

Review Article

The Use of Stem Cell Therapy in the Treatment of Primary Central Nervous System Lymphoma

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Abstract

Lymphomas are a broad category of cancers in which malignant cells form in the lymphatic system and they are among the most common cancers in the United States. Primary Central Nervous System Lymphoma (PCNSL) is a lymphoma affecting the structures which make up the central nervous system: the brain, spinal cord and meninges, with the pathology of most cases belonging to the diffuse large B-cell category. Neurocognitive symptoms of PCNSL range in severity and onset, depending on the location of the tumor and the health of the patient. The prognosis of PCNSL upon diagnosis is poor, with 5-year survival rates of around 33%, contingent on patient age, gender, race, initial health, presence of autoimmune disorders or other comorbidities and access to treatments. There is a clear role of Human Immunodeficiency Virus and Epstein-Barr Virus in lymphomagenesis, making these two diseases a major risk factor for the development of PCNSL. The treatments for PCNSL are most commonly high-dosage chemotherapy and whole brain radiation, with some cases requiring surgery. The exploration of the efficacy of autologous stem cell transplants in combination with high-dosage chemotherapy is an emerging area of study with great promise for the extension of overall survival rates and quality of life of PCNSL patients.

Keywords: Primary Central Nervous System Lymphoma; Epstein-Barr Virus; Human Immunodeficiency Virus; Autologous Stem Cell Transplant; Stem Cell Therapy

Abbreviations

ADC: Apparent Diffusion Coefficient; AIDS: Acquired Immune Deficiency Syndrome; ART: Antiretroviral Therapy; ASCs: Adult Stem Cells; ASCT: Autologous Stem Cell Transplant; BBB: Blood-Brain Barrier; BP: Base Pair; BL: Burkitt Lymphoma; cGAS: Cyclic GMP-AMP Synthase; CR: Complete response; CSF: Cerebrospinal Fluid; CNS: Central Nervous System; CT: Computed Tomography; DLBC: Diffuse Large B Cell; EBNA-1: EBV-Encoded Nuclear Antigen-1; EBV: Epstein-Barr Virus; ES: Engraftment Syndrome; ESCs: Embryonic Stem Cells; GBM: Glioblastoma; GVHD: Graft Versus-Host Disease; HD: High-Dosage; HIV: Human Immunodeficiency Virus; HLAs: Human Leukocyte Antigens; HSCs: Hematopoietic Stem Cells; LCL: Lymphoblastoid Cell Lines; LMP-2a: Latent Membrane Protein 2a; MRI: Magnetic Resonance Imaging; MSCs: Mesenchymal Stem Cells; MTX: Methotrexate; MZL: Marginal Zone Lymphoma; NHL: Non-Hodgkin Lymphoma; NK: Natural Killer; OI: Opportunistic Infection; OS: Overall Survival; PBL: Peripheral Blood Lymphocyte; PBSCT: Peripheral Blood Stem Cell Transplant; PCNSL: Primary Central Nervous System Lymphoma; PET: Positron Emission Tomography; PFS: Progression-Free Survival; PTL: Peripheral T-cell Lymphoma; PTLD: Post-Transplant Lymphoproliferative Disorder; R-MPV: Rituximab, Methotrexate, Procarbazine and Vincristine; SEER: Surveillance, Epidemiology and End Results; SBB: Stereotactic Brain Biopsy; TGF- β : Transforming Growth Factor- β ; USP: Ubiquitin-Specific Protease; WBRT: Whole Brain Radiation Therapy

Introduction

About Primary Central Nervous System Lymphoma

The lymph system of the human body consists of tissues and organs that produce, store and carry white blood cells. The purpose of these white blood cells, known as lymphocytes, is to fight infections and other diseases as part of the larger human immune system. Lymphomas are a large family of over 70 cancers affecting the lymph system [1]. The transformation of lymphocytes into malignant cancer cells over time is generally hypothesized to be the cause of lymphatic neoplasm in the human body [1]. Lymphomas are broadly categorized into two categories: Hodgkin Lymphomas and Non-Hodgkin Lymphoma (NHL). Hodgkin Lymphoma represents approximately 10% of total lymphomas diagnosed in the United States and most commonly involves contiguous lymph node groups [2]. Hodgkin Lymphoma is marked by the presence of Reed-Sternberg cells. These abnormal and malignant cells contain multiple nuclei and are identifiable by microscope, following biopsy [2]. The presence of Reed-Sternberg cells is necessary for a diagnosis of Hodgkin Lymphoma. NHL does not contain Reed-Sternberg cells and makes up the vast majority (approximately 90%) of lymphoma causes in the United States [3]. Patients with NHL present with a wide variety of clinical symptoms and histological features, making diagnosis more difficult [3].

Primary Central Nervous System Lymphoma (PCNSL) is a non-Hodgkin lymphoma affecting the structures of the human Central Nervous System (CNS), which include the brain, spinal cord and meninges. There is an identified ocular variant of PCNSL, involving the retina, vitreous fluid and subretinal epithelial space [4]. Primary CNS Lymphoma is among the leading types of malignant tumors affecting the central nervous system. It has an incidence rate of 0.45 per 100,000, placing it behind glioblastoma (3.26/100,000), glioma not otherwise specified (0.54/100,000) and diffuse astrocytoma (0.46/100,000) [5]. PCNSL is an especially rare cancer, with an annual incidence rate of 0.5 per 100,000 in the United States. In a 42-year span between the years of 1975 and 2017, the incidence rate of PCNSL substantially increased from 0.1 per 100,000 to 0.5 per 100,000. This is a fivefold increase, with a steady climb after the onset of the 21st century (Fig.1,6).

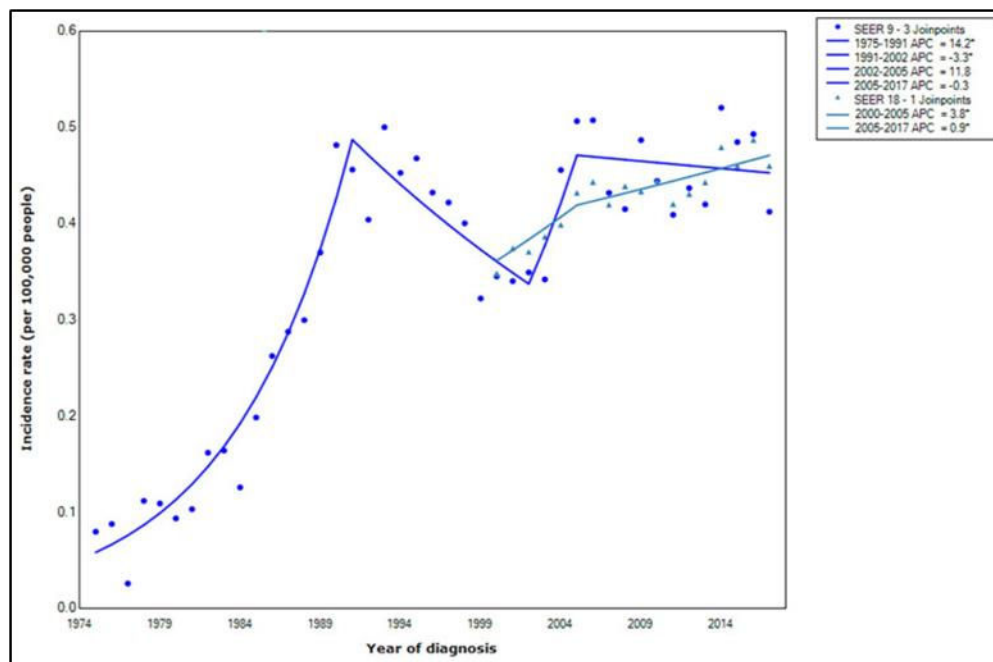


Figure 1: The increase in incidence rate of PCNSL between the years of 1975 and 2017 [6].

Symptoms of PCNSL

The symptoms of PCNSL differ from patient-to-patient; they are heavily dependent on the location of the mass, as well as the immune status of the patient. The severity of symptoms, as well as the ones that present upon examination, are variable [7]. Symptoms include, but are not limited to, nausea and vomiting, seizures, headaches, generalized weakness, confusion, double or blurry vision and hearing loss. It is important to note that PCNSL exhibits a diffuse distribution and that prevalent symptoms correlate with tumor location. The most common site for PCNSL tumors is the frontoparietal and temporal hemispheres,

followed by the basal ganglia, corpus callosum, periventricular regions and most rarely, the cerebellum. The brainstem is one of the least affected structures and only about 1% of patients have spinal cord involvement [8].

As many as 80% of patients with PCNSL present with neurological deficits, with symptoms often correlating to the location of the cancerous lesion [9]. Clinically, patients with PCNSL most commonly present with cognitive impairments, followed by neurological deficits, seizures, difficulty walking or with other motor skills and symptoms of increased intracranial pressure [9]. Symptoms of increased intracranial pressure include nausea, vomiting, optic papilledema and headaches [10]. The prevalence of headaches in brain tumor cases falls between 32.2% and 71%, with no statistically significant difference between the severity of symptoms in primary or metastatic tumors [11]. Other neurological signs and symptoms develop according to patterns of cranial or extracranial involvement. Neurological deficits of the frontoparietal lobes occur in 39% of patients [9]. Patients with PCNSL originating in the frontoparietal lobe can experience behavioral problems such as apathy, cognitive impairment and motor deficits, such as difficulty with grasping objects or walking [12]. Symptoms involving the eyes, including double or blurry vision, pain and decreased visual acuity, can be indicative of an ocular tumor. This occurs in approximately 15% to 25% of PCNSL patients [9]. Between 7% and 42% of patients develop acute symptoms based on Cerebrospinal Fluid (CSF) involvement [9].

Because these symptoms are non-specific to PCNSL and can be characteristic of other diseases, patients often confuse their manifestation for feeling under the weather. Early detection in any type of cancer, including PCNSL, is critical to the successful treatment and management of the disease. Any delay of interventional treatment, including chemotherapy or whole brain radiation, can markedly decrease treatment efficacy or survival rate [9]. It is important to always see a primary care provider if any of these symptoms are present and persistent.

Diagnosis

Following the completion of a physical exam and a patient work-up including questions about personal and familial health history, there are multiple options for tests and procedures for diagnosis.

Computed Tomography (CT) is a non-invasive imaging modality that produces high-quality cross-sectional images using a 360° ring and a rotating X-ray tube [13]. The first use of a CT scan was to depict the brain anatomy of a patient in the UK in 1971. Since then, the CT scanning methodology has evolved to a more continuous and accurate scanning process [13]. A CT scan can show the size, shape and location of a lesion in the brain; however, it is not the most sensitive scanning method available and is more often used in combination with magnetic resonance imaging [9]. Magnetic Resonance Imaging (MRI) can generate a comprehensive image of a cancerous mass using magnetic fields and radio waves. In suspected cases of PCNSL, the clinically recommended first step is for an MRI scan with contrast [9].

Once a tumor is confirmed to be present through the combination of scans, the pathology of the mass must be confirmed to move forward with treatment. Biopsy is preferred when imaging is insufficient to establish a diagnosis and can help oncologists in choosing the appropriate treatment [14]. Biopsy is a surgical procedure under general anesthesia involving the excision of neurological tissue for histological analysis. Although MRI scans and other imaging technology can suggest and support a tentative PCNSL diagnosis, the only way to achieve a definitive diagnosis is through histopathological confirmation by open or Stereotactic Brain Biopsy (SBB) [15]. Image-guided stereotactic frame-based brain biopsy is one of the most frequently used techniques; it is a minimally invasive, quick, efficient and safe procedure [14]. In patients presenting with symptoms suggestive of PCNSL, biopsy is the preferred diagnostic method in 95% of cases, followed by CSF analysis (3.1%) and vitreous sampling (1%) [15]. Other diagnostic modalities (CSF analysis, vitreous sampling, lumbar puncture) may be chosen over biopsy to obviate the need for an invasive procedure, but this choice can cause delay of treatment [15].

In a retrospective study of the clinical efficacy and safety of early brain biopsy in immunocompetent PCNSL patients treated at the University of Miami Miller School of Medicine, brain biopsy was diagnostic in 92.3% of cases, or 24 of 26 [15]. In the 2 cases in which brain biopsy was inconclusive, a second procedure was performed for confirmation of diagnosis. A second biopsy was needed for these patients because both were on steroids prior to the procedure, which can compromise the efficacy of test results [15]. It is recommended that steroid treatment is withheld for 14 days prior to surgical biopsy for maximum efficacy of results [15]. Both patients received confirmational diagnosis of PCNSL after their second SBB [15].

Biopsy methodology in the retrospective study of 26 PCNSL patients was not uniform. The biopsy strategies studied included frameless SBB in 16 cases (61.5%), craniotomy intended for tumor resection in 8 cases (30.8%) and endoscopy-guided biopsy in 2 cases (7.7%) [15]. The location of lesion biopsied also varied across the cases. Half of the PCNSL patients (13) treated had lesions located in the frontal lobe, followed by 6 patients with masses in the temporal lobe. Parietal lobe (3), thalamic region (2), occipital lobe (1) and brainstem (1) were the other locations of lesions represented in this study. Historically, early brain biopsy has been recommended in the oncology community due to low rates of complications, high diagnostic rates and prevention of diagnostic delay which can hinder treatment progression [15]. The retrospective study of 26 patients supported by a 92.3% diagnostic rate in the first surgical intervention supports this notion of advocacy for early brain biopsy [15].

When the neurological tissue is extracted through biopsy, a series of tests are performed to determine if the cells are cancerous and if so, what T-cell lineage they are a part of. Differential diagnosis is an important process since the clinical symptoms of patients with PCNSL present similarly to other disorders. The differential diagnosis for PCNSL include high-grade gliomas, metastatic lesions, demyelinating diseases (multiple sclerosis, for example), granulomatous lesions and cerebral toxoplasmosis [9]. PCNSL is more hypermetabolic than glioma, another type of prevalent brain cancer and therefore results in increased uptake in a metabolic testing modality such as a Positron Emission Tomography (PET) scan [9]. MRI scanning can differentiate PCNSL from toxoplasmosis, due to the varying biochemical properties characteristic of each disease [9].

PCNSL presents with similar clinical symptoms to several diseases. Glioblastoma (GBM) is the most common malignant brain tumor in adults, with overlapping symptoms upon presentation and a rapid growth pattern [16]. GBM is primarily treated with surgical resection, while chemotherapy and radiation are the preferred methods of treatment for PCNSL [16]. It is difficult to differentiate between these two brain malignancies because they present with similar symptoms and there can be considerable overlap between the appearance of the lesions when visualized through imaging techniques. PCNSL and GBM are most frequently located in the cerebral hemisphere [16]. Lesions in PCNSL and GBM are within the same size range [16]. Similar symptoms, same general locations and no significant variation in size between PCNSL and GBM can cause difficulty in achieving a definite diagnosis. The use of a statistical metric known as an Apparent Diffusion Coefficient (ADC), in combination with the use of multiple imaging techniques, can help physicians accurately diagnose a patient [16].

Prognosis

The prognosis for PCNSL is poor. According to data from the Surveillance, Epidemiology and End Results (SEER) registry databases 9 and 18, the 5-year Overall Survival (OS) rates were 30.5% and 37.4%, respectively. The data from this case study was analyzed from two cohorts of patients; SEER 9 registries were taken between 1975 and 2017, while SEER 18 registries were recorded between 2000 and 2017 [6]. It is important to note the 6.9% increase in 5-year OS rate between the SEER 9 and SEER 18 registries, which is likely due to a combination of factors, including better treatment options, earlier detection of cancer and more awareness. In terms of duration of life, the 30.5%-37.4% translates to a range of between 10.9 to 61.9 months [6].

There are numerous factors that impact the prognosis of a patient diagnosed with PCNSL. These include but are not limited to age, gender, race, site of tumor, pathological type and progression of cancer at diagnosis. Age is a major component of prognosis in PCNSL cases due to increasing physiological dysfunction and incidence of comorbidities, which affects how much and how intense of treatment a patient can tolerate. The prognosis of patients above the age of 60 years old remains poor, at around 30% [6]. More cases of PCNSL are seen in the elderly population, with a five times higher incidence rate [6]. Gender, though not as drastic of a factor as age, can affect the outlook of diagnosis, with many studies confirming that females have a longer cancer-specific survival than men (Fig. 2) [6]. The site of the tumor is important, with brain parenchyma PCNSL having a worse prognosis when compared with other anatomical locations (Fig. 2) [6]. Pathology of the PCNSL is impactful, with Diffuse Large B-cell Lymphoma (DLBCL) having one of the lowest survival rates (Fig. 2) [6]. The difference in OS rates when diagnosed in the 2000s as opposed to the 2010s are substantial, most likely due to increased efficacy of treatment and the introduction of high-dose chemotherapies, such as methotrexate (Fig. 2) [6]. Progression of disease upon diagnosis is also important to prognosis in any type of cancer. Because PCNSL has multiple non-specific symptoms, it can be difficult to detect and is often misdiagnosed for other diseases. It is ideal for any type of cancer to be diagnosed at an early point in its manifestation, as early intervention and treatment can make a substantial difference in patient outcome.

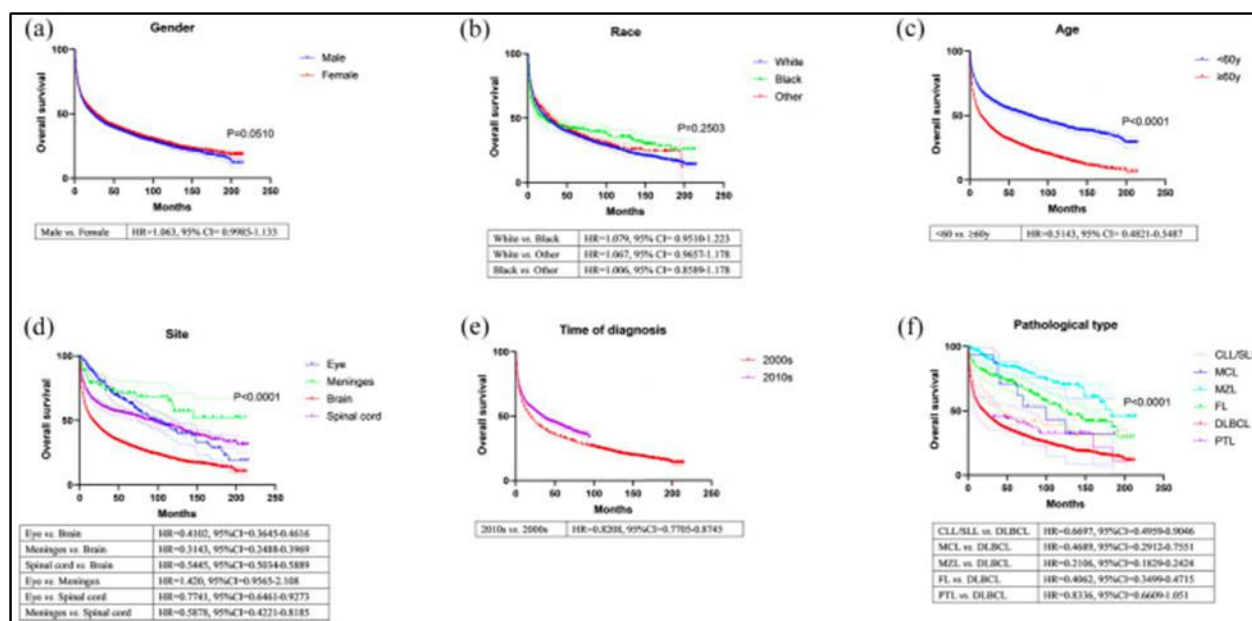


Figure 2: Kaplan-Meier survival groups by patient demographics. (a) Gender, (b) Race, (c) Age, (d) Site, (e) Time of Diagnosis, (f) Pathological type [6].

Physiological Pathology

PCNSL most typically manifests in the brain, with a small percent of cases originating in the spinal cord [6]. The frontoparietal and temporal lobes are the most common sites of PCNSL, making up 38% of cases [8]. The basal ganglia (16%), corpus callosum (14%), periventricular regions (12%), cerebellum (9%) and spinal cord (1%) are the other sites of genesis for PCNSL [8]. Symptoms, such as neurological deficits, headaches and deficits in language or sensory processing, can occur gradually or suddenly. The onset and severity of symptoms depends on location of the tumor and intracranial pressure [8]. PCNSL cases typically exhibit a diffuse distribution, meaning the tumor has spread and does not have a distinct border or edge [8].

In most cases of immunocompetent patients, there is a solitary and intensely homogeneously enhancing brain mass [7,9]. Homogeneously enhancing mass is a term used to describe a consistent increase in the signal intensity, or how bright or dark an area appears on an MRI, within an observed mass (Fig. 3,7). CT scan typically shows a high-density lesion in a central hemispheric location, near or crossing the midline [7]. A high-density lesion, also known as a hyperdense lesion, appears bright on a CT scan due to high levels of attenuation and hypercellularity [17]. The reason for the presence of elevated attenuation in CT scans of patients with PCNSL is thought to be the densely packed malignant cells [7]. In most immunocompetent patients, MRI imaging displays a low-to-intermediate signal-intensity tumor on a T1 weighted MRI [7]. On a T1 weighted MRI, low-to-intermediate signal intensity frequently indicates a pathological abnormality, such as cancer.



Figure 3: CT scan showing homogeneous enhancement (white arrows) of a PCNSL lesion near the midline. 64-year old woman presented with left-sided weakness [7].

The appearance of PCNSL tumors in HIV positive, or immunocompromised, patients are variable in their contrast enhancement due to a more inhomogeneous distribution pattern [7]. More than half (55%) of HIV positive patients present with a cerebral mass in the upper part of the brain, with common locations including the corpus callosum, basal ganglia and other deep cerebral areas [7]. Unlike the presentation of PCNSL in immunocompetent patients as a solitary mass, multiple lesions can be seen in as many as 50% of HIV positive patients [7]. It is also important to note that the onset of symptoms in HIV positive patients may be more aggressive than in immunocompetent patients, due to the possibility of multiple lesions.

The average size of a solitary mass in patients presenting with PCNSL is 2.64 cm, which is roughly the size of a peanut [16]. For reference, large brain metastases are typically defined as lesions greater than 2 cm in diameter [18]. The management and treatment of a larger brain mass is of increased complexity for the oncology team and increased burden for the patient. When considering the treatment plan for a PCNSL in which the lesion is of large brain tumor size, a multimodality treatment plan is recommended over a single-method approach [18]. A multimodal approach to the treatment of a larger mass yields better local control results than the use of a single method [18].

PCNSL is a highly infiltrative tumor, displaying a diffuse distribution and a growth pattern called angiotropism [9]. Angiotropism is a process of extravascular migration of tumor cells, allowing cancer to migrate without intravasation, or the movement through blood vessels (Fig. 4) [19,20]. In other forms of cancer, an angiotropic growth pattern is a risk factor for metastasis since there is a migration of cells beginning to occur. Angiotropism promotes a process known as pericytic mimicry, which is the spreading of tumor cells along outer vascular surfaces (Fig. 4) [19,20]. However, it is rare for PCNSL to spread systematically beyond the central nervous system [9]. Despite PCNSL not metastasizing through the blood like other cancers, pericytic mimicry promotes an aggressive and quick spreading mechanism through the central nervous system [19].

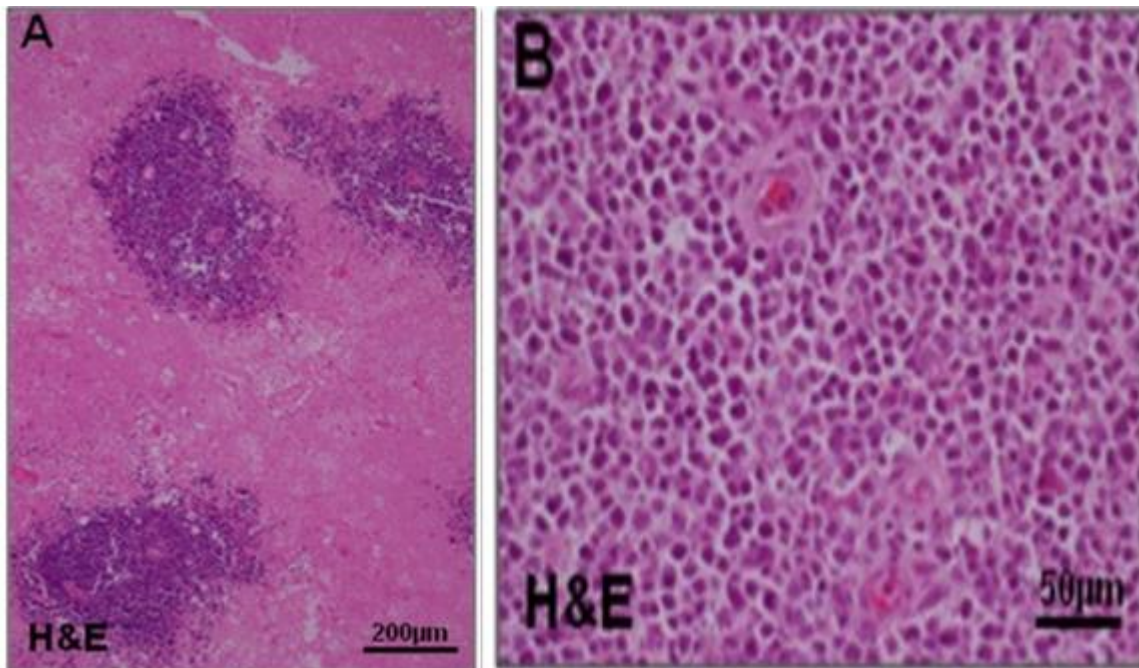


Figure 4: (A) Hematoxylin and eosin staining of a PCNSL biopsy sample, demonstrating angiocentric growth patterns; (B) Higher magnification of a hematoxylin and eosin-stained biopsy sample showing blood vessels.

Lymphoma of the central nervous system that does not originate in the central nervous system is known as secondary central nervous system lymphoma. Secondary central nervous system lymphoma is seen in patients with systemic NHL that has spread to structures of the CNS [9]. Systemic NHL spreads to the CNS via hematogenous dissemination, the process of cancer cell migration through the bloodstream [9]. Systemic lymphoma affecting the central nervous system has a particularly poor prognosis. Patients with aggressive systemic NHL have between a 2% and 27% risk of developing secondary CNS dissemination. Following confirmation of the systemic lymphoma's spread to the CNS, the median survival rate is 2.2 months [9]. Dissemination to the CNS occurs frequently in patients with HIV-associated systemic lymphoma [21]. In a study consisting of 62 patients with HIV-associated systemic lymphoma, CNS involvement occurred in 8% of patients at the start of the trial and 21% of patients at any point during the trial [21].

Histopathology

Most cases of PCNSL belong to the Diffuse Large B-cell (DLBC) category. In the SEER 18 retrospective case study consisting of over 6,000 patients, DLBC lymphomas made up 78.2% and 72.6% of lymphomas, respectively, followed by smaller percentages of Marginal Zone Lymphoma (MZL) and T-cell lymphomas (Fig. 6) [6]. DLBC is the most common lymphoma, accounting for between 25% and 30% of non-Hodgkin's lymphomas. Another source estimates that DLBC accounts for up to 95% of PCNSL cases, with low-grade B-cell lymphoma, T-cell lymphoma and Burkitt Lymphoma accounting for the rest [9].

Diffuse Large B-cell (DLBCL) lymphoma results from the malignant proliferation of B-cells at one of their three stages of development: pre-germinal, germinal and post-germinal center [22]. B-cells, named for the bone marrow in which they are derived, are a population of lymphocytes that express a variety of diverse surface immunoglobulin receptors recognizing specific antigen epitopes [23]. These surface immunoglobulin receptors are the membrane-bound form of an antibody and are important to immune function. Antibodies are a critical aspect of recognizing foreign substances in the body. DLBC is the most common lymphoma, making up between 25% and 30% of NHL cases [22]. Lymphomagenesis can result from several different factors, including genetic mutations of the proto-oncogenes or tumor suppressor genes, or environmental factors [22]. Risk factors for DLBC lymphoma include the use of immunosuppressant medications, personal or family history of lymphoma and age (risk increases with age) [22].

Most patients with DLBCL display gene rearrangements in the heavy and light chains of immunoglobulin, the surface receptor characteristic of B lymphocytes [22]. Approximately 80% of cases of DLBCL express the B-cell leukemia or lymphoma 2 (BCL2) protein and 70% present with the B-cell lymphoma 6 (BCL6) gene [22]. Of the patients presenting with the BCL6 gene, between 20% and 40% also show genetic alterations of the BCL6 gene [21]. The BCL6 gene is a proto-oncogene that codes for a zinc-finger protein with connections to several different transcription factors [24]. Rearrangement or alteration of the BCL6 gene in DLBCL cases can result in unregulated protein expression [24]. Histological features of PCNSL with interruption of the BCL6 gene is shown in Fig. 5 [20].

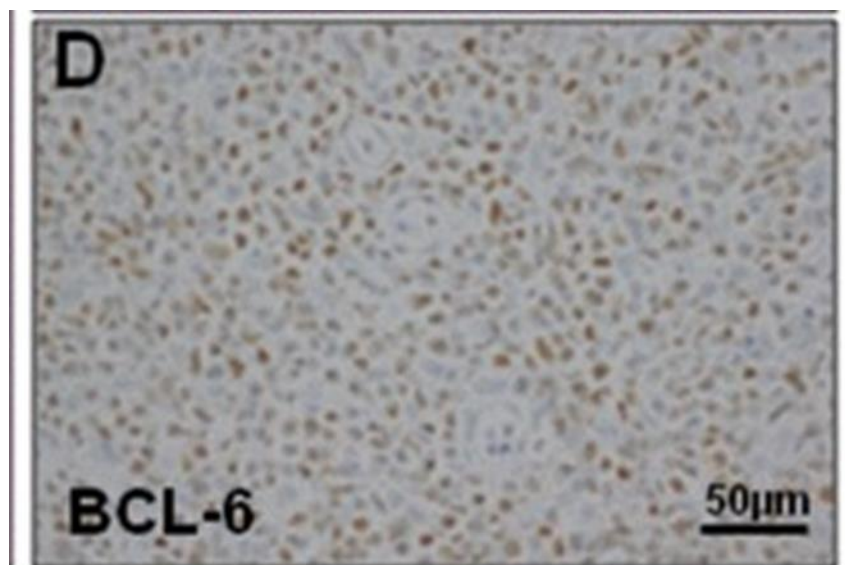


Figure 5: Non-germinal center DLBCL with BCL6 positive gene disruption [20].

Marginal-Zone Lymphoma (MZL) is among the most common types of PCNSL, following DLBC [6]. MZLs are hypothesized to arise from a marginal-zone B-cell mutating in the lymph nodes or extranodal tissue [25]. Marginal-zone B-cells are functionally heterogeneous, so the pattern of mutation in their immunoglobulin regions may vary [25]. Extranodal MZL is the most common subtype, comprising 5% to 8% of all NHL [25]. Nodal and splenic MZLs are less common, each making up less than 1% of NHL cases [25]. MZLs are usually not associated with rearrangements of the B-cell lymphoma genes. However, a recent study indicated that chromosomal translocations in MZL cases appeared to correlate with expression of the BCL6 gene [25]. Major risk factors for MZL include autoimmune disease and *H. pylori* infection in the stomach [25].

Peripheral T-cell lymphoma (PTL) is a less common subset of PCNSL. PTL is a heterogeneous subset of clinically aggressive lymphomas associated with a particularly poor prognosis [26]. PTL is an extremely rare manifestation of NHL, with an estimated incidence of <1 case per 100,000 people in the United States [26]. Studies focusing on PTL are emerging, but the rarity of this NHL subtype has resulted in difficulties understanding the manifestation and progression of this disease [26]. Patients with PCNSL had a very poor outcome when compared to patients with B-cell lymphomas, with a 10% OS rate at 10 to 15 years post diagnosis [26]. PTLs are usually treated with a similar oncological approach of a combination chemotherapy regimen [26]. Autologous stem cell transplantation is an emerging management method for younger patients who have been deemed strong enough for endurance of the rigorous treatment [26].

Burkitt Lymphoma (BL) accounts for a small percentage of PCNSL cases [9]. It is an aggressive and highly proliferative non-Hodgkin B-cell lymphoma associated with Epstein-Barr virus, HIV and chromosomal translocations that result in the increased expression of the oncogene C-MYC [27]. The MYC gene family consists of regulator genes and oncogenes important in the modulation of the cell cycle. In 95% of cases, BL results in the translocation of the c-MYC gene on chromosome 8 [27]. BL accounts for approximately 1% to 5% of NHL cases and is more common in males than females with a 3-4:1 ratio [27]. There are three distinct clinical entities of BL: endemic, sporadic and immunodeficiency related. The endemic group is linked to abnormalities caused by malaria and Epstein-Barr virus. The EBNA-1 protein, a viral protein associated with EBV, is expressed in endemic

cases of BL [27]. The immunodeficiency-related group of BLs are highly associated with HIV and sometimes correlated with organ transplantation. Patients who have undergone organ transplantation are at risk of BL because they are taking a regime of immunosuppressant drugs, which attenuate the strength of the immune system. The sporadic class of BL refers to cases affecting patients of pediatric and young adult age groups [27].

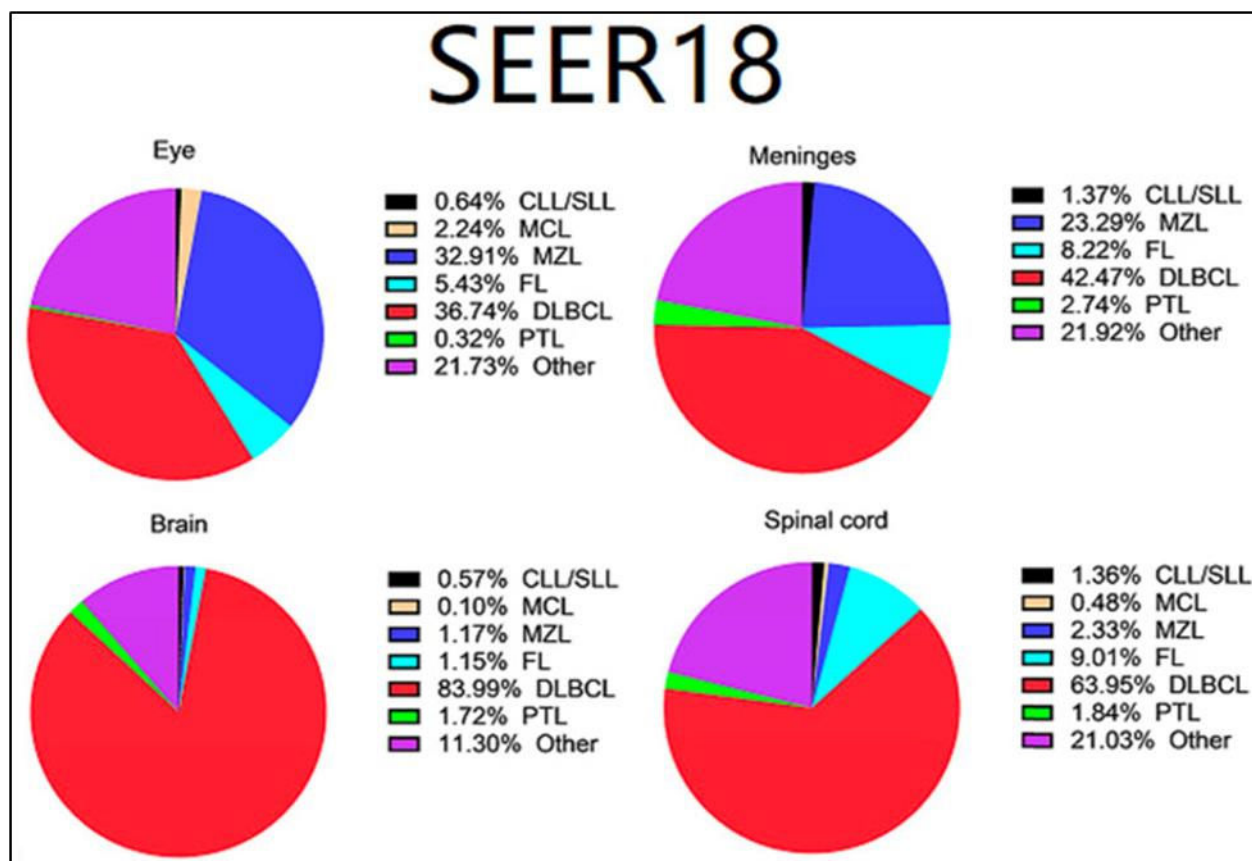


Figure 6: Histological distribution of PCNSL in SEER 18 registries [6].

Etiology

Immunodeficiency, whether congenital or acquired, is a substantial risk factor for the development of PCNSL. As an AIDS-defining illness, PCNSL is seen in approximately 6% of patients with AIDS [9]. These patients usually have a very low CD4 cell count, considering the attenuated state of their immune system. CD4 T cells are a type of lymphocyte that play an integral role in the immune system. They coordinate both adaptive and immune responses [28]. Several studies and clinical trials have supported the notion that the CD4 cell count is the strongest predictor of disease progression and survival in patients with HIV [29]. Anytime CD4 counts are lower than usual, susceptibility to illness or opportunistic infection, including PCNSL, is increased [29].

Patients who have received an organ transplant are also at risk for the diagnosis of PCNSL. Between 2% and 7% of cardiac, liver, renal and lung transplant patients ultimately develop PCNSL as a complication of their procedure [9]. The incidence rate for the development of PCNSL following heart and lung transplant is highest in the first-year post-operation [9]. Lymphomas developing because of organ transplantation are referred to as Post-Transplant Lymphoproliferative Disorder (PTLD) and most often involve the site of the donor organ, as well as multiple extranodal sites [30]. PTLD is rarely localized to structures of the CNS [30].

Risk of PTLD is increased to the patient taking a regime of immunosuppressants, which can increase susceptibility to infectious disorders [9]. There is a correlation between the use of pharmacological therapies such as tacrolimus or cyclosporine, immunosuppressants commonly prescribed after organ transplantation and the development of PCNSL [30]. These

immunosuppressants are commonly prescribed after organ transplantation for prophylaxis of organ rejection following transplantation surgery. When actively taking immunosuppressants, organ transplantation patients experienced PTLD and when reduction or cessation of these therapies occurred, there was a regression in PTLD [30].

Primary immunodeficiencies are congenital disorders that affect immune system function. There is a 4% risk increase of the development of PCNSL if a patient has a primary immunodeficiency, such as Wiskott Aldrich, ataxia telangiectasia, common variable and severe combined immunodeficiency syndrome [9]. PCNSL is the most frequently occurring brain tumor in the population of patients with acquired or congenital immunodeficiency [30]. This population of patients with an attenuated immune system are highly predisposed to develop PCNSL [30]. There is epidemiological evidence that chronic immune system activation, as seen in patients with immunodeficiencies, is correlated with occurrence of systemic lymphoma [30].

There is an associated risk with the development of PCNSL and the presence of Epstein-Barr virus. The specific mechanism of action of Epstein-Barr virus is discussed in the comorbidities section below.

Epidemiology

PCNSL has an annual incidence rate of 0.5 per 100,000, which amounts to approximately 1,500 cases in the United States [6,9]. It comprises about 3-4% of diagnosed primary CNS tumors and 1% of non-Hodgkin lymphoma cases [6,9]. These statistics confirm that PCNSL is a rare form of lymphoma. PCNSL has seen a fivefold increase in incidence rate in the span of 42 years, from 0.1/100,000 in 1975 to 0.5/100,000 in 2017 [6].

The median age of diagnosis of PCNSL is approximately 65 years [9]. The aging population in the United States is a possible confounding factor in the substantial increase in PCNSL diagnosis. Most PCNSL cases are seen in the older population and the population of people over 60 years is growing faster than any other age group, resulting in an increase in incidence rate [6]. It is important to note that the risk of PCNSL in immunocompetent patients increases with age [6]. In cases of immunocompromised patients, symptoms of PCNSL can present earlier in life, sometimes as early as ages 30-40 years old [9].

Gender does not have as profound of an effect on epidemiology as age does, regarding statistical distribution of PCNSL cases. Multiple studies have confirmed that PCNSL is more common in males than females [6,9]. However, these differences are less than 10% and there is no substantial gender difference in post-transplant PCNSL cases [6,9]. In patients aged 20-49 years, there was a definite difference in incidence rates based on racial groups. Black patients had twice the incidence of PCNSL as white patients in the 20-49-year-old age group, but not in those aged 50 years or older (most patients). For patients over 50 years of age, incidence in white patients was double that of black patients [31]. In other racial groups, the number of cases were not high enough for analysis [31]. Although there is no definite reason for the difference in PCNSL incidence rates between racial groups, there are some proposed theories. Socioeconomic status and environmental factors are hypothesized causal factors for the influx of black patients in the younger (20-49-year-old) age group. There is also a rising HIV infection incidence in the US Black population, which can account for the spike in younger cases of PCNSL consisting of predominantly black patients [31].

Whether a patient has HIV is a strong risk factor for the development of PCNSL. During the peak of the HIV epidemic in the 1990s, there was also a sharp spike of PCNSL incidence [6]. Since that peak, HIV cases have decreased globally and the number of patients progressing to the AIDS stage of infection has diminished due to interventions such as antiretroviral therapy and more advanced diagnostic techniques [6,9]. The incidence of PCNSL is 1,000 times higher in HIV-positive patients than in immunocompetent patients [32]. The causal mechanisms of HIV and how it acts as a risk factor for PCNSL, are discussed below.

Comorbidities

The risk of contracting PCNSL is heightened by the comorbidity of an autoimmune disease, such as Human Immunodeficiency Virus (HIV), or the presence of Epstein-Barr Virus (EBV) [30]. Patients who have an autoimmune disease already suffer from a weakened immune system; PCNSL is a cancer which attacks a large subset of the body's immune system, the lymph system. The severity of PCNSL is worsened by such comorbidities since the attenuated immune system is unable to fight the lymphoma as effectively. It is also important to note that patients who have taken immunosuppressants for an extended amount of time, such as people who have received an organ donation, are at a higher risk of infection [30]. However, despite these risk factors, most

people diagnosed with PCNSL are elderly and immunocompetent. [8]. Immunocompetent patients have normal immune system functioning and do not possess any major risk factors for the development of PCNSL.

Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome

Human Immunodeficiency Virus (HIV) is a virus that attacks the immune system, primarily CD4+T-cells which causes a host of immunological abnormalities that can lead to infectious and oncological complications [33]. There are approximately 37 million individuals currently living with HIV [33]. HIV is transmitted through contact with the bodily fluids of an HIV-positive person. Spread of HIV occurs through sexual contact across mucosal surfaces, by maternal-infant exposure and by percutaneous inoculation, usually via needles, syringes, or an open cut [34]. Sexual transmission is the leading mode of HIV infection, accounting for over 75% of the current active HIV infections worldwide [35].

There is currently no cure for HIV, but there are extensive options for the management of symptoms and the progression of the disease. Antiretroviral Therapy (ART) is an effective treatment for HIV working to suppress HIV replication, which can improve immune function and reduce the risk of HIV progression towards AIDS [33]. ART works to lower the amount of virus in the blood, also known as the viral load, to a very small quantity. This process is referred to as viral suppression [36]. HIV-positive patients who remain rigorous about their ART therapy and preserve a low viral load can maintain lifelong suppression of viral replication, with immune recovery and near elimination of the risk of developing AIDS [33].

There are three stages of HIV infection characterized by clinical symptoms and biological markers [36]. The first stage is known as acute HIV infection, in which there are high levels of HIV virus and p24 antigen, an HIV-specific protein used in the early diagnosis of HIV in the blood [37]. High levels of viral content in the blood coincides with a steep decline in the concentration of circulating CD4+T cells (Fig. 7) [33,38]. The acute stage of HIV infection is when the patient is most contagious due to the spike in viral replication, the amount of virus in the blood and the lack of antibodies [39]. Some patients experience flu-like symptoms during the acute stage, such as headache, fever and rash, sometimes lasting for multiple weeks [36].

The second stage, known as chronic HIV infection, is defined by continued viral replication at a decreased level [36]. The immune system of the host begins to produce effective antibodies, causing a decline in the viral load to a steady state [36]. The development of specific antibodies against an infection, in this case HIV, is known as seroconversion [36]. In the second stage, there is also a paired decline in the p24 antigen levels as the viral load drops [36]. This is due to the binding of p24 antigen to antibodies and the creation of an antibody-p24 antigen complex [36]. The amount of free p24 antigen in the blood is decreased due to this immune process [36]. Chronic HIV infection is also referred to as the asymptomatic stage because the infected individual may not experience any clinical symptoms due to low and stable viral load [36].

The third and final stage of HIV is known as the Acquired Immune Deficiency Syndrome (AIDS) stage [36]. At this point of infection, there is a rapid rise in the viral load coupled with a near depletion of CD4 cells (Fig. 7) [33,38]. Patients in the AIDS stage of HIV infection present with a CD4+T-cell level of 200 cells/mm³ or less (Fig. 7) [33,38]. For reference, a normal CD4+T-cell count is in the range of 500 to 1400 cells/mm³; the drastic drop-off seen in AIDS patients contributes to weakened immune function and increased susceptibility to opportunistic infections [40]. Opportunistic Infections (OI) are common in immunosuppressed patients and there is a heightened risk when the patient has entered advanced immunosuppression, or a CD4+T-cell count of less than 200 cells/mm³ [41]. OIs can range in severity from a mild diagnosis of a respiratory infection to a severe diagnosis such as cancer. Common OIs in patients with AIDS include but are not limited to bacterial pneumonia, COVID-19, cryptococcal meningitis, toxoplasmosis, PCNSL, tuberculosis and candidiasis [41].

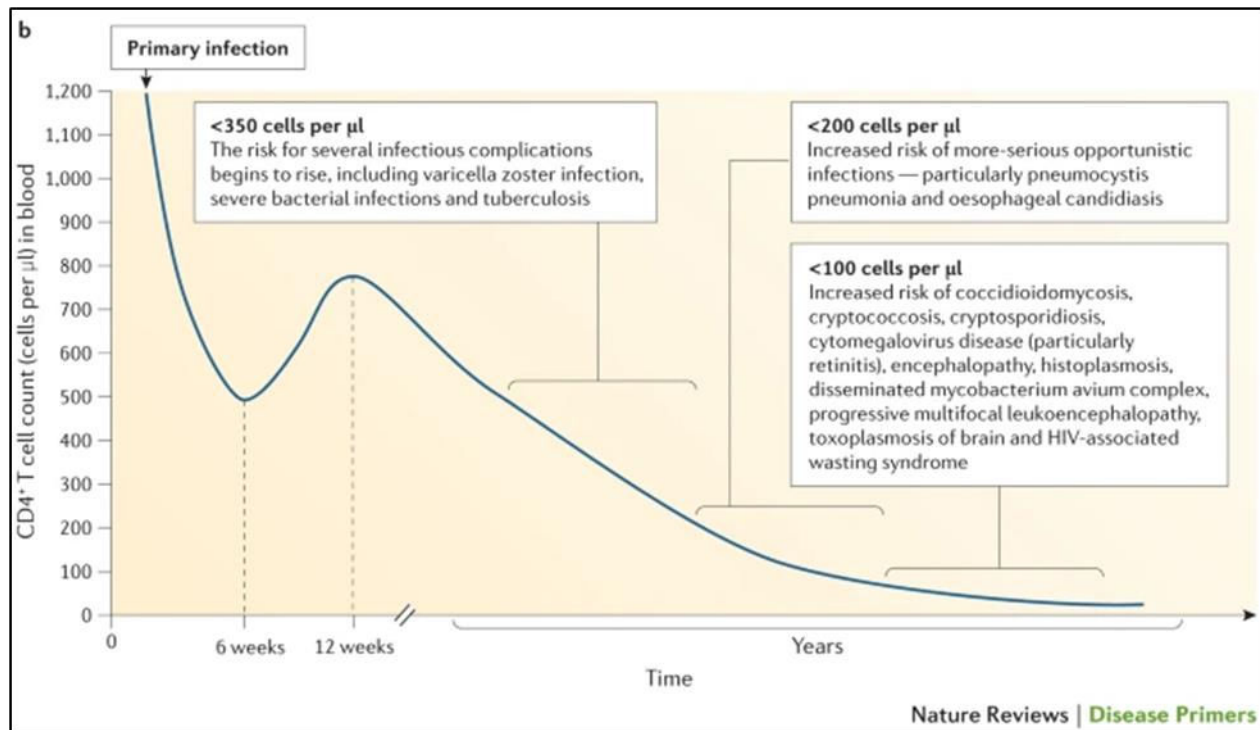


Figure 7: CD4+T-cell count over the course of infection with HIV. Average CD4+T-cell counts for a healthy adult are between 500 and 1,200 cells/mm³. As the HIV infection progresses, a CD4+T-cell count of <350 cells/mm³ can lead to serious infection and a count of <200 cells/mm³ marks the progression into the AIDS stage [33].

PCNSL accounts for up to 15% of the NHL cases diagnosed in HIV positive patients and is classified as an OI for AIDS patients [42]. The prognosis of HIV-related PCNSL is poor, with the median survival rate varying between 2 and 4 months. There is a marked improvement of 1.5 years when PCNSL is treated with chemotherapy [42]. The HIV epidemic reached its peak during the 1990s, which is reflected in a sharp spike in PCNSL cases during this decade. This peak is seen through the analysis of patient data from the SEER 9 and 18 databases and is demonstrated visually in Figure 1 [6]. Since the peak of the epidemic in the 1990s, there has been a consistent decline in overall HIV incidence in the United States, among both sexes and all racial groups [43]. In turn, this has resulted in a decrease in HIV-associated PCNSL cases since 2000 [6]. In the past couple of decades, considerable progress has been made towards earlier HIV diagnoses, more efficient treatment methods, such as cART and better prevention of patients reaching the AIDS stage of infection [42].

In a San Francisco study of over 20,000 AIDS patients over a 31-year period between 1981 and 2012, mortality occurred in 82% of patients due to AIDS OIs [44]. This study was broken down into 3 observation periods based on the distinct treatment available at the time: pre-ART (1981-1986), mono/dual ART (1987-1996) and cART (1997-2012) [44]. The pre-ART group saw the highest mortality levels due to AIDS related OIs, at a considerable 98.2%. The invention of mono or dual ART as an interventional therapy for HIV/AIDS had a positive effect on mortality rates, dropping them to 89.2% for the second observational group. The largest progress against AIDS related OI mortalities was seen in the third observational group, with the introduction of combination ART (cART). This group saw a substantially lower mortality rate of 41.9% over the 15-year period [44]. With continuity of efficient management of HIV and less patients progressing to the AIDS stage of infection, it is hopeful that HIV-associated PCNSL cases and AIDS related OI mortalities will continue to decrease.

Epstein-Barr Virus

Epstein-Barr Virus (EBV), or human herpesvirus 4, is a member of the herpes virus family. EBV maintains a dominant prevalence globally, with most sources estimating that over 90% of the world's population is infected [45]. Primary infection with EBV generally occurs during early childhood and is asymptomatic [46]. If infection does not occur until adolescence or later, it can be associated with the clinical effects and symptoms of infectious mononucleosis, also known as "mono" [46]. Symptoms of infectious mononucleosis include fever, pharyngitis, malaise, lymphadenopathy and hepatosplenomegaly [46,47]. Infection

occurs through transmission of bodily fluids, including saliva and respiratory secretions which allow access to the reticuloendothelial cells of the upper respiratory tree [47]. The primary target T-cell of EBV is the B-lymphocyte [47].

Following primary infection of EBV, the virus manipulates memory B-cells, allowing it to become latent in the body [45]. The latent phenotype becomes immortalized in the B-lymphocyte population, granting the virus a lifelong source of low-grade and stable viral load [47]. This means that patients who are positive for EBV will have it for the rest of their lives. In most cases, the virus remains latent, but in some instances, reactivation can occur. Patients are at a higher risk of reactivation of EBV during times of stress, infection, or immunosuppression [45].

EBV was accidentally first discovered in the 1960s, when a researcher studying cells of Burkitt Lymphoma discovered viral particles upon subsequent examination [45]. Those viral cells were later identified as EBV and are understood to be one of the few viruses that can lead to the development of cancer [45]. Like other oncogenic agents, EBV has built-in mechanisms to evade the human immune system and prevent the body's physiological response to tumorigenesis [45]. There are multiple molecular mechanisms in which the EBV genome contributes to malignant T-cell proliferation. EBV gene variants such as EBV-encoded nuclear antigen-1 (EBNA-1) and latent membrane protein 2a (LMP-2a) are the reason for the differentiation of primary B-cells into lymphoblastoid cell lines (LCLs) [48]. LCLs are established through the *in-vitro* infection of B-cells sourced from the peripheral blood, known as Peripheral Blood Lymphocytes (PBL), with EBV [49]. PBLs are mature lymphocytes circulating through the bloodstream rather than maintaining localization to one specific organ or organ system [49]. The development of LCLs has been found to cause an actively proliferating B-cell population due to the anti-apoptotic mechanisms of EBV [49]. LCLs are commonly used in research because they are immortalized due to their infection with EBV [49].

In specific regard to PCNSL, the oncogenic activity of the EBNA-1 protein associated with EBV is the hypothesized mechanism of lymphomagenesis [45]. The EBNA-1 protein is expressed in both the lytic and latent forms of EBV infection [50]. Functions of the EBNA-1 protein in the persistence of the EBV genome include DNA replication, mitotic segregation, transcriptional activation and autoregulation [50]. The DNA-binding domain of EBNA-1 binds a specific 18 Base Pair (BP) palindromic sequence on human chromosome 11 [51]. Repetitive DNA sequences present a challenge to genome stability and are prone to breakage due to their unstable structure [51]. In cells latently infected with EBV, the buildup of EBNA-1 protein accumulates at this site, which can lead to breakage of chromosome 11 [51]. This fragile site breakage is hypothesized to enable deletion of tumor suppressor genes and promote amplification of oncogenes [51]. If breakage is left unrepaired in the cell cycle and mitosis continues, fragments of genetic material can be mis-segregated into structures known as micronuclei [51]. Micronuclei are small membrane bound compartments that have been linked to chromosomal instability, genome rearrangements and mutagenesis [52]. They play an important role in tumorigenesis by being the source of complex genome rearrangements called chromothripsis, which is a genetic signature of various types of cancer [52]. Micronuclei drive tumorigenesis by also promoting a cyclic GMP-AMP synthase (cGAS) mediated cellular immune response, with a proposed connection to metastasis of cancer [52].

In a study of 18 cases of EBV positive head and neck cancers, 100% had chromosome 11 rearrangements [51]. In addition to contributing to the latency of EBV in the body, the EBNA-1 gene directly contributes to cell proliferation [50]. EBNA-1 is the only EBV protein expressed in all EBV-positive tumors; in some cases, it is the only EBV protein expressed [50]. There is also substantial evidence that the EBNA-1 gene contributes to oncogenesis due to multiple effects on cellular proteins [50].

Proteomic methods have helped to visualize several proteins that bind to EBNA-1 [50]. One of these proteins is the cellular ubiquitin-specific protease (USP) USP7, which is located primarily in the nucleus [50,53]. The functions of USP7 include protein degradation and the regulation of proteins involved in a variety of cellular processes including DNA damage response, transcription, epigenetic gene expression, immune response and viral infection [53]. USP7 possesses the ability to regulate the p53 tumor suppressor gene and the HDM2 oncogene through deubiquitination of the chains that signal for degradation [53].

EBNA-1 functions to destabilize the function of tumor suppressor genes through its affinity for USP7 [50]. The USP7 protein is intended to bind to the p53 tumor suppressor gene and the Mdm² gene, a regulatory gene of p53 [50]. EBNA-1 competitively inhibits the binding of these targeted genes with USP7, which disrupts their function [50,53]. This competitive inhibition can lead to lower p53 levels, resulting in prolonged cell survival and increased cell proliferation because of downregulation of tumor-

suppressing functions [50]. Based on how involved USP7 is in multiple cellular pathways, overexpression or upregulation of the protein can contribute to tumor progression through dysregulation of the pathways of DNA damage response, apoptosis and control of the cell cycle [53].

The activity of the EBNA-1 protein has been proven to affect several cellular signaling pathways. One of these is the Transforming Growth Factor- β (TGF- β) signaling pathway, which plays an essential role in the regulation of multiple cellular processes including growth, proliferation, differentiation, migration and survival [50,54]. The TGF- β signaling pathway plays an important role in hematopoiesis as a negative regulator of proliferation, while also promoting apoptosis or differentiation when necessary [54]. This regulatory pathway ensures that healthy cells move onto differentiation and abnormal or potentially malignant cells undergo apoptosis. In hematologic cancers such as lymphoma and leukemia, cellular resistance to the TGF- β signaling pathway can arise through mutation, deletion of components of the pathway, or disruption of the signaling cascade by oncogenes [54]. Like other oncoproteins, an increased amount of the EBNA-1 protein has been found to decrease expression of TGF- β genes which interferes with the TGF- β signaling cascade [50]. This inhibition of the TGF- β pathway results in the decrease, or even absence, of cellular proliferation regulation [54]. Disruption of this pathway can lead to uncontrolled cell growth, which is understood to be the foundation of tumorigenesis [54].

Patients with EBV-positive PCNSL have a poor prognosis. They showed shorter survival rates than those with EBV-negative tumors, at medians of 4 months vs. 26 months, respectively [55]. It is also important to note that EBV is associated with 100% of PCNSL cases in patients with AIDS [6]. The induction of oncogenic protein expression coupled with increased proliferation of lymphocytes, as induced by EBV, is the likely etiology for why most HIV patients with PCNSL are EBV related [42].

Immunocompetency

Although immunodeficiency of any kind is a major risk factor for developing PCNSL, most patients are immunocompetent [56]. Specifically, cases of PCNSL are most seen in immunocompetent and elderly individuals, with incidence rate positively correlating with an increase in age [8]. More than 50% of PCNSL cases seen in the SEER 9 and 18 registries were white people >60 years of age [6]. The age of diagnosis for immunocompetent patients varies but is most often seen between the ages of 50 and 70 years old, with increasing age acting as a risk factor [9]. The median age of diagnosis for PCNSL is 65 years old [17]. In the SEER 9 and 18 studies, incidence rates of PCNSL in patients aged 60-69 years old was two times higher than patients in the younger age group of 50-59 years old [6]. On the other hand, a younger average age of diagnosis is seen in immunocompromised patients, ranging between 30 and 40 years old [9]. Most immunocompetent patients present with a single brain mass, with a small percentage (20-40%) presenting with multiple lesions [17]. Patients diagnosed with a single brain mass typically undergo more aggressive treatment than those with multiple metastases [57].

Discussion

Usual Treatments

Chemotherapy is a treatment that gained prominence at the beginning of the 20th century and involves the use of chemicals to destroy cancer cells [58]. In combination with prevention of cancer and earlier diagnosis due to better technology, chemotherapy has been cited as a major component in the decline of cancer mortality in the United States since the beginning of the 21st century [58]. Chemotherapy inhibits the proliferation of malignant cells, but it does not possess anti-tumor specificity. Lack of specificity to abnormal cells leads to damage of healthy cells with high proliferation rates, such as hair follicles, epithelium of the digestive tract and bone marrow stem cells [59]. DNA damage of normal cells can lead to serious toxicities including acute kidney injury, hepatotoxicity, generalized weakness (among other neurological symptoms), myocardial infarctions, cardiomyopathy and rhythm disturbances, cytopenia, anemia, nausea, diarrhea and vomiting [60].

There are different chemotherapy delivery methods, dependent on multiple factors, including the location of the mass, whether the cancer has metastasized and if there are single or multiple masses. For patients with PCNSL, there are two options for delivery methods of chemotherapy: systemic or intrathecal [20]. Systemic chemotherapy consists of small molecule chemotherapy drugs targeting the cell cycle or cell surface receptors and their associated pathways [61]. This delivery method has been cited as ineffective due to the Blood-Brain Barrier (BBB) acting as a significant barrier to the transvascular extravasation of systemic chemotherapy drugs [61]. With a short blood half-life and a limited ability to penetrate the BBB, systemic chemotherapy is largely

ineffective at reaching malignant brain cells [61].

Intrathecal chemotherapy is a regional form of chemotherapy developed with the intention of bypassing the BBB by directly injecting the chemotherapy into the CSF surrounding the brain and spinal cord [62]. The goal is to maximize CNS drug exposure while also reducing or altogether avoiding drug toxicity [62]. Intrathecal chemotherapy can be delivered via a previously inserted intraventricular device, such as an Ommaya reservoir, or through direct intralumbar injection [62]. The intraventricular device requires a neurological procedure for placement, which can be risky and associates with the postoperative risk of infection (Fig. 8) [62]. However, if placed correctly and closely monitored for signs of infection, an intraventricular device is efficient at ensuring direct access to the CSF for maximum efficacy of chemotherapy delivery [62]. The placement of an intraventricular device allows for repeated access to the intrathecal space and therefore improved flexibility in dosing schedules [62].

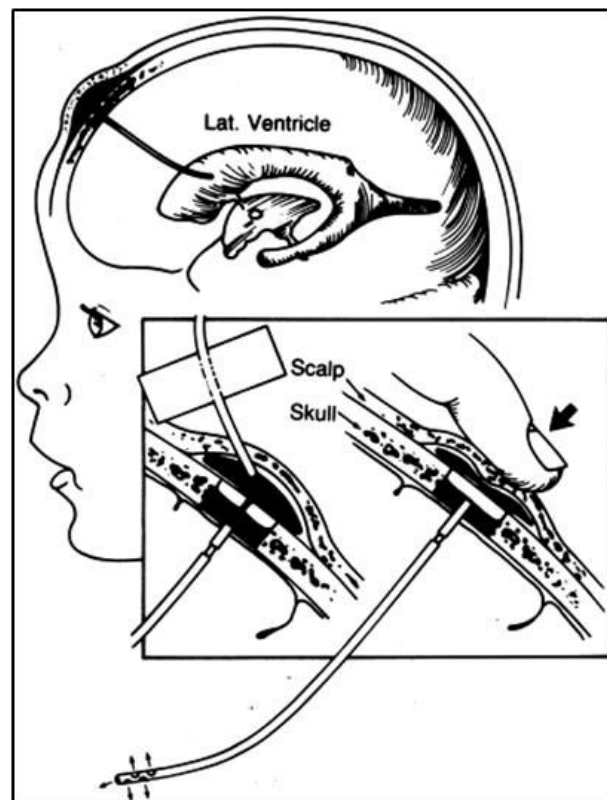


Figure 8: Representation of an intraventricular drug delivery system made up of an Ommaya reservoir attached to a catheter placed in the lateral ventricle for direct access to CSF [62].

Administration of High-Dosage (HD) methotrexate (MTX) has been described as the key drug of the chemotherapy regime used in the treatment of PCNSL [63]. HD-MTX induction chemotherapy is the standard for newly diagnosed cases of PCNSL [17]. MTX doses of at least 3 mg/m² allow for an adequate therapeutic concentration of chemotherapy to be reached in the brain parenchyma or CSF [17]. The combination of HD-MTX with other chemotherapeutic agents or whole-brain radiation therapy (WBRT) is the most effective treatment for new cases of PCNSL [17]. In fact, when the combination therapy approach of HD-MTX and WBRT was introduced in the 1980s and 1990s, overall and 5-year survival rates improved [64]. Although effective at prolonging survival, patients treated with this combination therapy developed neurotoxicity, presenting with symptoms of cognitive decline, memory problems, changes in behavior and gait ataxia [17,64]. This emergence of neurotoxicity led to the investigation of the efficacy of HD-MTX administration with reduced or no WBRT [64]. One trial, investigating a polychemotherapy regime consisting of HD-MTX in combination with Rituximab, a monoclonal antibody against a B-cell surface antigen, proved an overall response rate of between 35% to 74%, with comparable overall survival rates to chemoradiation therapy [64]. One disadvantage of the use of HD-MTX in the treatment of PCNSL is the drug's nephrotoxicity [64]. Many patients receiving HD-MTX are admitted to the hospital during treatment, which places a larger burden on the patient and their families when compared to the typical outpatient chemotherapy regimen [64].

Radiation therapy is the use of ionizing radiation to form ions and deposit energy in cells, which can damage or kill cancer cells [65]. High-energy ionizing radiation damages genetic material, specifically DNA, which inhibits proliferation abilities of cells [65]. Radiation, like chemotherapy, does not possess anti-tumor specificities and can cause damage to both normal and malignant cancerous cells [65]. The goal of radiation therapy is to minimize damage to healthy cells through targeting and maximization of the radiation dose towards malignant cells [65]. Approximately 50% of cancer patients receive radiation at some point during their treatment [65]. It is estimated that radiation therapy contributes 40% towards curative cancer treatment [65]. WBRT is not typically used as a primary or solitary treatment method due to its inability to control the disease without combination therapy and the effects of neurotoxicity [17]. High doses of WBRT have been identified as a major risk factor for the development of radiation-related neurotoxicity, with patients over the age of 64 years old at increased risk [17,64]. Before neurotoxicity, WBRT was used as a first-line defense against the progression of PCNSL. This resulted in a high proportion of radiographic responses, but the effects did not last, with high rates of early relapse occurring in patients [17].

WBRT is an effective oncological method when used as treatment for refractory or relapsed cases of PCNSL, or in combination with chemotherapy [17]. In a study of 48 patients with refractory or relapsed PCNSL treated with WBRT, 58% achieved a complete response (CR) with a survival rate of 28 months as compared to 4-5 months in partial response [17]. However, of the 48 patients, 29% developed serious neurotoxicity with major cognitive decline [17]. Another study of 52 patients focused on reduced-dose WBRT in combination with cytarabine, an antimetabolite chemotherapy, following usual chemotherapy treatment with Rituximab, Methotrexate, Procarbazine and Vincristine (R-MPV) [66]. 60% of the group achieved a CR following treatment with R-MPV and were administered reduced-dose WBRT [66]. The 2-year progression-free survival (PFS) rate for this group was 77%, with a median PFS of 7.7 years [66]. The 3-year OS rate of this group was 87% [66]. Neurological assessment of the patients treated showed improved cognitive function and memory, with no signs of neurotoxicity from radiation [66]. R-MPV in combination with consolidation reduced-dose WBRT and cytarabine showed promising results in high patient response rates and outlooks, long-term management of PCNSL and minimal neurotoxicity as a side effect of radiation [66].

Except for stereotactic biopsy, which is highly recommended for accurate diagnosis if accessible, surgical interventions are not typically used during treatment for PCNSL due to the multifocal properties of the tumor [17].

Surgery increases the risk of other neurological deficits in a cancer that often involves deep structures of the brain not easily accessible [20]. Surgery in a cancer that is so highly chemosensitive is regarded as risky, especially when retrospective studies have shown that there is no survival benefit from surgical resection [20]. Further reason for physicians to avoid surgical intervention is supported by a retrospective study of 32 patients treated for PCNSL at Memorial Sloan Kettering Cancer Center [67]. 10 of the 32 patients underwent gross total resection of their tumors, with 40% of them developing postoperative deficits [67].

Overview of Stem Cells

Stem cells are undifferentiated cells of the human body with the potential to develop into any cell of the organism [68]. They possess the abilities of differentiation into various types of cells and self-renewal [68]. Stem cells are found in both embryonic and adult cells and the two major types are known as Embryonic Stem Cells (ESCs) and Adult Stem Cells (ASCs) [68]. There is great hope in the scientific community about the potential of stem cells to become a prominent treatment method for diseases which were once thought to be untreatable [68]. Stem cells are a turning point in modern medicine due to their ability to differentiate into virtually any cell and their use of the patient's own immune system and body cells [68].

Stem cells range in their levels of developmental potency, or number of cells or tissues a stem cell can differentiate into based on progression of specialization [68]. Totipotency is the highest level of differentiation. Totipotent stem cells possess the ability to differentiate into cells of the entire organism [68]. An example of a totipotent stem cell is a zygote, which is formed following the fertilization of an egg by a sperm [68]. Pluripotency is the next level of differentiation, where stem cells can divide into any body cell or tissue excluding embryonic structures such as the placenta [68]. ESCs are pluripotent stem cells [68]. Multipotent stem cells can develop into cells of specific lineages or tissue families [68]. Hematopoietic stem cells can differentiate into various types of blood cells [68]. Oligopotent stem cells can differentiate into some cell types and unipotent stem cells can form one cell; these stem cells represent the lowest level of potency but are still promising for therapeutic methods in the medical field [68].

ASCs, sometimes referred to as somatic stem cells, are undifferentiated cells found among differentiated cells in tissues such as the umbilical cord, bone marrow, adipose tissue, menstrual blood and endometrium [69]. The function of ASCs is to promote healing, growth and replacement of cells that may be lost in daily bodily activities [68]. The proliferation time of ASCs is longer than that of ESCs, but they do possess the ability to return to the pluripotent state [68]. The use of ASCs avoids some of the ethical considerations that arise when considering the use of ESCs [69]. There are different types of adult stem cells, including mesenchymal stem cells, hematopoietic stem cells, neural stem cells, epithelial stem cells and skin stem cells [68].

Mesenchymal Stem Cells (MSCs) are a lineage of ASCs with the ability to self-renew and differentiate into a variety of body cells [69]. Many tissues house MSCs, including those of the umbilical cord, endometrial polyps, menses blood, bone marrow and adipose [69]. A major appeal of using MSCs in clinical applications is the ease of harvesting these cells, as well as the abundant amount obtained from bodily sources [69]. MSCs can differentiate into tissues and cells of the mesoderm, endoderm and ectoderm and the specialization process is regulated by transcription factors and regulatory genes [69]. Hematopoietic stem cells (HSCs) are multipotent stem cells with the ability to differentiate into all types of blood cells [70]. HSCs are in the bone marrow, peripheral blood and umbilical cord blood and are regarded as a pillar of regenerative medicine, useful in the treatment of blood disorders and hepatic malignancies [70]. 53% of global HSC transplants are autologous, with a 68.8% 10-year survival rate for patients with NHL [70]. In cancer patients, HSC transplants are performed after chemotherapy with the intention of immune cell restoration [70]. HSCs are a powerful cell source in the treatment of a wide spectrum of disorders.

Embryonic stem cells, unlike ASCs, can differentiate into every cell type for which a treatment has been developed [71]. The only cells that ESCs cannot differentiate into are extraembryonic structures, such as the placenta [71]. Human ESCs can be derived from a singular cell derived from an eight-celled embryo blastomere, without the destruction of the embryo or surrounding tissues [71]. With their pluripotent features, ESCs could specialize into all types of cells in the body; the clinical applications of ESCs cannot be understated [71]. In comparison to induced pluripotent stem cells, another type of stem cell used in treatments, ESCs are not genetically modified and are normal, previously existing cells from a human embryo [71].

In the past, human ESCs were extracted from the inner cell mass of blastocysts, ultimately causing the destruction of the embryo [71]. This process raised major ethical questions, sparking debate and restrictions (by law in some countries) of the use of ESCs [71]. Various religious groups have advocated for the protection of preimplantation embryos because of strong beliefs that they should not be used for any purpose [71]. Specific to the United States, there are imposed limitations on deriving human ESCs when it results in the destruction of an *in-vitro* fertilization embryo [71]. The development of new technology allowing for the creation of viable ESCs from a single biopsied blastomere of an IVF embryo, without any damage to the embryo, has expanded the clinical application of ESC use as a treatment method [71]. The improved procedure also eliminates any ethical debate since it is safe and inflicts no harm on the embryo.

A stem cell transplant is a therapeutic procedure aimed to restore blood-forming stem cells in patients who have had theirs destroyed by chemotherapy or radiation. This procedure can be autologous, allogeneic, or syngeneic [68]. In an Autologous Stem Cell Transplant (ASCT), the cells are sourced from the patient themselves which eliminates any risk of immune rejection [68]. ASCT, in combination with HD chemotherapy, is a very promising treatment option for PCNSL patients [17]. The ASCT/HD chemotherapy regimen involves leukapheresis (the process of separating white blood cells from the blood sample) and peripheral blood stem cell harvest before treatment with HD chemotherapy [17]. Following chemotherapy, the harvested stem cells are reinfused to promote blood and immune cell production [17]. Allogeneic stem cell transplants extract cells from a donor who is most often a blood relative [68]. It is important before an allogeneic stem cell transplant that the hematological profiles of both the patient and the donor are a “match” [68]. A potential match for a patient is evaluated through Human Leukocyte Antigen (HLA) typing [72]. HLAs are protein markers present on stem cells; the more similar the HLA profiles, the more likely an allogeneic transplant will be successful [72]. Finding a compatible donor can be a difficult and time-consuming process, especially if the patient does not have close family members, or donors are not readily available [72]. Allogeneic transplants also pose the risk of Graft-Versus-Host Disease (GVHD), a serious immune response to transplanted cells [72]. GVHD can present as acute or chronic; it can be characterized as limited, which is localized to the skin or affecting only a single organ, or clinical extensive, involving multiple organs or generalized to the skin [73]. The final type of transplant is syngeneic, which uses stem cells from an identical twin [68]. The risk of GVHD, even if the HLAs are deemed compatible, is a factor that oncologists heavily

consider when considering stem cell transplantation as a therapeutic option for PCNSL patients.

Autologous Stem Cell Transplant in consolidation with chemotherapy for treatment of PCNSL

Stem cell therapy is proving to be a promising option for the treatment of PCNSL [17]. Autologous Stem Cell Transplant (ASCT) in consolidation with high-dosage chemotherapy (methotrexate, for example) is demonstrating efficacy in prolonging OS rates and PFS rates for patients with PCNSL [74,75].

The process of ASCT in combination with chemotherapy begins with the removal of the patient's own stem cells [17]. Stem cells are harvested from peripheral blood stem cells (PBSCs) [17]. Patient PBSCs, following extraction, are cryopreserved for reintroduction following chemotherapy treatment [76]. The consolidative approach of HD chemotherapy with ASCT utilizes leukapheresis, a type of apheresis. Apheresis is a broad family of procedures involving the separation and retention of blood components [77]. Methods of apheresis include therapeutic plasma exchange, extracorporeal photopheresis, thrombocytapheresis, erythrocytapheresis and leukapheresis [77]. Leukapheresis, the separation and retention of leukocytes, follows PBSC harvest and is specifically designed to isolate leukocytes from peripheral blood sources [17,77].

Following PBSC extraction and leukapheresis, a HD chemotherapy is administered [17]. This chemotherapy treatment destroys the bone marrow's ability to produce new blood cells, a process known as myeloablative conditioning [78]. Myeloablative chemotherapy can cause oxidative stress, inflammation and tissue damage to the body [78]. A study of 38 patients undergoing hematopoietic stem cell transplant in combination with myeloablative chemotherapy measured Vitamin C levels, which are indicative of immune status [78]. The average Vitamin C concentration for pre-transplantation patients was approximately $44 \pm 7 \mu\text{mol/L}$ (Fig. 9) [78]. This dropped to $29 \pm 5 \mu\text{mol/L}$ in the first week following transplantation and decreased even more to $19 \pm 6 \mu\text{mol/L}$ in the second week following treatment (Fig. 9) [78]. A gradual recovery was seen in the fourth week, with average Vitamin C levels rising to $38 \pm 10 \mu\text{mol/L}$ (Fig. 9) [78]. When considering the diverse and important functions of Vitamin C in the body, supplementation of Vitamin C for patients receiving myeloablative chemotherapy regimens would be beneficial [78]. In oncology patients, high-dosage administration of Vitamin C has been shown to improve appetite, decrease nausea/vomiting (which increases quality of life) and decrease symptoms of gastrointestinal toxicity [78].

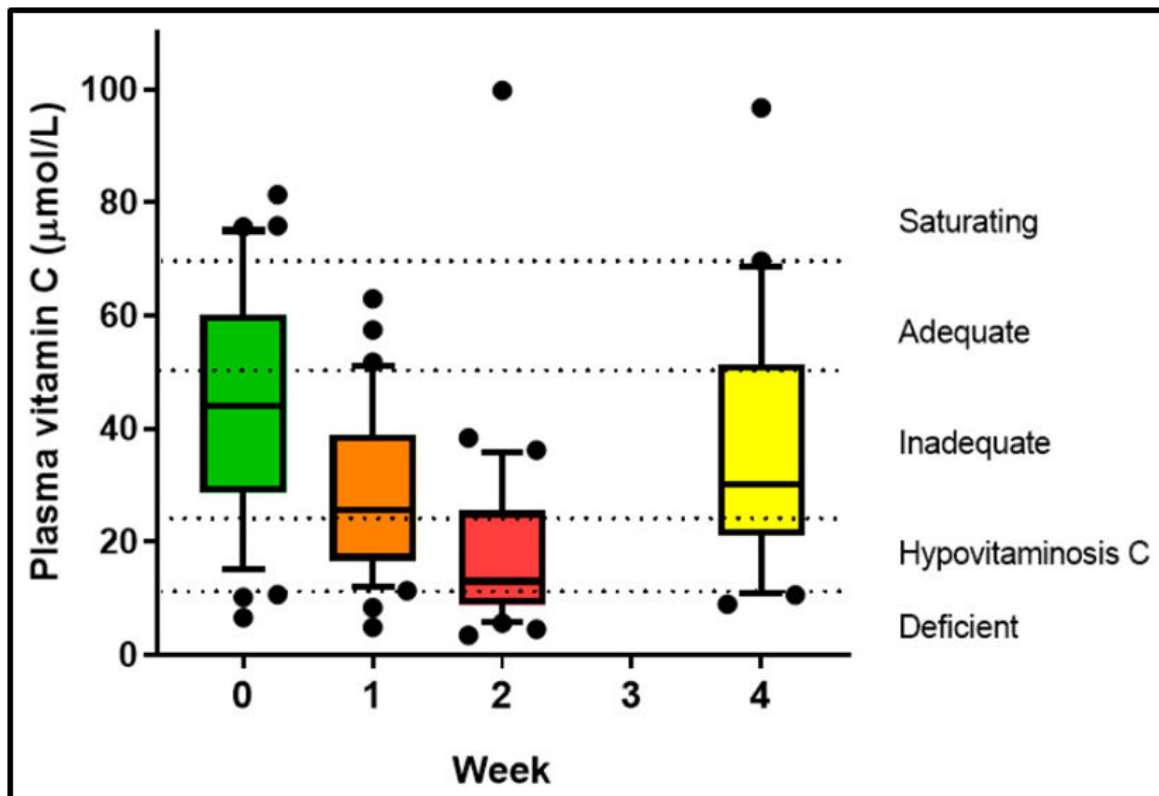


Figure 9: Vitamin C levels of patients undergoing hematopoietic stem cell transplant and myeloablative conditioning [78].

Following treatment with high-dosage chemotherapy, patient stem cells are thawed and transplanted back to the patient, a process known as engraftment [76]. The optimal method of injection, time between chemotherapy and apheresis and number of cells reintroduced continue to evolve and may vary from patient-to-patient [76]. The current minimum threshold for engraftment is $1-2 \times 10^6$ CD34 + cells/kg [76]. Ultimately, the goal of ASCT treatment is that transplanted cells will travel back to the bone marrow to begin reproduction and the growth of healthy new cells [17].

An advantage of ASCT is that there is no risk of GVHD, which is of major concern for allogeneic stem cell transplants [73]. The primary risk factor of GVHD in allogeneic stem cell transplant remains to be histocompatibility, although other metrics have been identified such as diagnosis, recipient-donor sex mismatch, recipient age, female-donor male-recipient pair and an increase in radiation dosage [79]. However, ASCT is not a risk-free procedure. Engraftment syndrome (ES) is a spectrum of peri-engraftment complications following hematopoietic autologous stem cell transplant [80]. ES can range in severity from mild to severe with symptoms including fever, skin rash, diarrhea, hepatic and renal dysfunction and capillary leak features [80]. Because of the vague clinical presentation of ES, the etiology of the disease is misunderstood, with the transplant field struggling to define symptoms and diagnosis metrics [80]. The mean onset of ES is between 3 and 7-days post ASCT treatment [80]. In a vast majority of cases, ES patients suffer mild symptoms that resolve following no intervention, or the use of corticosteroids [80]. Despite the absence of HLA and histocompatibility in ASCT, the immune system and associated mechanisms are currently suggested to play a major role in the development of ES [80]. Suggested treatment for ES includes early diagnosis and management of symptoms, while ruling out infection using broad-spectrum antibiotics [80].

Clinical Trials and Case Studies

ASCT in combination with high-dosage chemotherapy is an emerging treatment for PCNSL, showing great potential in the extension of life and progression of symptoms. There are numerous clinical trials and case studies reinforcing the efficacy of this treatment method.

A case study of 53 patients with PCNSL treated at the Montefiore Medical Center in the Bronx, New York demonstrates encouraging results. Patients were treated in between June 2000 and April 2022 and a retrospective analysis of medical records was performed. The mean age of diagnosis was 61 years and the gender distribution was nearly even, at 47.2% female and 52.8% male (Fig. 10) [74]. The patients treated were minority-rich, with more than 50% of the group consisting of Black and Hispanic individuals (Fig. 10) [74]. 82% of the group was HIV-negative, so the study largely consisted of immunocompetent patients (Fig. 10) [74]. Of the 53 patients, 17 (32%) received ASCT. It is important to note the difference between induction and consolidation chemotherapies, as the case study of the Montefiore patients involved both techniques. Consolidation chemotherapy indicates systemic chemotherapy following a treatment of radiation or chemoradiation [81]. Induction chemotherapy refers to the primary treatment of a metastasis before radiation therapy or another type of chemotherapy [81].

The trial was split between patients receiving induction chemotherapy (22 patients or 41.5% of the cohort) and patients receiving consolidation chemotherapy (35 patients or 66% of the cohort) [74]. The most common induction chemotherapy regimen used by patients in the trial consisted of Rituximab, high dose Methotrexate and Vincristine (RMV). Consolidation chemotherapies included high-dosage chemotherapy in combination with ASCT, used by 17 patients (32%), WBRT for 12 patients (22%) and Cytarabine in 4 patients (7.5%) [74]. The mean OS rate in patients with ASCT was significantly better than patients receiving the other two consolidation methods. One year OS rates favor ASCT over WBRT, at 87% vs 76%. ASCT consolidation in patients with PCNSL resulted in a 10-year survival rate of 87.5%, which is a very promising and impressive figure [74]. As compared to the average OS rate of PCNSL being between 30.5-37.4%, this is an increase of over 50% which is quite substantial [6,74]. It should be noted that the 32% of patients receiving ASCT is a small percentage, which the researchers recognized as an issue of underfunding and less allocation of resources to an underserved hospital [74]. Improving access to resources, as well as increasing the amount of money going into patient care, will hopefully be able to expand the number of patients able to access stem cell therapies.

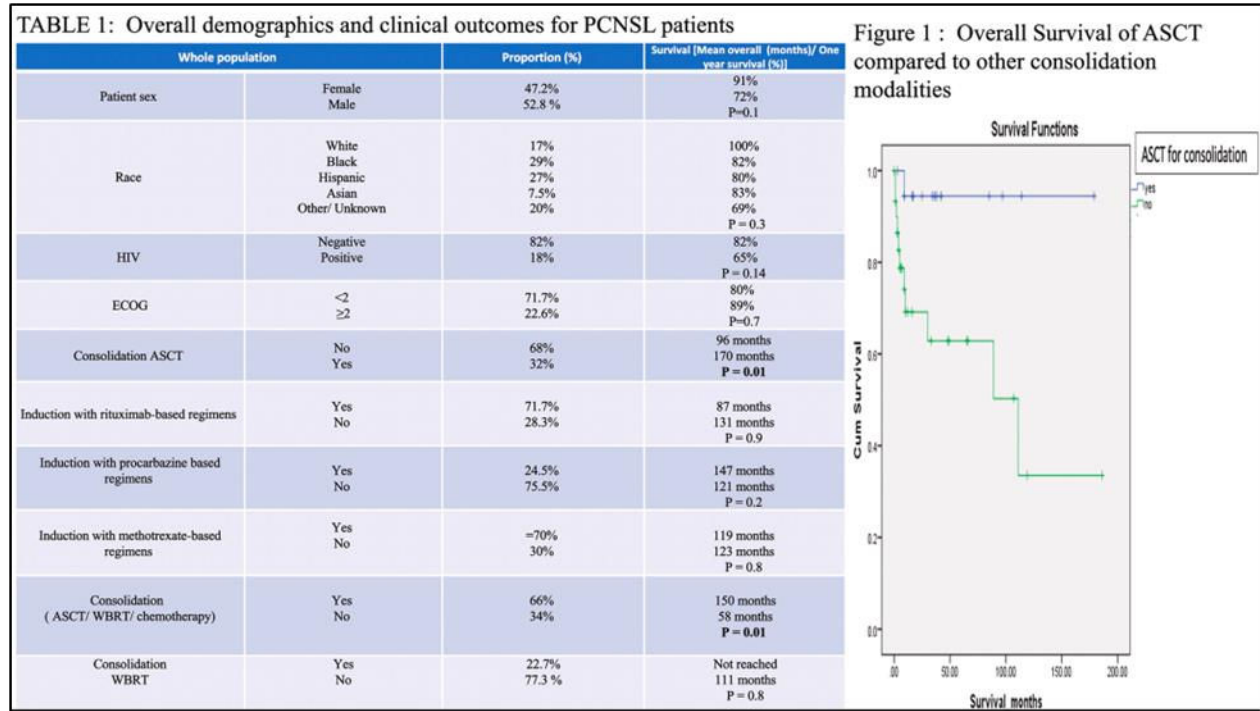


Figure 10: Overall demographics and clinical outcomes of PCNSL patients [74].

A retrospective study out of China followed 47 HIV-negative patients with PCNSL between the years of 2010 to 2021. The median age of patients was 51 and more than half (28 patients) were male (Fig. 11) [75]. 45 of the 47 PCNSL cases were categorized as DLBCL [75]. Following treatment with high-dosage methotrexate, patients were selected for consolidation therapy with ASCT. 20 patients received the ASCT and 27 did not. Treatment with ASCT resulted in longer PFS rates than treatment without ASCT (Fig. 12) [75]. Patients who received ASCT had a 2-year PFS rate of 89.1%, which is more than double the median 2-year PFS rate of 43.8%. This study demonstrated that there is a drastic difference in PFS rates when considering treatment with or without ASCT. However, there was no significant difference between OS rates. The 2-year OS rate with ASCT was 100%, while the 2-year OS rate without ASCT was 95.1% [75]. From a perspective that considers the management of symptoms and quality of life of patients, the results of this study suggest that ASCT is favorable.

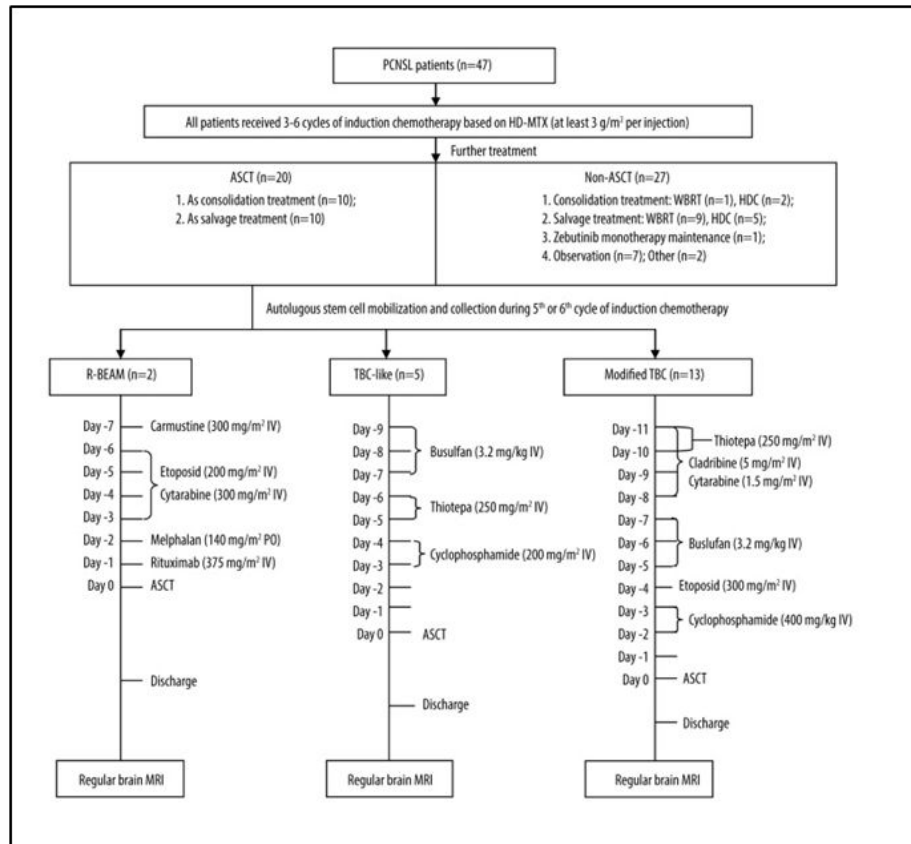


Figure 11: Treatment procedures in the Chinese retrospective study [75].

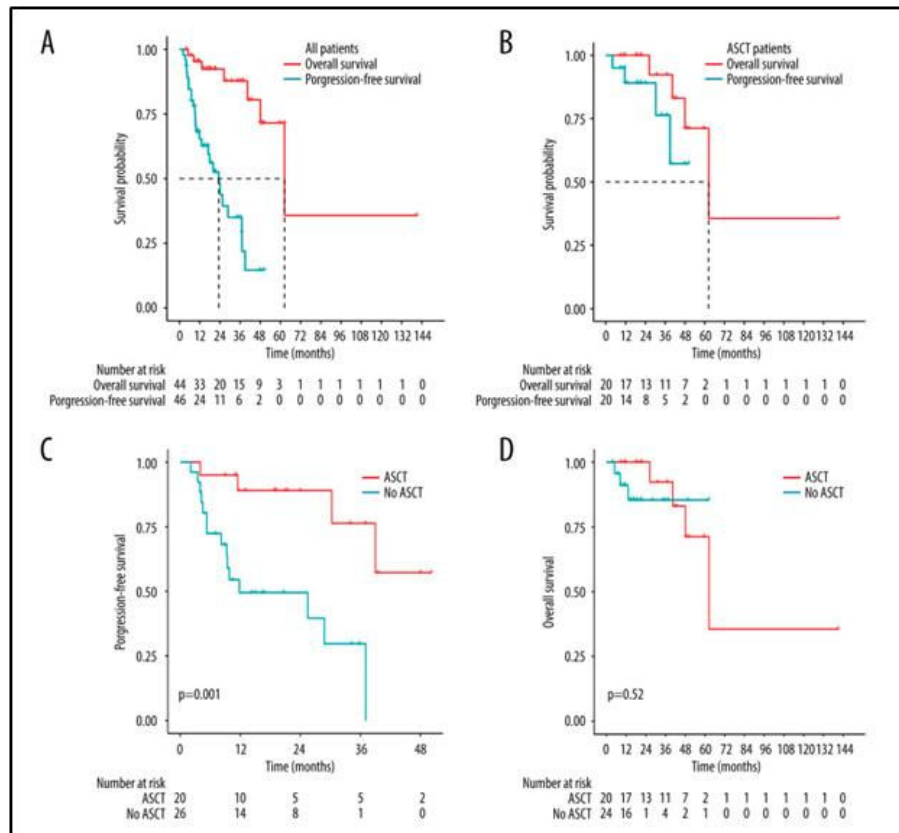


Figure 12: Kaplan-Meier analysis of survival in PCNSL patients [75].

A meta-analysis of over 43 studies regarding the use of ASCT to treat PCNSL reinforces the efficacy of this treatment method [82]. In these studies, ASCT was used as a consolidation treatment. Patients who received ASCT consolidation therapy averaged an overall 5-year survival rate of 70% [82]. This is nearly double the median overall 5-year survival rate of PCNSL patients, which is between 30.5% and 37.4% [6]. This is a substantial increase with the potential to be life-changing for patients with PCNSL.

Given the virtual four-fold event-free survival benefit of marrow transplantation for systemic lymphoma, it is not surprising that PCNSL has been treated with high-dose chemotherapy supported by autologous stem cell transplantation. In 20 patients with relapsing and refractory disease, 3-year probability of overall survival after intensive therapy was 60% [60]. Results from a clinical trial for newly diagnosed PCNSL, however, were disappointing: 14 patients who had achieved a complete response to high-dose methotrexate and cytarabine achieved an overall median event-free survival of 9.3 months after further stem-cell-supported high-dose chemotherapy [61].

Intensive Chemotherapy with Autologous Stem Cell Transplantation

Intensive Chemotherapy (ICT) with Autologous Stem Cell Transplantation (ASCT) is the standard treatment for chemosensitive relapsing systemic NHL. Because ICT is expected to improve BBB crossing, allowing cytotoxic agents to reach the brain at higher doses, this strategy has been evaluated for PCNSL. This procedure was first evaluated in refractory and recurrent cerebral and intraocular lymphoma with promising results in a single-institution pilot study [100]. The protocol consisted of an induction cytarabine-etoposide combination (the CYVE regimen) followed by high-dose chemotherapy with thiopeta, busulfan and cyclophosphamide (the TBC regimen). These results were recently confirmed in a multicenter phase II trial using the same regimen and including 43 patients [101]. Twenty-seven patients (62% by the intention-to-treat analysis) completed the full ICT-ASCT procedure, including 15 responsive and 12 nonresponsive patients to CYVE induction salvage chemotherapy. Twenty-six of these 27 patients achieved a CR with prolonged remission; the median PFS and OS times were 41 and 58 months, respectively. Interestingly, all but one patient in whom the disease was refractory to salvage chemotherapy achieved a CR after ICT-ASCT (Fig. 2). The intent-to-treat median PFS and OS times of the whole population of this trial were 11 and 18 months, respectively. Together, these results compare favorably with those reported for other salvage treatments, including second-line conventional chemotherapy regimens and RT alone [102-105]. The favorable impact of ICT-ASCT on survival, regardless of the chemosensitivity status before ICT, which contrasts with what is reported in relapsing systemic NHLs, suggests that ICT-ASCT might overcome resistance mediated by the BBB.

Conclusion

PCNSL is a subset of lymphoma, a broad category of cancers affecting the lymph system, originating in the structures of the central nervous system. The incidence rate is very low and the current prognosis upon diagnosis is poor, with a 5-year OS of between 30.5% and 37.4% [6]. Early diagnosis is imperative to the patient's outcome. The neurocognitive symptoms that many patients with PCNSL present can cause a later diagnosis due to how broad they are. Once diagnosed through imaging techniques or a biopsy, management plans for PCNSL typically include chemotherapy or whole-brain radiation, or a combination of both. In some cases, surgery is an option, but due to the way that PCNSL spreads in the brain, it is usually an ineffective treatment plan. The emergence of ASCT, a procedure in which the patient's stem cells are extracted and frozen while the patient receives high-dosage chemotherapy and then returned to the patient to reproduce and make new cells, has shown promising results in the treatment and management of PCNSL. ASCT consolidation therapy not only has been shown to extend OS rates, but also PFS rates.

One of the largest barriers in the United States to receiving adequate medical treatment when diagnosed with PCNSL is the cost. Cost is variable depending on patient insurance, at which facility the treatment is administered and other factors. One retrospective study analyzing the data of 1,267 patients with DLBCL concluded that the per-patient per month cost of managing the disease was \$11,890 [83]. Depending on the type and severity of lymphoma, Medicare may cover some chemotherapy treatment and service, but full coverage is rare. The financial burden of receiving a cancer diagnosis in the United States cannot be overstated; relocation cost, home health, physical therapy and temporary housing due to proximity to care are all other factors in the steep cost of medical treatment.

The progress of ASCT in the medical community is being halted by access and cost. Access to resources involved in stem cell

therapy are usually only available at large, teaching hospitals with an abundance of funding. Patients receiving treatment at smaller hospitals or medical centers are not given the option for stem cell therapy. Another major restricting factor against stem cell therapy is the high cost. From a sample of 249 patients, the average total cost of receiving ASCT was \$146,890, with conditioning therapy (43%) and mobilization/apheresis (23%) comprising the largest cost percentages (Fig. 13) [84].

	Mean (SD)	% of Total Costs
Total Costs from Mobilization through 100 Days Post-ASCT	\$146,890 (87,628)	--
Mobilization/Apheresis	\$38,803 (31,060)	26.5%
Conditioning	\$63,369 (70,836)	43.1%
Transplant	\$22,032 (30,960)	15.0%
Follow-up	\$22,686 (38,129)	15.4%

Figure 13: Total medical costs from mobilization through 100 days post-AST in 249 ASCT patients [84].

Modern medicine has progressed tremendously in the short 24 years since the onset of the 21st century. It is difficult to imagine how much progress will be made in the next 20 years. In the case of PCNSL, diagnostic techniques have improved and become more accurate, giving patients a faster diagnosis, which allows them to begin treatment sooner. A better and deeper understanding of human anatomy, oncogenesis and the cellular processes that lead to malignant T-cell proliferation have improved the efficacy and aggressiveness of anti-cancer drugs. Progress has been made in imaging techniques, which allow oncologists to direct radiation to certain parts of the brain without damaging the rest, or to surgically remove the tumor without the invasiveness of a craniotomy. The use of stem cells as a treatment method is an emerging field that has made significant progress during the 21st century. The scientific community's deeper understanding of the cellular mechanism of stem cells has allowed the utilization of the human body's natural defense system in fighting diseases, such as cancer.

With increased understanding of stem cell therapies and continued demonstration of their efficacy, it is expected that they will rise to the forefront of medicine during this century. The use of autologous stem cell transplantation in the treatment and management of PCNSL is undeniably effective. Stem cells are not only an emerging treatment methodology for PCNSL, but for other cancers and other disorders, such as multiple sclerosis, diabetes and muscular dystrophy. The next step in the progression forward with such a promising therapy for PCNSL is increased access for patients. Limitations of stem cell therapies include how expensive it is and that many hospitals and treatment centers do not offer it. Increasing access for all patients, regardless of where they are being treated, will allow stem cell therapies to help as many people as possible. Management of cost, including expansion of insurance policies to include stem cell therapies, will allow patients to receive the treatment they deserve. For a cancer like PCNSL, with such a poor prognosis, stem cell therapy may just be the key to an improvement in quality of life for thousands of patients.

Conflict of Interest

The authors have no conflict of interest to declare.

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