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Short Communication

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Managing Primary Central Nervous System Lymphoma in Immunocompetent Elderly Patients

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Abstract

There are many names for primary central nervous system lymphoma (PCNSL), such as reticulum cell sarcoma, diffuse histiocytic lymphoma, and microglioma. Initially, there was uncertainty about the origin of the cell, which is reflected in the proliferation of names. PCNSL is an extranodal, high-grade non-Hodgkin B-cell neoplasm that usually consists of large cells or immunoblasts. Brain tissue, cerebrospinal fluid, the spinal cord, or the eyes can produce it. The disease typically affects the CNS, but systemic manifestations may occur in 4 - 7% of patients with newly diagnosed PCNSL and 10% of patients with relapsed PCNSL. A high level of suspicion is required to diagnose this disease since the affected areas of the CNS differ from patient to patient. PCNSL accounts for 4 - 6% of extranodal lymphomas as well as 4% of newly diagnosed CNS tumors. The condition is more common in males than in females, and it can affect both immunocompromised and immunocompetent patients. Despite its lymphocyte origin, PCNSL should be considered a brain tumor because its therapeutic challenges are the same as those associated with other brain tumors. Because of the blood-brain barrier, drug delivery is impaired, and treatment modalities are limited by cerebral toxicity. Approximately 90% of PCNSLs are diffuse large B-cell lymphomas (DLBCL); the remaining 10% are T-cells, mantle cells, Burkitt lymphomas, or indolent B-cell lymphomas. Depending on the histologic subtype, 5-year survival rates range from 30% in DLBCL to 79% in marginal zone lymphoma. As mentioned, PCNSL is a rare lymphoma that occurs in the CNS and has a low chance of spreading to other parts of the body. It is often difficult for patients with PCNSL to achieve a positive outcome. Since PCNSL is uncommon, we know little about its optimal treatment. The standard treatment for PCNSL patients who can tolerate it is chemotherapy based on high-dose methotrexate (HD-MTX). Even though whole-brain radiotherapy (WBRT) can lead to remission in 90% of patients, it is often associated with poor long-term disease control when given alone and with delayed neurotoxicity when given after HD-MTX. PCNSL is prevalent in the elderly, and they account for the majority of cases. Patients older than 70 years have experienced a median survival rate of 6 - 7 months over the last 40 years. It is difficult to determine treatment tolerability or predict treatment-related toxicity based on chronological age alone, and the definition of elderly is not uniform. When patients are fit, they may be able to tolerate induction, consolidation, and even high-dose chemotherapy with autologous stem cell transplantation (ASCT), whereas others with multiple comorbidities may only be able to tolerate intermediate doses of methotrexate with decreased renal and bone marrow function. There may be a benefit to maintenance treatment in the latter case. A high-dose chemotherapy alternative such as whole-brain irradiation can also have detrimental cognitive side effects on the elderly. It remains unclear

what is the best treatment. To evaluate the risk of CNS and systemic toxicity associated with treatment, a comprehensive comorbidity and geriatric assessment is necessary. Optimal survival must be achieved while minimizing adverse effects. It would be helpful for future studies to assess how new agents can improve outcomes and maintain quality of life.

Keywords

Autologous stem cell transplantation, Chemotherapy, Clinical trials, Elderly, High-dose methotrexate, Primary central nervous system lymphoma, Survival, Toxicity

Introduction

Most PCNSLs occur in elderly patients. PCNSLs are highly aggressive non-Hodgkin lymphomas confined to the brain. According to a recent study, PCNSL incidence increased from 0.1 - 0.4 per 100,000 in the 1980s, correlating with an increase in the number of patients diagnosed at age ≥70 years [1]. Elderly patients aged 70 - 79 have the highest incidence, 4.32, whereas those in their third decade have the lowest, 0.08. Although PCNSL often responds to initial treatment, survival is inferior when compared to lymphomas located outside the CNS, and despite the fact that overall survival (OS) of all patients has doubled over the last 40 years (from 12.5 - 25 months), this survival benefit continues to be limited to patients younger than 70 years old. A devastating fact is that the median survival rate for the elderly population (aged 70 years or older) has remained at 6 - 7 months during this period [2, 3]. Treatment strategies for the elderly must anticipate factors that contribute to treatment failure in order to improve outcomes. To design and conduct future clinical trials successfully, it is crucial to have an understanding of aspects such as comorbidities and treatment-induced CNS and systemic toxicity. We discuss delays in diagnosis, therapeutic options, and factors related to treatment failure in PCNSL patients in this review [4].

In medical literature, the definition of elderly is not uniform. Over the years, systemic diffuse large B-cell lymphomas have shifted to older stages, above the common cutoff age of 60 [5]. Researchers who assessed prognostic factors for PCNSL have consistently pointed to older ages (over 50 - 60 years) as predictive of poorer outcomes, as well as a higher risk of neurotoxicity following chemoradiation [6]. As a consequence, 60 years of age is often used as a cutoff for defining PCNSL patients as elderly. Nevertheless, several studies have demonstrated that fit patients above the age of 60 can tolerate high-dose chemotherapy and even an intensive up-front treatment with a high overall response rate (range: 60 - 89%) and a high proportion of long-term survivors [7]. In spite of this, most clinical trials exclude patients older than 70 years from participation, and about one quarter of PCNSL patients who survive more than 3 months from diagnosis do not receive any chemotherapy. From 14 to 23, and from 61 - 70, 71 - 80, and >80 years, 44% of patients have not received chemotherapy [8]. It has been recognized that based treatment can improve survival for older individuals with adequate organ function, which has led to a decrease in the number of elderly patients not receiving chemotherapy, especially in academic research centers. PCNSL patients treated outside of clinical trials, however, have a poorer outcome, probably due to more unfavorable prognostic factors, according to a study comparing characteristics and outcomes in "real-life" settings with clinical trials [9, 10]. In clinical trials, expert management has been demonstrated to be effective for selected subgroups of elderly patients who are relatively fit and younger. Moreover, inconsistencies in the definition of "elderly" patients complicate the interpretation of many studies, especially because most published clinical trials do not provide treatment outcome stratification by age groups (e.g., outcome for 60 - 69 years old versus 70 - 79 years old) [11]. Most clinical trials and treating centers tend to consider PCNSL patients up to 70 years of age to be candidates for intensive upfront therapy while reserving less aggressive approaches for those over 70 years. It is important to take into account other intervening factors when tailoring a treatment approach to a patient. Age is not the only factor that should be considered [12].

Comorbidities prevalence in elderly patients

In spite of the fact that there is a great deal of heterogeneity among patients of the same age, age alone is not a reliable criterion for PCNSL treatment. In older patients, there are physiological deficits that affect pharmacokinetics and pharmacodynamics of therapy and may lead to toxicities (nephrotoxicity, hepatotoxicity, myelosuppression, and neurotoxicity) [13, 14]. OS and drug toxicity may be predicted by both functional status at diagnosis and premorbid status. The elderly PCNSL patient's performance status, comorbidities, functional reserve, and tolerance to drug toxicity should all be considered when selecting treatment [15].

In a guideline published by the American Society of Clinical Oncology, geriatric assessment tools are recommended for patients who receive chemotherapy who are 65 years old or older. It is important to use geriatric assessment tools in order to identify nononcological problems that may be treated. It is possible to predict chemotherapy toxicity and mortality using these tools [16]. It is possible that a decreased functional reserve will increase the susceptibility to chemotherapy-related complications in PCNSL, but many of these impairments can be reversible, so chemotherapy or HD-MTX should still be administered. PCNSL patients often experience acute deterioration of aspects of aging that are examined in geriatric assessments, such as motor function, cognitive decline, depression, and frequent falls. Symptoms of PCNSL are associated with CNS involvement, so regular geriatric assessments may be less applicable. As the neurocognitive and functional deterioration is often reversible with treatment, an adaptive new geriatric assessment might be needed for this malignancy. PCNSL patients older than 50 have not had geriatric assessment tools applied prospectively, but their utility for clinical use should be determined in the future. Caregiver collaboration is another essential aspect of implementing geriatric assessment-guided interventions [17].

The treatment options offered to older patients are generally less aggressive and less effective. An adverse outcome may be partly caused by suboptimal treatment due to age. It

is noteworthy that an elderly individual who is in good health may tolerate standard doses and schedules of chemotherapeutic medications. Chemotherapy risk assessment scale for high-age patients score assesses functional, mental, and nutritional status, lab values, and specific chemotherapy regimens [18]. Such scores may increase the proportion of elderly patients who are offered optimal treatment if they are routinely used (Figure 1).

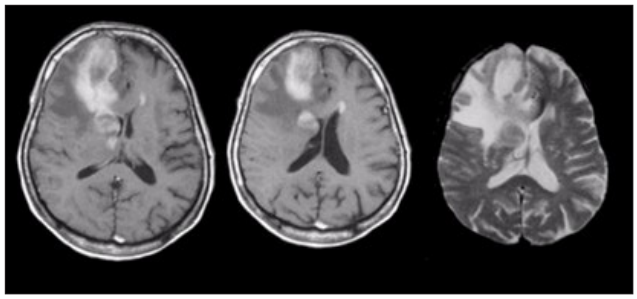

Figure 1: PCNSL axial scan of a 72 year old woman on chronic steroids and immunosuppressants.

There are two phases of treatment for PCNSL one is induction and the other is consolidation. Among all age groups, HD-MTX is the most important agent for generating a response [19]. Patients with reduced creatinine clearance and limited bone marrow reserve may require dose adjustments when using HD-MTX. 110 elderly PCNSL patients were treated with MTX (4 mg/m^2 per cycle) in a prospective study that found mild toxicity. In 18% of patients aged ≤60 and older, dose reduction was necessary to compensate for low glomerular filtration rates. It was statistically significant (p = 0.001) that these age groups differed. In all age groups, the incidence and severity of grade 3 - 4 toxicity were similar, with less than 10% experiencing it. MTX toxicity was also not associated with age differences, with 5 - 8% of patients discontinuing therapy. The treatment of PCNSL patients with HD-MTX seems safe regardless of age, when adherence to dose reduction is adapted to kidney function. Ineffectiveness of treatment may be affected by dose reduction [20-22].

Additionally, to frequent dose reductions of MTX, elderly PCNSL patients are highly susceptible to more toxic drugs, especially myelosuppressive agents, included in MTX-based multidrug protocols. Consolidation treatments are also based either on WBRT or on high-dose chemotherapy with or without ASCT. Therefore, induction chemotherapy is of utmost importance in elderly patients who cannot be treated with the current consolidation modalities [23].

Diagnosis and treatment of elderly patients with PCNSL

Diagnosis

There are no specific symptoms or signs associated with PCNSL. The most common presentation (in 50 - 70% of cases) includes personality changes and cognitive impairment, both of which are associated with mental deterioration in later life [24]. It is common to mistake focal neurological deficits for cerebrovascular disorder in half of patients. Therefore, a delay in diagnosis may contribute to poor functional status at the time of diagnosis. High cell density often indicates the diagnosis of contrast-enhanced magnetic resonance imaging lesion(s) with significant diffusion restriction. However, imaging alone cannot differentiate malignant tumors from inflammatory lesions, so a tissue diagnosis should be obtained immediately [25].

Treatment

Because of the low incidence of PCNSL, large, randomized studies are difficult to conduct, so there is still no standard treatment. Radiation and chemotherapy can be harmful to PCNSL. However, since the widespread realization of treatment-induced neurotoxicity in the past few decades, the treatment approach has shifted to chemotherapy [26]. In elderly patients, radiation-induced neurotoxicity causes progressive cognitive dysfunction, ataxia, and incontinence. After MTX-based chemotherapy, WBRT caused neurotoxicity in 19 - 83% of patients older than 60 years old. Additionally, it tends to be more severe and rapid as one ages. Chemotherapy-only regimens have been explored as a way of reducing neurotoxicity without impairing outcomes, but few studies have examined the effects of chemotherapy alone on elderly PCNSL patients. As a result, the optimal management of elderly patients is still a subject of debate [27-31]. A lack of prospectively collected data prevents treatment decisions in this patient population from being guided. It summarizes the outcomes of first-line chemotherapy in elderly patients with PCNSL. There were 18 studies involving elderly patients, and 9 studies which enrolled adult patients of all ages but included information about the elderly subgroup. Among 61 elderly lymphoma patients, 18 were treated as first-line with thiotepa-based chemotherapy with ASCT in one retrospective study. Four of the 16 studies dedicated to elderly patients, and one was designed as a randomized phase II study, were retrospective studies. There were six phase II studies that reported on elderly subgroups, and one phase III study that included elderly patients retrospectively. There were a variety of treatment regimens, from monotherapy to HD-MTX combination therapies. Additionally, rituximab has been added to chemotherapy regimens to improve PCNSL outcomes. However, it is uncertain whether rituximab improves PCNSL outcomes or increases immunosuppression, especially in the elderly and vulnerable [31-36].

According to all studies of the elderly, the complete response (CR) rate ranges from 30 to 69%, which is similar to the CR rate reported across all age groups in a 3-arm randomized multicenter study comparing 2-, 3-, and 4-drug combinations of intensive HD-MTX-based chemotherapy protocols (HD-MTX-cytarabine, HD-MTX-cytarabine plus rituximab, and HD-MTX-cytarabine plus thiotepa). Additionally, it appears that less toxic regimens like HD-MTX or MTX-procarbazine-vincristine (MPV) with or without cytarabine consolidation provide the same CR rate as HD-MTX. There were similar observations in a meta-analysis of 741 immunocompetent patients with newly diagnosed PCNSL aged 60 or older. Survival did not differ between patients treated with HD-MTX plus oral alkylating agents or with more intensive intravenous combinations [36-39].

The median progression-free survival (PFS) is 7.9 months, while the median OS is 36 months, which is signifi-

cantly longer than the relatively short PFS. The quality of life is likely to be negatively impacted by salvage therapy (such as WBRT), which prolongs survival beyond progression [32]. Despite published treatment series, median OS for the elderly remained in the range of 6 - 7 months in real-life conditions. PCNSL patients of any age can tolerate HD-MTX treatment (such as MPV) despite its relative safety, and even those aged 80 or more can receive HD-MTX. PCNSL patients are aging more rapidly, with 20% over 80 years old [40-44]. The elderly should not be denied treatment solely based on their age since those who respond to induction therapy gain substantial benefits in terms of performance status and survival, whereas those who do not benefit from induction therapy are unlikely to see improvement [45-47].

ASCT with high-dose chemotherapy

Refractory and relapsed PCNSL patients can benefit from this approach. Most conditioning regimens use thiotepa-based combinations. As a consolidating therapy, it is still being evaluated. Patients with a good performance status are usually offered this treatment due to the high risk and associated toxicity. Using thiotepa-based conditioning with ASCT (39% as first-line treatment) for 52 patients with PCNSL [48-50]. When conducted at experienced centers, this treatment is effective and safe in selected elderly patients.

Treatment-related toxicity

Chemotherapy-induced toxicity may be directly caused by the drug (e.g., nephrotoxicity, hepatotoxicity, and myelosuppression), and as such it is discovered relatively early. In contrast, neurotoxicity may occur during or after a successful treatment, so its identification is delayed. Various therapeutic regimens were associated with grade 3 - 4 treatment-related toxicity and grade 5 treatment-related death rates. With monotherapy, the risk of toxicity is substantially lower and there is no treatment-related death, while with multidrug treatment, grade 3 - 4 toxicity increases with the addition of myelosuppressive agents. There is a link between more intensive regimens and severe toxicity (81 - 89%). It is not surprising that the rate of treatment-related deaths increases as well (ranging from 2 - 14%). Chemotherapy alone, WBRT, or their combination appears to cause neurotoxicity more frequently in the elderly. In patients older than 60 years of age, signs and symptoms of HD-MTX-induced leukoencephalopathy are recognized more quickly when WBRT is given following MTX-based chemotherapy [26]. As radiation-induced neurotoxicity increases over time, those who survive for longer periods because of effective treatment tend to experience more pronounced effects. Conversely, subtle cognitive changes often caused by chemotherapy are likely underestimated due to the need for routine neurocognitive testing.

In elderly patients who are unable to tolerate consolidation therapy, maintenance treatment might be a viable alternative. A number of chemotherapeutics and targeted agents may have a role in maintaining PCNSL (e.g., procarbazine, temozolomide, lenalidomide, and ibrutinib), but their effectiveness must be studied prospectively. The use of metronomic chemotherapy or targeted therapy for maintenance therapy has the potential to delay relapses and maintain the dormancy of tumors. In spite of this, all maintenance regimens in PCNSL are highly empirical in terms of dose and schedule due to the investigational nature of these approaches [51]. PCNSL maintenance treatment is currently experimental because no randomized clinical trial has proven its effectiveness. It is planned or ongoing to evaluate maintenance therapy for elderly patients in several studies: Ibrutinib phase II, temozolomide maintenance versus observation phase III study, and lenalidomide and procarbazine phase II study, which is not yet recruiting participants.

Conclusions

Despite this infrequent disease's rarity, the optimal treatment for PCNSL remains a mystery, especially regarding the management of elderly patients. Numerous challenges face us. Uncertainty about the definition of "elderly" contributes to uncertainty regarding treatment tolerability and treatment-related toxicity. Current and historical definitions of the term "elderly" are not reliable. The functional status and comorbidities of patients aged 60 or older vary greatly. HD-MTX is well tolerated by many of them, and MTX remains the most important element of all effective treatment regimens. The treatment approaches used in the elderly differ from those used in the young. The goal of treatment in younger patients is curative, and the highly toxic and intensive treatments necessary to reach this goal are unacceptable to the vast majority of elderly patients. Some elderly patients may still be able to tolerate it, though.

Upon mapping the published literature, it was revealed that sample size, treatment protocols, and toxicity data were heterogeneous. Evidence from the existing literature is limited and heterogeneous, which reduces its usefulness for informing clinical treatment choices. The incidence of PNCSL in the elderly is growing, as is the incidence of other hematological malignancies. Patients with elderly PCNSL are more resource-intensive, and their treatment is more likely to be complicated. Diagnosis and treatment of PCNSL pose significant challenges to clinicians. Additionally, there is little evidence specifically available for this age group. For this reason, geriatric assessments are becoming increasingly recognized as valuable and reproducible tools in diagnosing and treating geriatric patients. It is important to consider pre-morbid PS when making decisions about treatment for elderly patients, since the disease will have a greater impact on their PS. At least three-quarters of the elderly population can benefit from HD-MTX-based therapy. Despite HDT-ASCT remaining an option for a minority, it should be considered in 'fit' patients since outcomes compare to those of younger individuals.

PCNSL patients with dismal prognoses are most likely to have unmet needs in the unfit to HD-MTX and the relapsed populations. In addition to age-adapted therapies, combinations of novel agents with moderate toxicity profiles should be tested in well-designed trials. As a result, future studies should focus on stratifying the elderly with the goal of achieving and maintaining remission, improving tolerability, minimizing treatment-induced toxicity, and preserving function and quality of life. By accomplishing these objectives, a more individualized approach will be used to prolong PFS, OS, and preserve

function while minimizing toxicity. A multidisciplinary team of researchers will hopefully assess the potential of new agents for improving outcomes and maintaining quality of life in future studies.

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Conflict of Interest

None.

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