E-ISSN: 3068-5052
Journal of Regenerative Medicine & Biology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

*Review Article*

# The Role of Stem Cell therapies in the Treatment of Burkitt's Lymphoma: Exploring Changes in Stem Cell Function caused by Pathogenic Infections

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Citation: Benson M, et al. The Role of Stem Cell therapies in the Treatment of Burkitt's Lymphoma: Exploring Changes in Stem Cell Function caused by Pathogenic Infections. J Reg Med Biol Res. 2026;7(1):1-13.

https://doi.org/10.46889/JRMBR.2026.7105

Received Date: 21-01-2026

Accepted Date: 12-02-2026

Published Date: 19-02-2026



## Abstract

Burkitt's Lymphoma (BL) is a rare form of B-cell non-Hodgkin lymphoma. BL is aggressive and tumors can double in size in only 24 hours. BL is caused by a mutation in the c-MYC oncogene. c-MYC is translocated to immunoglobulin enhancers, which then cause uncontrolled cell proliferation. The translocation is most linked to the Epstein-Barr Virus (EBV). When EBV infects B-cells of the host leads to uncontrolled cell proliferation. Advancements continue for EBV-targeted treatments to act as intervention in EBV-infected cells. Other factors that lead to uncontrolled cell proliferation include mutations in the apoptotic regulators, TP53 and BIM. Histology of BL presents a uniform "starry sky" pattern. This unique appearance is the hallmark of BL diagnoses. Treatment for BL includes intensive chemotherapy and can be followed by Hematopoietic Stem Cell Therapy (HSCT). Peripheral blood and bone marrow stem cell transplantation are used for stem cell therapies that treat BL. Peripheral Blood Stem Cells (PBSC) are commonly used over Bone Marrow (BM) due to faster engraftment and lower risk of infection. Both autologous and allogeneic Stem Cell Treatments (SCT) have been shown to improve and accelerate recovery post-chemotherapy treatment. Healthcare improvements have been made in low-income regions, leading to improved survival rates for BL. This is a review of assembled evidence on the influence of pathogens such as EBV on molecular pathways that drive BL. This review also assesses therapeutic approaches such as hematopoietic stem cell transplantations to treat BL.

**Keywords:** Burkitt's Lymphoma; Hematopoietic Stem Cell Transplantation; Epstein-Barr Virus; C-MY Translocation; Peripheral Blood Stem Cells; Autologous Transplantation; Immunotherapy; Global Epidemiology

## Introduction

Burkitt's Lymphoma (BL) is a highly rare and specific domain of B-cell non-Hodgkin's lymphoma that is both aggressive and fast-growing. The first symptoms of BL include the presence of rapidly growing tumors and lesions. The tumor size in the cells of BL doubles in size within 24-48 hours [1]. Cytomorphology is used to diagnose BL due to the cells sharing exclusive characteristics throughout all subtypes [2]. Subtypes of BL include Endemic, sporadic and immunodeficiency-related BL. Sporadic BL is most prevalent in North America and Western Europe. Endemic BL is most prevalent in Sub-Saharan Africa and Papua New Guinea. Immunodeficiency-related BL is most prevalent in Sub-Saharan Africa, Eastern Europe and Central Asia. All subtypes look almost indistinguishable due to extensive overexpression of the c-MYC oncogene proliferation without differentiation but differ in the location of tumor lesions [2].

The c-MYC protooncogene is responsible for cell growth, regulation and division. When the c-MYC protooncogene is mutated, it leads to uncontrolled B-cell proliferation. The c-MYC protooncogene is mutated into an oncogene through a translocation. The

c-myc is translocated and placed under the control of an immunoglobulin enhancer. The cause of the c-MYC translocation ranges from Epstein-Barr Virus (EBV) infection, which is most common, to mutations in pathways such as TP53 and BIM, which are rarer but not unseen.

BL is the first cancer linked to a virus, EBV. EBV uses two phases which allow the virus to successfully infect B-cells for such a long period of time (Fig. 1). One of the phases is the latent phase. The latent phase hides EBV inside the host B-cells while it expresses a minimal set of genes such as EBNA1, LMP1 and LMPA2. There are four latency programs which include latency 0, I, II and III. These latency programs are found in diseases such as BL, Hodgkin lymphoma, nasopharyngeal carcinoma and Post-Transplant Lymphoproliferative Disorder (PTLD). When EBV is in Latency I phase it expresses Epstein-Barr Nuclear Antigen (EBNA1). EBNA1 reduces immune signal response which is the reason EBV can go undetected for a long period of time. EBNA2 uses the host transcription factor CBF1/CSL for chromatin loops that regulate c-MYC [3]. Latent membrane protein 1 (LMP1) is an oncoprotein that acts as a CD40 receptor which activates NF-kB, MAPK/ERK, PI3K and JNK pathways. The enhanced activation of these pathways leads to B-cell proliferation [3]. Latent membrane protein 2A (LMP2A) prevents be cells from undergoing apoptosis by acting as a B-cell receptor signal. Blocking the B-cell receptor signal prevents lytic reactivation. During the latency phase, the EBV virus continues to grow and express genes, increasing the chances of a c-myc translocation in B-cells.

EBV is activated and begins replication in the lytic phase. The genes BZLF1 and BRLF1 are turned on by the EBV genome. These genes begin the process of replication. The increase of viral burden spreads the infection to new B-cells in the host. The EBV lytic proteins that damage the stability of the B-cell genome are BNRF1, BGLF5, BALF3 and BGLF4. BamHi N Rightward frame 1 (BNRF1) is a major tegument protein that causes chromosome mutations. When BNRF1 is removed it reduces damage to the host genes [4]. BamHI G Leftward Frame 5 (BGLF5) is a viral DNase that cuts DNA before the lytic phase begins to replicate the DNA. Studies have concluded that reactivation of the lytic phase elevates the likelihood of tumor growth. When EBV cannot enter the lytic cycle tumor formation is less frequent [4]. BamHI A Leftward Frame 3 (BALF3) is a viral terminase protein that also breaks DNA causing genomic instability [4]. BamHI G Leftward Frame 4 (BGLF4) is a viral kinase that modifies chromosome condensation and disrupts mitosis [4]. EBV mircroRNAs also contribute to tumorigenesis. MiR-BHRF1-2 downregulates tumor suppressors such as PTEN and PRDM1, further enhancing tumor growth. miR-BHRF1-1 controls host genes by reducing RNF4 preventing its ability to tag other proteins for modification. EBV super enhancers drive the growth of the c-MYC oncogene eventually leading to EBV- related cancers such as BL. Research has shown that finding ways to prevent the reactivation of the lytic phase of EBV can prevent oncogenesis all together [4].

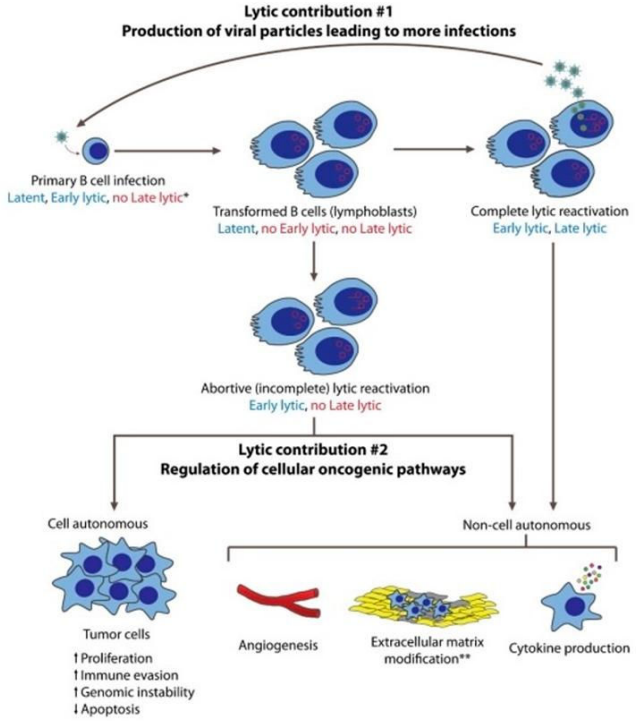


**Figure 1:** This model shows the two mechanisms of how EBV lytic Reactivation promotes viral spread and oncogenesis [4].

The goal of this review is to conduct and in-depth analysis of the current research of BL and its correlation to EBV-induced

molecular pathogenesis. The developing stem-cell based therapies and future treatment directions for BL will also be discussed.

**Methodology**

A traditional review was executed to evaluate cellular biology, epidemiology, identification of disease and treatments of BL. Google scholar, Web of Science, PubMed were databases used to locate peer-reviewed articles. Search terms included, Burkitt's lymphoma, c-MYC oncogene, Epstein-Barr virus, hematopoietic stem cell transplantation, peripheral blood stem cells and clinical trials. Studies on clinical trials, research on diagnostic tests, treatment strategies and new therapies were evaluated that were published predominantly between the years 1980 and 2025. A discussion of these articles was included, along with animal model studies which were relevant to the development of stem cell transplantation. Qualitative data was provided to integrate currently used treatment strategies along with future research directions.

**Results and Discussion**

*Epidemiology of BL*

Although BL is rare overall, pediatric BL accounts for 30-50% of all childhood lymphoma cases making it the fourth most common cancer in children [5]. A study utilized data from the Global Burden of Disease (GBD) from 1990 to 2021 to analyze trends of BL worldwide in children aged 1 to 14 [5]. The data indicate that global cases of BL increased significantly, starting at 2,800 cases in 1990 and 31 years later, the cases increased to a little more than 4,000 cases in 2021, presenting a 31.45% increase in case count over this period of time. The highest incidence rates are in sub-Saharan East Africa. It is essential to note that sub-Saharan Africa bears the largest disease burden due to its high incidence rate and low Socio-Demographic Index (SDI). Meaning, there is restrain on access to proper treatment and efficient diagnoses. On the other hand, Central sub-Saharan Africa presented a drastic decline in BL incidence rates. This can be an indication of less exposure to malaria in this region of Africa [5].

Globally, children ages from five to nine years old tend to be at the highest risk of developing BL. Data shows that this age group consists of one third of all diagnosed cases of BL and includes the highest mortality rate [5]. The next highest incidence rate is children from ages 10 to 14 years old, although significantly lower than the five to nine group. Infants show the lowest incident rates. At mostly all age groups, there is a higher incidence of BL in males than there is in females. There was a very pronounced difference in the age group from five to nine years old. There is a change in trend at ages 12 to 23 years old, females have a higher incidence rate.

The mortality rate from the years 1990 to 2021 slightly increased from 2,450 to 3,000 deaths per year, worldwide [5]. The slow progression of mortality rates compared to incidence rates reflects a positive trend of treatment improvements, specifically in high SDI regions. There are unique drivers for BL that vary by region. In sub-Saharan Africa there is an increased risk for BL due to exposure to endemic malaria and EBV exposure. In this region, low access to effective chemotherapy treatments drives the higher mortality rate compared to middle or high SDI region. Upon the overview of consistent data, using Bayesian forecasting (a method that uses Bayes theorem), it has been predicted that by the year of 2035 incidence and mortality rates will have a modest decline under the assumption that improvements to the global health systems are continued [5].

*Pathophysiology of BL*

BL is caused by a translocation in chromosomes, which leads to the activation of the c-MYC oncogene. During normal function, the c-MYC gene is a proto-oncogene that manages cellular growth, proliferation and division. c-MYC protooncogene contains three exons, the first remains untranslated to provide RNA regulation and stability, with higher c-MYC gene expression increasing the ability to enter the S-phase [6]. Due to its ability to bind to DNA, it has been determined that the c-MYC is presumably involved in transcriptional stability and post-transcriptional regulation caused by a short mRNA half-life controlled by the first exon [6]. c-MYC is highly conserved in vertebrates over a long evolutionary time. An over 90% amino acid similarity has been found between the human and mouse c-MYC genes, along with 70% similarity with chickens and 62% similarity with trout [6]. This data expresses the importance of the protein and structure of the c-MYC genes due to the lack of change throughout different vertebrate species in evolution. The conservation of the c-MYC gene elucidates why a mutation in this gene, like in BL, can have such a negatively impactful effect on growth regulation (Fig. 2).

When c-MYC is translocated next to immunoglobulin enhancers, this causes uncontrolled proliferation due to how highly active the enhancers are in B cells (Fig. 2) [1]. The most common c-MYC translocation in BL is the t(8;14) (q24;q32) translocation [1]. The

mutation of the c-MYC protooncogene into an oncogene leads to a translocation associated with moving the c-MYC next to immunoglobulin loci located on chromosome 14. The classic t(8;14) (q24;q32) translocation is found in 70-80% of BL cases [1]. The deregulated c-MYC gene in BL gives c-MYC gene control of B-cell immunoglobulin enhancers, inducing malignant cell growth that is uncontrolled, blocking differentiation [6]. Variant translocations of chromosomes involving immunoglobulin light chain loci that lead to the activation of c-MYC include t(2;8) (p12;q24) and t(8;22)(q24;q11) [1]. During the process of t(2;8) (p12;q24), c-MYC gains control of enhancer elements that influence kappa light chain expression, leading to the overexpression of c-MYC in B cells [1]. During the process of t(8;22) (q24;q11), c-MYC is translocated to the immunoglobulin lambda light chain locus, gaining control over lg lambda enhancer elements, leading to overexpression of the c-MYC gene [1]. Both variant translocations combined make up 10-15% of BL cases [1]. In normal cells, c-MYC overexpression leads to apoptosis; this confirms that for BL to occur, there must be an additional mutation that blocks the process of apoptosis [1].

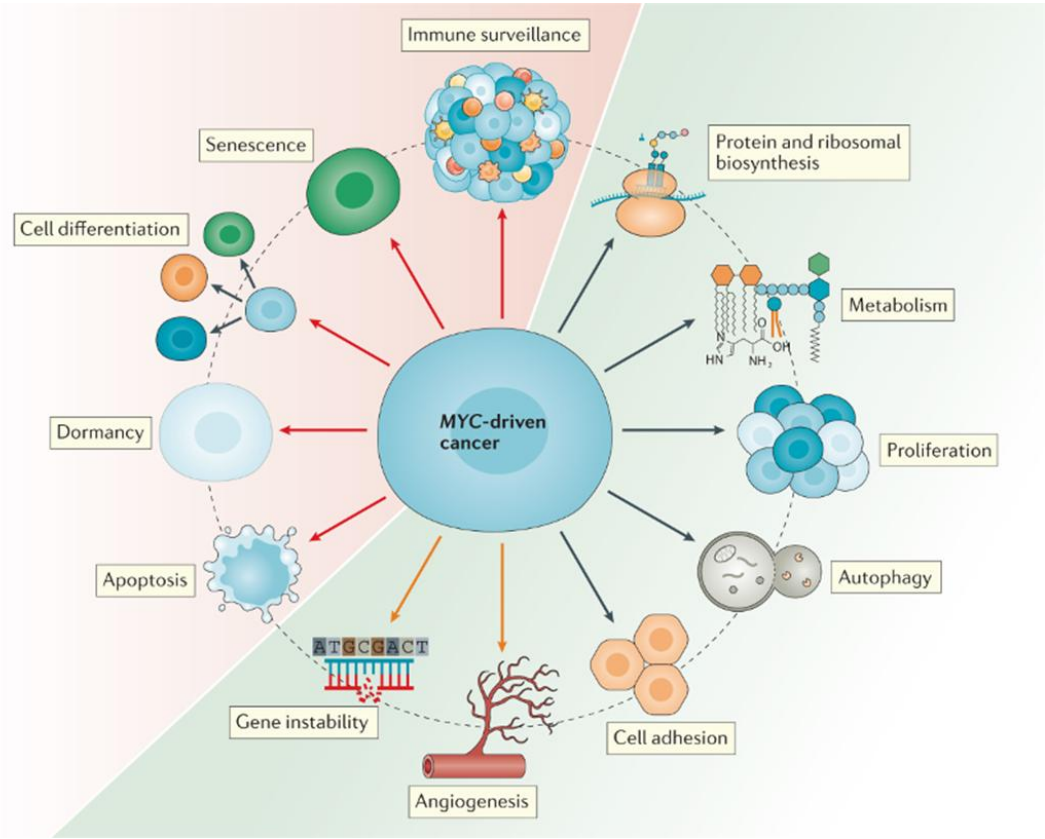


**Figure 2:** Cellular processes regulated by c-myc driven cancers. This figure represents the multiple roles of the c-MYC oncogene in contribution to malignancies once a mutation has occurred [8].

The cause of deregulation of the c-MYC oncogene in BL is the EBV. BL was the first form of cancer of which the cause was discovered to be a virus [1]. The EBV infects over 90% of the entire human population [7]. EBV infects B-lymphocytes and epithelial cells of the human body [8]. In rare cases, EBV can also infect T-cells, smooth muscle cells, monocytes and Natural Killer cells (NK cells). Instead of using one or two glycoproteins for entry, EBV uses multiple glycoproteins. Gp350/200 glycoprotein binds to B-cell receptor CR2/CD21, initiating endocytosis. For the EBV virus to enter the cell, gp42 is used to attach to the HLA class II and "unlocks" the cell to gain entry [8]. The gHgL complex and gB glycoproteins serve as an official attachment and integration protein of the EBV to the cell cytoplasm. There is still more research that needs to be done on the unknown mechanisms of EBV fusion to the cell and post-fusion [8]. What has been proven is EBV's astonishing ability to adapt and successfully authorize infection into a human host cell. EBV switched through a constant cycle of lytic and latent phases to achieve long term survival inside the host cells. The lytic phase is considered the active phase where EBV consistently replicating new viral DNA and proteins. The latent phase is considered the dormant phase, where EBV remains hidden inside host B-cells and produces very little gene expression (Fig. 3). In BL cases, where malaria (*Plasmodium falciparum*) is a high environmental factor, the constant reactivation of EBV occurs leading to the reoccurrence of c-MYC oncogene translocation.

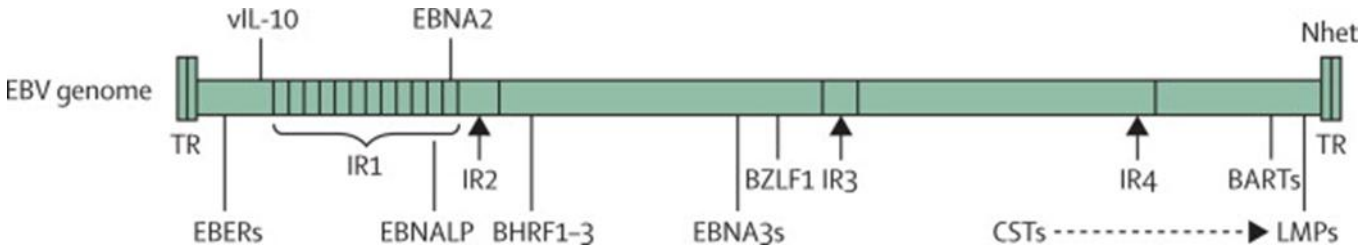


**Figure 3:** This figure presents the Expression of the Epstein-Barr virus transcripts in endemic Burkitt's lymphoma. EBV positive tumors express EBNA1. Repeat region in the EBV genome include TR and IR1-4 [8].

Although rarer than EBV, mutations in TP53 in BL also block apoptosis [1]. TP53 is a tumor suppressor protein which regulates the c-MYC gene by stimulating apoptosis or pausing the cell cycle so that mutations can be repaired. Mutations in TP53 impairs the ability of p53 to stop cell growth and overexpression. In some cases of BL, the TP53 pathway is not mutated into blocking apoptosis. Instead, downregulation of Bcl-2-Interacting Mediator of cell death (BIM) reduces apoptosis significantly. BIM is a pro-apoptotic protein that promotes the release of cytochrome c which then triggers caspase activation then apoptosis. The removal or downregulation of BIM in BL usually occurs through transcriptional silencing via epigenetic modification or repression by EBV, allowing the uncontrollable c-MYC overexpression to continue when c-MYC is mutated [1].

*Diagnostics and Standard Treatment*

A diagnosis of BL requires histopathological findings consistent with its established morphological features. The cell morphology of BL consists of uniform B cells, medium in size that contain chromatin that are irregularly distributed, reflecting an overly active nucleus giving it a darker appearance. Multiple nucleoli (ranging from 2-5) are visible which confirms rapid cell division [2]. When stained with Hematoxylin and Eosin (H&E), BL cells contain a basophilic cytoplasm with squared edges due to rapid tissue growth causing the cells to be compact [1]. BL also presents large nucleoli which is a key indicator of high proliferative activity in malignant cells. The hallmark histological criterion for BL resembles a "starry sky" pattern that contains scattered tangible-body macrophages (Fig. 4). The "tangible-body' refers to the apoptotic debris which creates the "star" look or dark spots under a microscope. The "macrophage" is the leukocyte that absorbs the debris and dead cells [1].

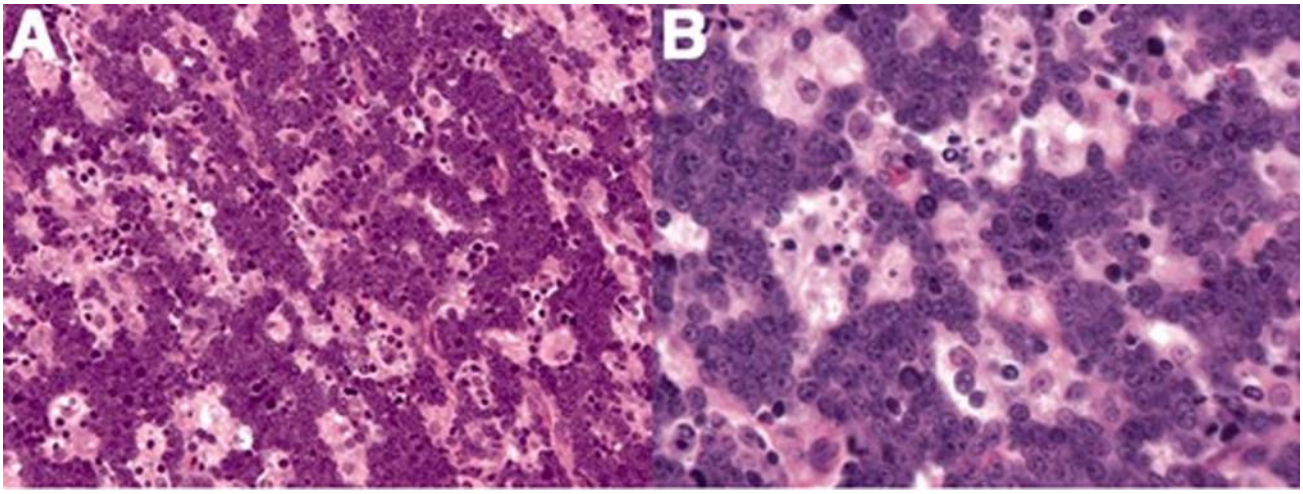


**Figure 4:** A): This figure shows a diffuse infiltrate of atypical lymphoid cells with multiple mitoses and a starry-sky due to the presence of tangible body macrophages; (B): This figure shows that the neoplastic cells are medium in size and uniform, with nuclei that are medium in size or smaller than the nuclei of the tangible body macrophages [1].

Immunophenotyping is an important aspect to diagnosing specific forms of lymphomas. Using immunophenotyping, the B-cell lineage markers CD20 and CD79a can be discovered (Fig. 5). CD20 and CD79a are proteins located on the surface of B lymphocytes, this concludes that BL does emerge from B cells instead of other cells like T cells. The presence of CD20 specifically is important because it indicates that BL will be responsive to rituximab, a form of chemotherapy [1]. Another important feature of immunophenotyping in the diagnosis process of different types of lymphoma is the ability to identify the presence of B-Cell Lymphoma 2 (BCL-2). BCL-2 is a protein located on the mitochondrial membrane that prevents the occurrence of apoptosis in

damaged or overexpressed cells. Patients with BL are Bcl-2 negative, allowing the ability to distinguish BL from other types of B-cell lymphomas. Immunophenotyping can also be used to detect EBV-encoded RNA (EBER) which would lead to a more specific BL diagnosis. Patients with EBV-encoded RNA present can then be diagnosed with endemic BL or immunodeficiency-related BL [1].

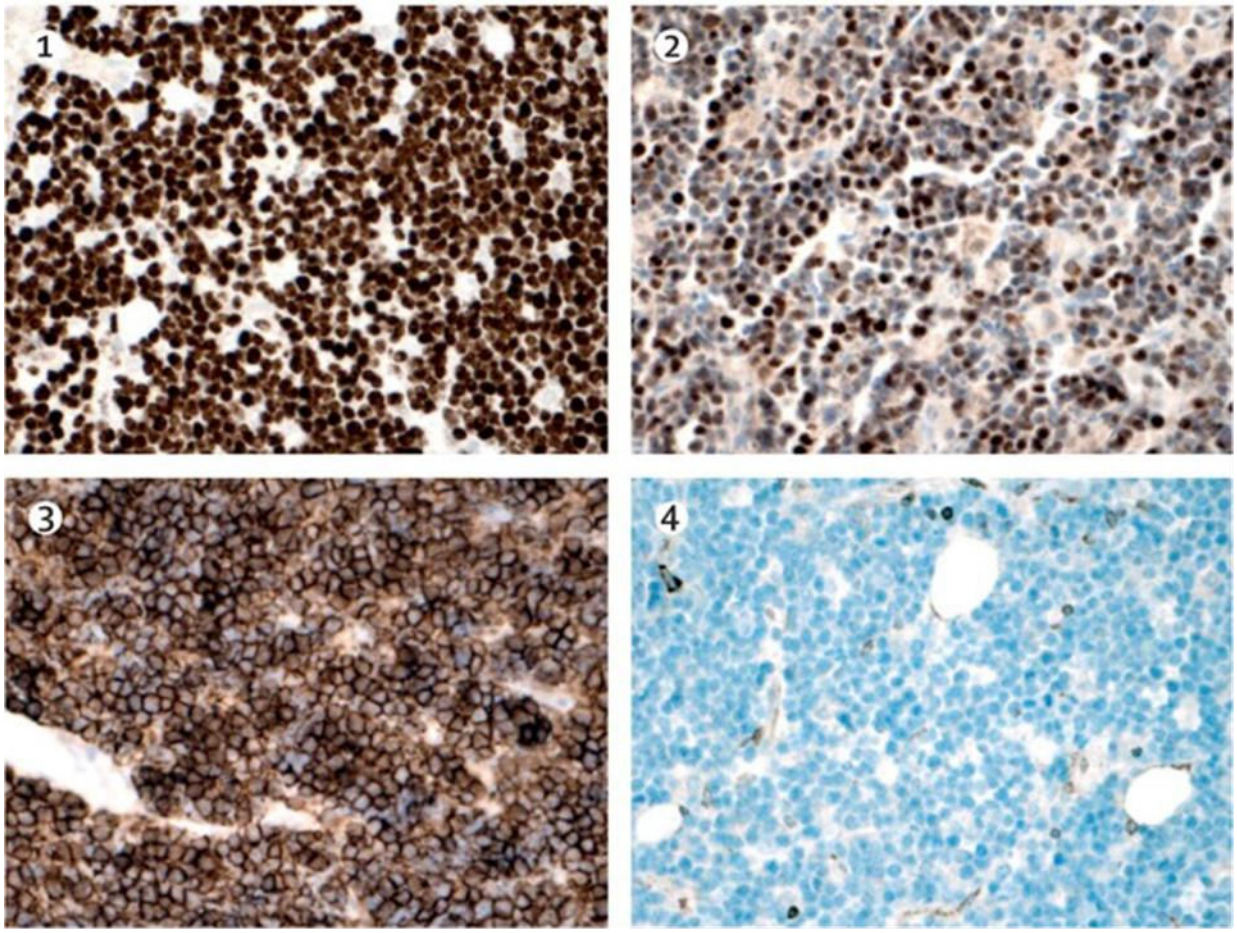


**Figure 5:** Immunocytochemistry of BL. (1) K-67 positivity; (2) Bcl-6 positivity; (3) CD20 positivity; (4) Bcl-2 negativity [1].

Following an initial diagnosis of BL tumors are assessed for identification of BL subtype. There are three clinical subtypes of BL: sporadic, endemic and immunodeficiency-related BL. Subtypes are classified based on location of tumors and lesions.

Endemic BL is mainly located in sub-Saharan Africa and Papua New Guinea. In this region malaria is always present at high levels (holoendemic). EBV is present in almost all cases of endemic BL (Fig. 6). Most cases of endemic BL are children at the median age of six years old. 40-50 per million children under the age of 18 in malaria- associated regions have developed BL per year, making up 50% of childhood cancers in malaria holoendemic regions. Diagnostic features of endemic BL include malignant lesions located on the jaw, facial bones, orbits and some abdominal organs. In rare cases, paraplegia can also occur if malignant growth compresses the spinal cord [1].

In contrast, sporadic BL involves 2 per million children making it rarer in non-endemic regions. Sporadic BL is found globally but is more prominent in locations like Europe and North America. Sporadic BL mainly effects children at ages 3-12 years old with a median of 6-8 years old [1]. Males are 3.5 times more likely to develop sporadic BL than females. Although sporadic BL is mainly found in children, it can also develop in adults. Diagnostic features of Sporadic BL mostly involve malignant lesions located in the abdomen and can be complimented by pain and bleeding [1]. Additional manifestations of sporadic BL disease include lesions in the head and neck, the central nervous system and bone marrow. Unlike endemic BL, jaw involvement in sporadic BL is rare. Sporadic BL is prominent in 30-40% of all childhood non-Hodgkin lymphomas in North America and Europe [1].

Immunodeficiency-related BL is common in patients who are HIV positive or patients who have undergone a transplant and are immunosuppressed as a result. There is a small link between immunodeficiency- related BL and EBV. Less than 40% of North American and European cases are EBV associated. HIV infection increases consistent B-cell activation and immune dysfunction leading to malignant growth in BL (Fig. 6). Immunodeficiency- related BL occurs most commonly in adults early in HIV infection when CD4 counts are elevated (greater than 200 microliters). Diagnostic features of Immunodeficiency-related BL are tumors in bone marrow, CNS and lymph nodes. Diagnostic features of immunodeficiency-related BL are often mistaken for sporadic BL with further aggressive qualities. The risk level of developing Burkitt's lymphoma is 1000 times more likely in individuals who are HIV infected compared to individuals who are not infected. Risk of developing BL is also slightly higher in individuals after organ transplantation [1].

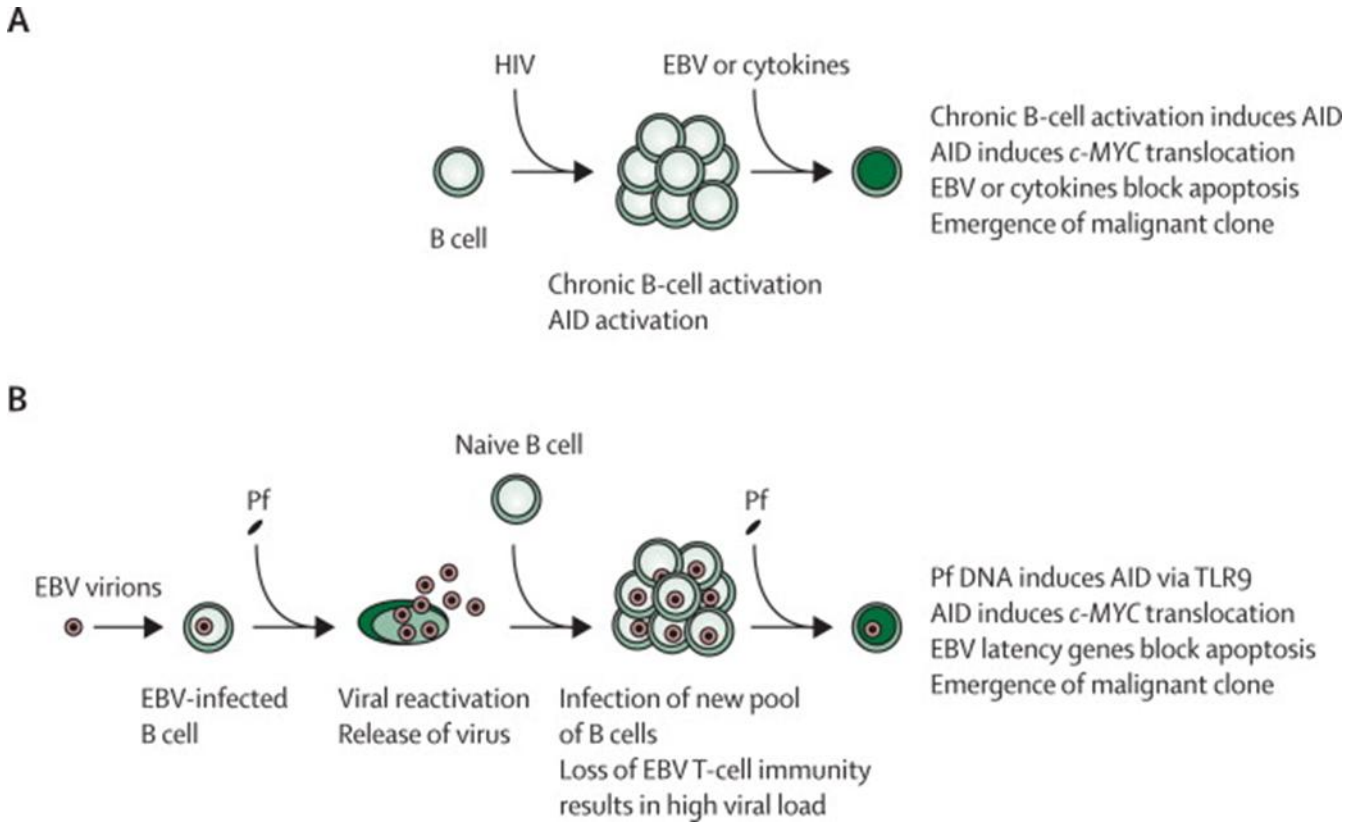


**Figure 6:** Mechanisms of EBV [8]. A) Immunodeficiency-related EBV mechanism; B) *Plasmodium falciparum* in endemic region reactivating EBV.

The most common treatment for BL is brief and intensive high-dose chemotherapy such as R-CODOX-M/R-IVAC, Hyper-CVAD, Dose-adjusted EPOCH-R. Cyclophosphoamide (CTX) is used as a primary drug in chemotherapy to treat BL. In one study, the effects of single-dose versus multiple-dose CTX are compared. 57 patients that have not been treated are given 40 mg/kg IV dose of CTX and the patients who achieved remission were either given five more doses of CTX administered every 2-3 weeks or treatment is not continued. The patients with stage I-II BL achieved long-long lasting complete remission in both single-dose and multiple-dose treatment regimens [9]. Patients with stage III BL, the ones that received multiple-dose CTX showed fewer relapse rates and longer remission trends compared to single-dosed treatments. When patients with stage III did experience a relapse, malignancies were located in new sites including the Central Nervous System (CNS). Patients with stage IV BL (and CNS involvement) had poor results with both single-dosed treatment and multiple-dosed treatments with the mortality rate at 100% past 34 weeks. With all stages of BL, 90% of the patients who relapsed after treatment with CTX achieved second complete remission for a short period of time with cyclic combination chemotherapy [9]. This study also found that using surgical debulking to remove tumors in patients with stage II BL improved survival rates significantly. Overall, this case study found that single-dose CTX is very successful in patients with localized BL (stage I and II), multiple-dosed CTX is effective in patients with higher stages of BL (stage III) and patients with CNS involvement require a longer and more aggressive treatment for better outcomes. This study identifies the importance of early detection and long-term treatment [9]. Although this is an effective form

of treatment, there are repercussions for doing high-dosed chemotherapy. High dose chemotherapy targets healthy cells along with cancer cells making it extremely toxic to the human body. Specifically, healthy hematopoietic stem cells located in bone marrow are destroyed and unable to divide and differentiate into new blood cells properly. If left untreated, the human body would not survive due to bleeding or infection [10]. Studies have concluded that stem cell transplants following chemotherapy have been successful in replenishing healthy hematopoiesis and bone marrow.

*Stem Cell-Based Treatment*

Researchers have studied stem cell transplantation for BL, with high success rates present. Various studies have studied the usage of Hematopoietic Stem Cells (HSC) in treating BL following standard chemotherapy treatment. Transplantation of such stem cells occurs in one of two methods: autologous and allogenic stem cell transplantation. Autologous stem cell transplantation is a treatment where a patient's own stem cells are collected before chemotherapy treatment and stored until chemotherapy treatment is over, then the stem cells are transplanted back into the patient's body. Autologous stem cell transplantation has been used in more cases to help replenish and cure the body after high-dosed chemotherapy [10]. Autologous stem cell transplantation has had higher success rates due to lower risk of rejection and Graft-Versus-Host Disease (GVHD). GVHD occurs when donor immune cells begin attacking the patient's tissue. There are cases where Autologous stem cell transplantation is unsuccessful due to reseeding cancer from cancer contamination preserved stem cells and the lack of Graft-Versus-Tumor effect (GVT). GVT effect occurs in allogenic stem cell transplants because the donor immune cells act as a secondary immune attack against any remaining cancer cells after chemotherapy treatment [11]. Allogenic stem cell transplantation has shown trends of lower relapse rates along with the potential to cure, however, there is also a high early mortality rate due to risk of rejection and toxicity [11].
HSCs are found in bone marrow that can replicate and differentiate into red blood cells (erythrocytes), white blood cells (leukocytes) and platelets (thrombocytes). HSCs are typically used to treat cancers such as lymphomas and leukemias and genetic blood disorders to replenish and treat bone marrow failure to treat BL, researchers have studied two types of HSCs, Bone Marrow (BM) and Peripheral Blood (PBSC). In general, Peripheral Blood Stem Cell Transplantation (PBSCT) is used more due to a faster engraftment, easier harvesting process, a larger abundance of stem cells and provides a faster recovery post transplantation [12]. Bone Marrow stem cell Transplantation (BMT) can be used when trying to minimize chronic GVHD, this is specifically important in cases where a patient is highly immunosuppressed. In BL, both forms of stem cell transplantation are used, it is case dependent. BM is more likely to be used in pediatric cases of BL [12].

Research has indicated that it is safer to harvest blood-derived stem cells especially if BM is compromised. The collection site for BM derived stem cells can be compromised from the presence of tumors and former irradiation exposure. This creates a riskier procedure when trying to harvest viable stem cells to use for treatment. Instead, PBSC are easily accessible and can be harvested without the use of general anesthesia [10]. Furthermore, there is a faster white blood cell count recovery when using peripheral blood stem cells. This significantly reduces bone marrow aplasia in the early stages of posttransplant period. Faster white blood cell count recovery lowering the risk of aplasia also reduces the risk of infections, severe anemia and bleeding further enhancing transplant recovery and survival rates post treatment [10].

*Clinical Trials*

Preclinical trials are the introductory stage for any form of treatment or therapy. Preclinical trials use animal models and systems which are *in-vitro* to examine how different drugs, therapies and gene editing can potentially be effective or ineffective in treating different diseases and conditions in the human body. Pre-clinical trials also aid in determining proper dosages for drugs before being tested on humans in clinical trials. Preclinical trials for BL have been used to test latency reversing agents for EBV, immunotherapies and stem cell treatment interventions before exposure to the human body.

Animal models are used to test success rates of using PBSCT and BM stem cell transplants. This case study refers to many historical animal models to substantiate a claim with scientific evidence that PBSCT can be successful in a human being. The first model mentioned is a rodent model conducted by Goodman and Hodgson [10]. This rodent model displayed the ability to take blood derived leukocytes from donor mice and transplant them into lethally irradiated mice, allowing successful reconstitution. The second animal model discussed in this case study was the success of BM and lymphoid reconstitution in canines after the transfusion of white blood cells [10]. The third animal model discussed was a cross-circulation experiment done on non-human primates (baboons). Blood from a donor baboon was taken and circulated into another baboon. This animal model demonstrated that donor PBSCs could successfully engraft and have long-term survival rates. This specific animal model is historically

predominant because it was the first document of experimental evidence that peripheral blood could be used for stem cell transplantation instead of BM stem cells [10]. This is important because PBSCT are more commonly used now in comparison to BM stem cell treatments. The following case studies give a comparison of the outcomes of using a variety of stem cell treatment therapies to combat BL. It is important to note that all cases are different therefore treatment plans differ based on what works for each patient specifically.

In a case study a 16-year-old male presented with high LDH levels (10,230U/I) and elevated uric acid, was diagnosed with stage IV BL [13]. Treatment regimen prior to SCT included. Mega III regimen with radiation therapy which achieved partial remission, Hic-COM regimen where a small mass was still present and high-dose chemotherapy with autologous SCT where there was remission but then the patient relapsed in 2 months. Relapses from autologous SCT was likely due to the belligerent nature of BL and the quick doubling time of cell growth that BL has. Undetectable microscopic lymphoma cells can repopulate instantly, essentially outworking the autologous stem cells making it impossible for them to terminate all cancer cells alone [13]. Another probable explanation for relapse could be the reduction of BM reserve and damage of immune recovery due to such high intensity treatments before ASCT [13].

The next step for this patient was to undergo allogenic SCT with non-myeloablative conditioning: The patient's HLA matched his sister. The conditioning regimen before stem cells are infused into the body consists of fludarabine (immune suppression), busulfan (low-dose chemotherapy) and anti-thymocyte globulin (ATG, immune suppression) [13]. The goal of using a non-myeloablative approach was to attain allogenic stem cell engraftment with less toxicity than complete myeloablative regimens. Mycophenolate and Tacrolimus were administered to prevent GVHD from occurring after engraftment. Engraftment was successful within 14 days of infusion. Results of the allogenic SCT included high levels of donor chimerism (< 95%) in blood cells by day 14 indicating success of transplant and dominance of donor cells in the patient (Fig. 7). The patient became disease free at 6 months post-transplant. It can be concluded that the GVL effect contributed to full remission. This case study expressed the importance of the non-myeloablative approach to allogenic stem cell transplantation and its effects on limiting toxicity of this form of treatment.

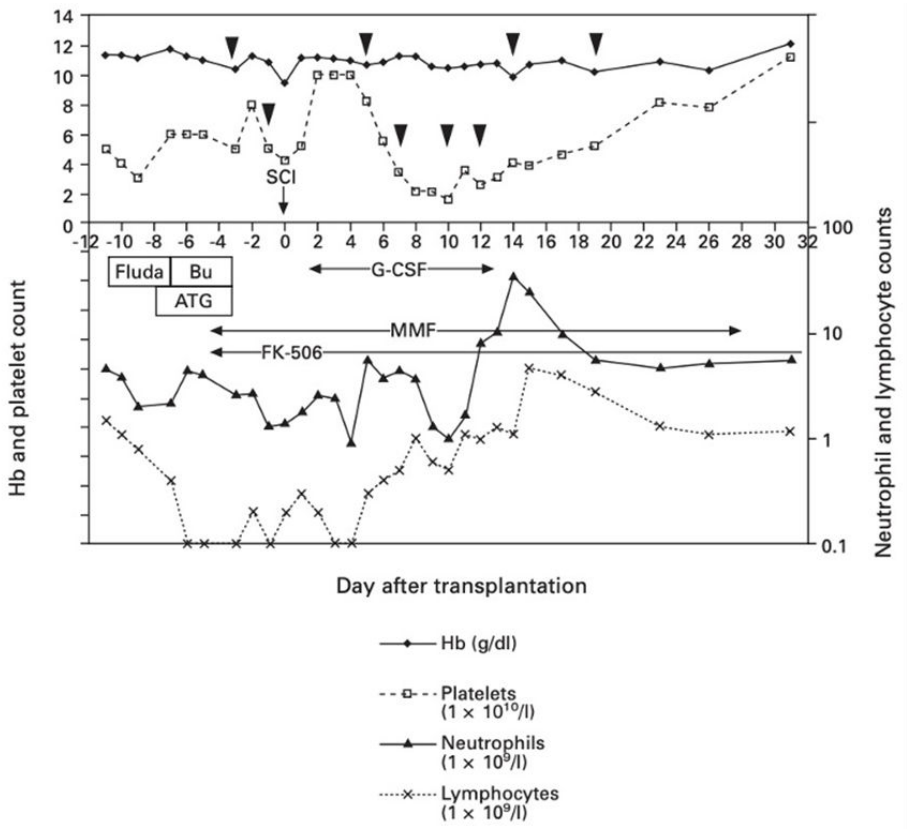


**Figure 7:** This figure represents the Complete Blood Count (CBC) during allogeneic SCT. SCI indicates the stem cell infusion. Fluda= fludarabine. ATG=antithymocyte globulin, Bu= Busulfan, MMF= mycophenolate, FK-506= tacrolimus [13].

A case study has presented success in treating sporadic BL with HSCT as the primary therapy after chemotherapy treatment [14]. In British Colombia, 43 adult patients with sporadic BL, 33 males, 10 females with median age being 36 (age range 16-63). 79% had advanced stage BL, 45% had BM involvement, 12% had CNS involvement and 70% had elevated LDH. The treatment approach consisted of chemotherapy; 79% of patients were given LYSNC, 19% of patients were given CHOP-like chemotherapy and 2% were given CODOX-M. 27 out of the 43 patients then received HSCT. 6 received allogeneic SCT (from HLA-matched sibling donors), 21 received autologous SCT (19 of the 21 were purged *in-vitro*). Conditioning from SCT included cyclophosphamide and TBI [14]. Survival outcomes included: those who processed to SCT experienced 51% 3-year event free survival rate and 57% if the BL was controlled before the start of the stem cell treatment [14]. It was found that half of the patients with chemo sensitive BL that receive stem cell treatment can be cured. Limitations of this case study include the limited number of patients that were able to receive SCT due to relapse or resistance. It is still uncertain if stem cell treatment is dominant to chemotherapy unaccompanied and it would be difficult to test this hypothesis thoroughly due to the rarity of BL. According to prognostic factors of this case study, patients with normal Lactate Dehydrogenase (LDH) levels resulted in a 100% survival rate and disease free [14]. LDH is an enzyme that is in body tissues. When those tissues are damaged, the LDH enters the blood stream where it is then detected. A higher LDH level in the bloodstream indicates a higher tumor burden. Normal LDH levels indicate a lower tumor burden which then leads to a better response to treatment.

In a case study, an investigation on whether using PBSC is more advantageous than using BM derived stem cells for the treatment of BL after myeloablative therapy. A 38-year-old male patient with stage 3 BL(b-lymphoblastic type) was treated with myeloablative chemotherapy which consisted of Cyclophosphamide, Vincristine, Methotrexate and Prednisone (COMP). The patient was then treated with PBSC instead of stem cells from BM because marrow aspiration was not feasible. PBSC were collected in seven leukapheresis sessions; a total of 5.52 x 108 mononuclear cells were taken (including progenitor stem cells). Cryopreservation (liquid nitrogen) was used to store the stem cells until treatment was ready. The specific conditioning regimen used before HSCT was super fractionated Total Body Irradiation (TBI) - 1320 rad along with cyclophosphamide - 200 mg/kg (Fig. 8). This procedure consists of exposing the entire body to radiation so that any remaining cancer cells are killed and downregulating BM and the immune system so that new stem cells can enter and begin to divide and differentiate [10]. Super fractioned TBI was used to reduce the toxicity entering the body. Cyclophosphamide is a form of chemotherapy that acts as an immunosuppressant which prevents the patient body from rejecting the donor stem cells.

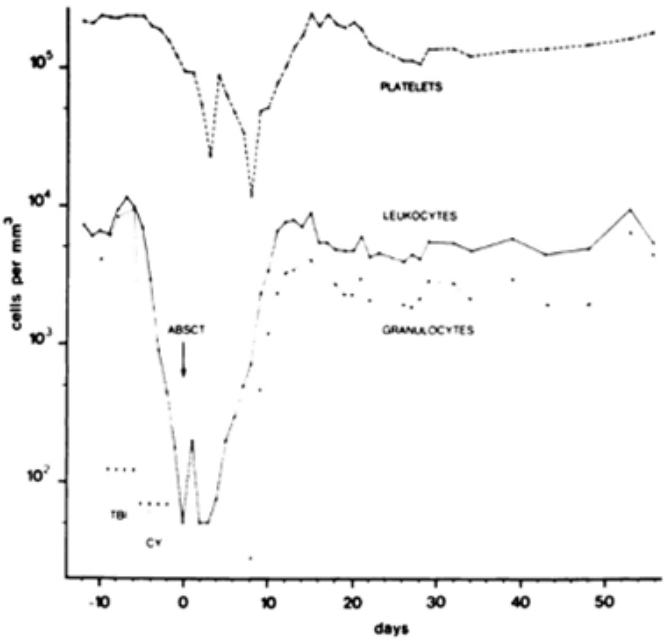


**Figure 8:** Reconstitution of platelets, leukocytes and granulocytes post-ABSCT [10].

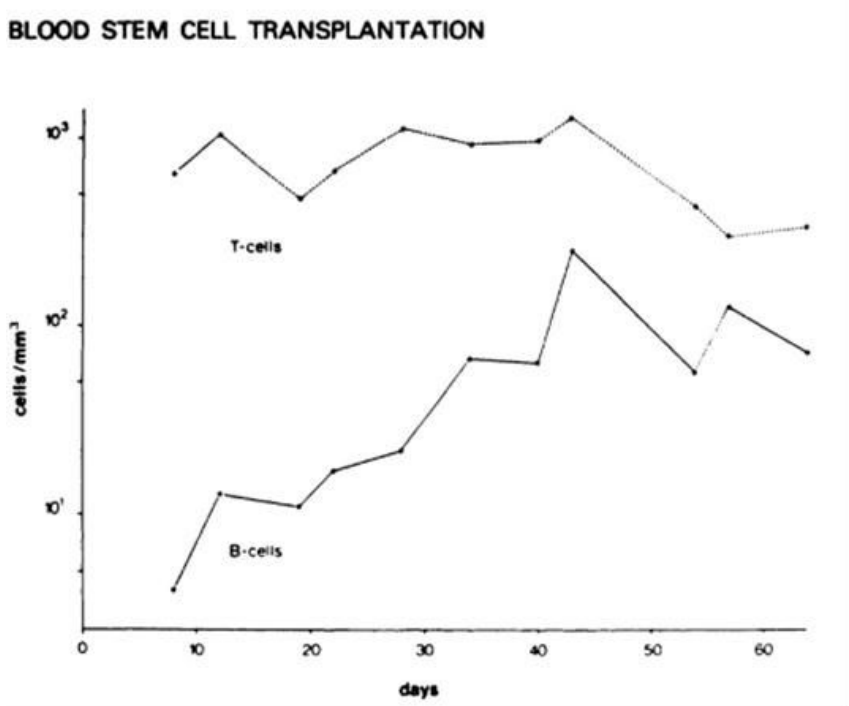


**Figure 9:** Reconstitution of T and B cells in peripheral blood post-ABSCT [10].

It was concluded that PBSCs can be a more efficient choice for treatment for the following reasons: PBSCT provides a faster engraftment process, meaning new cells are produced at a more rapid rate. This is especially important after high-intensity chemotherapy which produces severe pancytopenia, PBSCT rapidly counteracts this hematologic depletion. PBSCT also produces a higher number of HSC due to the circulation of the blood versus demobilized BM stem cells. Higher production of HSC makes recovery more successful and efficient. PBSCT decreases the amount of time a patient is in an immunocompromised state by increasing the number of neutrophils (white blood cells) present in the body (Fig. 9). This is important because it reduces the risk of infection while the body is recovering with a weakened immune system. In cases where BMT is used over peripheral blood transplantation, it is likely due to the number of T-cells present in peripheral blood. T-cells increase the risk of GVHD.

PBSCT have also shown to have a better ratio of normal to malignant stem cells in remission, meaning there is less risk of contamination. Another case study supports this concept by showing that PBSCs can be "purged" *in-vivo* with rituximab, reducing the chances of malignant contamination in PBSC grafts [11]. Purging during stem cell transplantation is a technique used to remove any remaining malignant cells before reinfusion. Purging is most commonly used when stem cells being used are autologous. In patients with BL, it is imperative that the autologous stem cell grafts are free of any detectable malignancies before being infused back into the patient's body. Although both studies have shown a better ratio when using PBSC, long term stability has not been proven [10]. To fully claim that PBSC creates a better ratio of normal to malignant cells, this would have to be proven without the use of purging PBSC with rituximab.

An ongoing case of BL in 2025 consists of a 21-year-old male diagnosed with stage IV BL on July 15th. Symptoms included aggressive tumor growths and lesions. The first tumor discovery was found on his tonsils. Malignant lesions were located on both calves, femurs and shoulders. A tonsillectomy was performed and the tonsils grew back to their original size of four centimeters in seven days. This individual began high intensity chemo treatment using HYPER-CVAD with rituximab for two cycles. Treatment however caused side effects; eyesight was affected by cytarabine. Treatment is to be continued for five cycles or R-EPOCH. This individual has been considered for allogeneic SCT if a second line of treatment is needed [15-18].

**Summary and Conclusion**

BL is a B-cell cancer driven by a genetic translocation of the c-MYC oncogene into immunoglobulin loci enhancers. BL is unique with features such as a rapid doubling time in tumor progression leading to its hallmark "starry sky" histology. The "starry sky" histology presents a connection to extensive cell proliferation and deregulation. The EBV in concurrence with cofactors such as

malaria infect B-cells and serve as the main driver of the c-MYC translocation. Overall, treatment for BL yields high success rates but is associated with considerable toxicity. This is especially true for Myeloablative regimens, imposing significant stress on HSC. Prognosis of this disease is monitored by LDH levels, malignant cell burden, presence or absence of CNS involvement and how well the patient responds to high intensity chemotherapy treatments. Stem cell-based therapies post chemotherapy treatment improve survival rates for BL patients as well as patients who have relapsed. HSCT restores hematopoiesis, facilitating a more rapid and successful recovery post chemotherapy treatment. Specifically, allogeneic SCT enhances immune-mediated tumor suppression known as the GVL effect. Case studies indicate that allogeneic SCT offer lower relapse rates, however, can be linked to increased risk of early treatment mortality and increased risk of GVHD. In comparison, BL patients that undergo autologous SCT experience a markedly lower GVHD risk but increased relapse rates due to potential contamination of the graft containing malignant B-cells. PBSC are used as preferred treatment over BM derived stem cells due to easier and faster engraftment, higher stem cell count post treatment and lower risk of infection resulting from accelerated neutrophil recovery. The support of preclinical trials using animal models demonstrated biological validation of PBSC in the ability to replenish the hematopoietic system. EBV targeted therapies such as HDAC inhibitors, valganciclovir and latency- reversing agents are actively being researched. Such therapies could significantly reduce the rates of BL across the globe by targeting and inhibiting the viral cofactor. EBV + KSHV co-infection models work to remove the lytic gene BZLF1 which has shown to significantly reduce tumor incidence. Acyclovir (ACV) experiments used to block EBV replication have shown to not reduce tumor growth, indicating that preventing the lytic phase of EBV could be enough to prevent BL [4].

**Challenges and Future Directions**

The cost of diagnostic and treatment of BL in high income regions and low-income region is another challenge that must be improved. The overall cost to treat a single child with BL in low-come region Uganda (East Africa) ranges from $1,351.72-$4,194. Specifically, average costs for laboratory test are $175.41, blood bank costs $65.11, pathology costs $35.16, chemotherapy drugs cost $34.46, radiology costs $32.89 and other medications cost $6.93. The Global HOPE program (Hematology-Oncology Pediatric Excellence) is actively working towards a long-term solution to alleviate the medical cost burden in low-income countries such as Uganda, Tanzania, Malawi, Botswana, Kenya, Rwanda and South Africa. The Global HOPE program works with hospitals located among these countries to increase the amount of healthcare providers and improve diagnostic systems so that they are more accurate and efficient. In Uganda, this program has successfully improved diagnostic efficiency. A diagnosis originally took from a few weeks to months now takes 12-24 hours at maximum. In comparison, cost of BL treatment in high-income countries such as the United States are also exceedingly overpriced. The overall cost for treatment of BL in the United States is $295,000 per patient and can range from $142,110-$483,360 per patient. BL is an exceedingly rare disease consisting of only small clinical trials, limited research and restricted clinical data. The aggressive nature of BL limits the ability to conduct randomized controlled trials. This makes it difficult to find a standard treatment regimen and timely administrating of stem cell treatments. Future Multi-center collaboration is essential for the growth and development of standard treatment and research advancement for BL.

**Conflict of Interest**

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

**Funding Statement**

This research did not receive any specific grant from funding agencies in the public, commercial or non-profit sectors.

**Acknowledgement**

None.

**Data Availability Statement**

Not applicable.

**Ethical Statement**

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

**Informed Consent Statement**

Informed consent was taken for this study.

**Authors' Contributions**

All authors contributed equally to this paper.

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