/or allow escape from immunosurveillance. Another hypothesis could be that

such lymphomas are so rare in the Western hemisphere and information so limited that what we can see are the outcomes of such lymphomas in other countries with blatant healthcare differences. However, the few case reports and series from the US and Europe do not provide the sense that those do any better than in other parts of the world. Given that these lymphomas seem to be driven by an infectious process, we might need to think about the host, agent and inoculum triad. In such case, the differences in the incidence, prevalence and clinical course of virally driven lymphomas can relate to either specific HLA differences that might make some individuals more susceptible, different strains of viruses that might be related with higher or lower risk of lymphomas or perhaps the viral load might dictate susceptibility and clinical course. However, in our opinion, it is probably a combination of all of the above.

As our understanding behind virally induced lymphomagenesis advances, so does the potential of treating patients with novel therapies. Such novel therapies would then have to take advantage of the specific biological mechanisms (pathways) by which viruses induce proliferation, maintenance and dissemination of lymphomas, providing the potential of improving the outcome on these patients with lower rates of toxicity. However, based on our review, it seems that the single agent activity of such therapies, aside from CTLs directed against EBV-expressed proteins, is rather limited. Future directions in the treatment of virally induced lymphomas include the design of clinical trials using a combination of standard chemotherapy and novel therapies. In fact, pre-clinical studies are showing synergism using these approaches in combination. We are fully aware, however, of the pitfalls and limitations of translating successful preclinical experience into a successful clinical one.

Virally induced lymphomas are relatively rare in Western hemispheres and the advancement on treatments will only depend on the careful (thoughtful) design of multi-institutional clinical trials. Collaborative efforts such as the acquired immunodeficiency syndrome (AIDS) Malignancy Consortium has proven to be effective in designing prospective studies focused on patients with HIV infection and malignancies. A similar platform could be designed to study lymphomas and cancers induced by other viruses. For this purpose, the collaboration between multiple centres and countries is mandatory if we want to move the field of virally induced lymphomas forward.

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JJC designed the structure of the review. JLR, KB and AE performed the literature search and gathered pertinent data. KB drew the figures. All the authors wrote and approved the manuscript.

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