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PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Summary

Primary central nervous system lymphoma (PCNSL) is a distinct form of aggressive non-Hodgkin's lymphoma (NHL) confined to the central nervous system. PCNSL typically affects older population. Individuals with HIV infection are especially at risk of PCNSL development and their outcome is extremely poor. Due to the presence of the blood-brain barrier, PCNSL is treated differently from other extranodal NHLs. The mainstay of treatment is the high-dose methotrexate (MTX). Despite the treatment, local relapses are frequent and almost inevitably fatal. Intensification of treatment is possible in patients younger than 60 years. Radiotherapy is effective but complicated with significant delayed neurotoxicity, especially in the elderly. There are no curative treatment options in older patients who represent the majority of patients. Novel less toxic agents have modest activity. Prospective multicentric trials are needed to establish the optimal treatment for PCNSL.

KEYWORDS: *central nervous system neoplasms; lymphoma, non-Hodgkin's – pathology, drug therapy, radiotherapy; antineoplastic agents*

PRIMARNI LIMFOMI SREDIŠNJEG ŽIVČANOG SUSTAVA

Sažetak

Primarni limfom središnjeg živčanog sustava (PLSZŠ) je poseban oblik agresivnog ne-Hodgkinovog limfoma (NHL) lokaliziran u središnjem živčanom sustavu. PLSZŠ tipično zahvaća stariju populaciju. Za razvoj PLSZŠ-a posebno su rizične osobe s HIV infekcijom čija je prognoza ekstremno loša. Zbog krvno-moždane barijere, PLSZŠ se liječi drugačije od ostalih ekstranodalnih NHL. Temelj liječenja su visoke doze metotreksata. Unatoč liječenju, lokalni relapsi su česti i gotovo uvijek fatalni. Radioterapija je učinkovita, ali kompliciran značajnom kasnom neurotoksičnosti, posebno u starijih. U starijih bolesnika, koji čine većinu, nema terapijskih opcija koje bi dovele do izlječenja. Noviji, manje toksični lijekovi, skromnog su djelovanja. Potrebne su prospektivne multicentrične studije kako bi se definiralo optimalno liječenje PLSZŠ-a.

KLJUČNE RIJEČI: *tumori središnjeg živčanog sustava; ne-Hodgkinov limfom – patologija, farmakoterapija, zračenje; protutumorski lijekovi*

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) represents a distinct form of extranodal non-Hodgkin's lymphoma (NHL) confined to the central nervous system without system involvement. The most frequent localization of PCNSL is the brain. However, PCNSL may also involve leptomeninges, spinal cord and the eye. The presence of the blood-brain barrier (BBB) requires specific treatment with antineoplastic agents that may achieve cytotoxic concentrations within the central nervous system (CNS). Therefore, management of PCNSL is different in comparison to other extranodal NHLs. This review summarizes new insights in the pathogenesis, diagnosis and treatment of PCNSL.

EPIDEMIOLOGY

Primary central nervous system lymphoma comprises about 2.7-5% of primary CNS neoplasms and less than 1% of extranodal lymhomas (1). After a progressive increase in the last three decades, recent epidemiologic data suggest stabilization or slight declining in the incidence of PCNSL (2). This trend is mainly observed particularly in younger males and patients with HIV (human immunodeficiency virus) infection, while the incidence remains high among older immunocompetent patients. The reasons for such variations are unknown. The incidence of PCNSL in the United States is 4-5 per 1,000 person-years among patients with AIDS (acquired immunodeficiency syndrome) and 0.3% per 100,000 person-years in immunocompetent patients (3, 4). PCNSL typically affects an older population with a median age in 60s and a male to female ratio 1.5:1 (5).

PATHOLOGY

In contrast to patients with HIV infection where Epstein-Barr virus and c-myc proto-oncogene translocation induce the proliferation, pathogenesis of PCNSL in immunocompetent patients is poorly understood (6). Athough CD4+ T cells are normally present in the CNS and B-cells are very rare, up to 90% of PCNSL are diffuse large B-cell lymphoma (DLBCL). The rest are low-grade B-cell lymphoma or T-cell lymphoma. T-cell PCNSL is more frequently associated with meningeal involvement (7). A recent study compared gene-expression of PCNSL and non-CNS DLBCL and revealed „true“ CNS signature different from peripheral DLBCL (8). The others failed to identify distinct genotype of PCNSL (9). It is likely that PCNSL has features of the activated B-cell-like phenotype that may in part explain its poor prognosis (9, 10). The rearrangements of bcl-6 may be involved in the pathogenesis and proliferation of PCNSL, and may positively (11) or negatively (12) affect the outcome.

DIAGNOSIS AND STAGING

Clinical presentation

PCNSL is by definition located in the CNS and therefore its clinical presentation is consistent with that of intracranial mass while systemic symptoms of lymphoma are rare. Depending of the localization of lymphoma, patients present with neurological symptoms: motor and sensory focal deficits, headache and other signs of intracranial hypertension such as nausea, vomiting, papilloedema. Personality changes due to the frontal lobe involvment are also frequent. Generalized seizures, extrapyramidal symptoms and signs of impairment of the brain stem and cerebellum are less frequent (13). Patients with intraocular lymphoma develop ocular symptoms similar to monolateral uveitis that eventually becomes resistant to corticosteroids and other ophthalmologic treatment (14). After prolonged latency, a true cerebral lymphoma will develop in the majority of cases. In more than half immunocompentent patients, PCNSL presents with a single, deeply localized lesion, usually in the periventricular regions infiltrating the corpus callosum and the basal ganglia (5). Only 10-15% of the lesions are located in the subtentorial fossa. In 5-20% of cases, more often in multifocal forms, PCNSL begins in an intraocular localization. PCNSL tends to infiltrate subependimal tissues and disseminate to meninges through the cerebrospinal fluid (15). Meningeal involvement was demonstrated in 100% cases on autopsy (16) while isolated leptomeningeal localization occurs in less than 10% of cases (17). However, lymphoma cells in the cerebrospinal fluid are detected only in about 20% of cases (5).

Diagnostic procedures

In patients with intracranial tumor and suspected PCNSL, magnetic resonance (MR) with gadolinium contrast should be performed. If there is a contraindication for such examination, contrast-enhanced computerized tomography scans (CT) may be an alternative. Although there is no specific pathognomonic radiological patterns of PCNSL, CT and MR images may suggest the lymphomatous nature of a cerebral mass. The use of contrast media produces an intense homogenous enhancement of the image. Only in 12% of patients with PCNSL the enhancement is not observed (5). Alternative diagnostic tools include proton magnetic resonance spectroscopy that is useful in diagnostic suspicion, response assessment and early detection of relapse (18). FDG-PET is highly sensitive and it may be suitable for therapeutic moni-

toring (19). Angiography is rarely used in diagnosis because PCNSLs have an intense proliferation of small caliber vessels which cannot be revealed by angiography.

Histopathological examination of tissue obtained by brain biopsy is needed to establish the diagnosis of PCNSL. It is generally recommended to avoid administration of corticosteroids before stereotaxic biopsy because it may induce temporary regression of the lymphoma and prevent histopathological diagnosis (20). In contrast, a recently published retrospective study did not confirm such approach (21).

When the diagnosis of PCNSL is confirmed, it is necessary to perform evaluation and staging as recommended by the International PCNSL Collaborative Group (22). The evaluation should include physical examination, blood counts and biochemical profile, a contrast-enhanced brain magnetic resonance imaging (MRI) study, a complete ophthalmology evaluation, cytological evaluation and flow cytometry of the cerebrospinal fluid, if a lumbar puncture can be safely performed. In addition, CT scans of chest, abdomen and pelvis and a bone marrow biopsy with aspirate are needed to exclude CNS affection by systemic lymphoma. Recent data suggest that F-18 FDG PET-CT may be used for detection and monitoring of systemic spread of the disease (23). Finally, HIV infection should be excluded.

PROGNOSIS AND PROGNOSTIC FACTORS

PCNSLs are characterized by a rapid growth limited to the CNS leading to fatal outcome in less than 3 months if untreated. The 5-year overall survival rate in patients with PCNSL treated with chemotherapy +/- radiotherapy is 25-40% (24-26). Surgery does not significantly improve survival and in many cases it can worsen the quality of life (20, 28). The outcome of patients with HIV and PCNSL is extremely poor with a median survival of 2 months (4).

An important issue in the treatment of PCNSL is the development of prognostic score such as the International Prognostic Index (IPI) used for systemic NHL (28). Since IPI is not applicable in PCNSL, efforts have been made to develop a PCNSL prognostic score (29). Recently, the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score was developed, identifying three distinct prognostic classes: class 1 (patients < 50 years), class 2 (patients ≥ 50 years; Karnofsky performance score [KPS] ≥ 70) and class 3 (patients ≥ 50 years; KPS < 70) (30).

TREATMENT

The presence of the blood-brain barrier requires specific treatment with antineoplastic agents that may achieve cytotoxic concentrations CNS such as methotrexate (MTX). Therefore, management of PCNSL is somewhat different in comparison to other extranodal NHLs. However, the general principle of treatment of aggressive lymphomas by chemotherapy and subsequent radiotherapy is adopted.

Treatment of newly diagnosed patients

Standard treatment of PCNSL includes high-dose methotrexate (3g/m^2 or more) followed by radiotherapy. This treatment is associated with a response rate of 80-90%, a 2-year survival of 60-70%, and a 5-year survival of 25-40% (24, 25, 31). Addition of other drugs did not consistently improve outcome when compared to standard high-dose MTX monochemotherapy (32-34). The whole brain radiotherapy (WBRT) is administered with the dose of 30-36 Gy followed by a tumor–bed boost of 10-15 Gy in patients with residual disease, while WBRT with 30Gy optionally followed by tumor-bed boost to reach 36 Gy is suitable for those in complete remission (5). However, necessity of additional radiotherapy in those who achieved remission is controversial because of treatment-related neurotoxicity. A direct relationship was observed between age and severe neurotoxicity (35). Its cumulative incidence is increased over the years after the treatment to 25-35% at 5 years (36). Such delayed neurotoxicity may be a result of vascular injury at the site of lymphoma and leads to recurrence of original symptoms without evidence of lymphoma and fatal outcome in one-third of the patients (37). To minimize neurotoxicity, several studies were performed where radiotherapy was delayed in complete responders until relapse (38-43). Two-year overall survival was 61-63% for high-dose MTX (38, 40-42) and 65-78% with MTX containing polychemotherapy (43). It is likely that radiotherapy in older patients following high-

dose MTX treatment does not improve survival (44). In younger patients, this strategy is still under investigation and prospective randomized studies are needed to validate and possibly improve this approach (20).

Administration of intrathecal therapy is controversial. It is limited by the lack of prospective assessment of its survival effect, the increased risk of severe neurotoxicity in patients treated with high-dose MTX and WBRT, and the impossibility of performing a lumbar puncture in up to one-third of the patients (45). However, some authors suggest intrathecal chemotherapy for patients with positive cytology of the cerebrospinal fluid at diagnosis due to a higher rate of meningeal relapses in those patients (31).

Treatment in the elderly

In elderly patients with a good performance status, chemotherapy alone is a suitable option. When radiotherapy was administered after high-dose MTX a high rate of severe treatment-related neurotoxicity was reported and therefore it should be avoided in these patients (5, 20, 24). However, radiotherapy as monotherapy is the conventional treatment in elderly patients who cannot receive high-dose MTX (e.g. renal failure) (5, 46). New agents such as temozolomide are still under investigation in this group of patients. Nonetheless, for patients aged more than 60 years, no curative regimen with acceptable toxicity has yet been established and their prognosis is dismal. Our recently published retrospective study also supports this notion (46).

Treatment of histologically unproved PCNSL

In some patients the diagnosis of PCNSL is based only on neuroimaging appearance because for various reasons biopsy cannot be performed. Regression of such lesions after corticosteroid treatment supports the diagnosis of PCNSL. However, only half of patients with such "vanishing" tumors have PCNSL (47). Nevertheless, even these patients may benefit from high-dose MTX followed by radiotherapy if there are suitable (48).

Salvage treatment

About half patients who achieved remission after the standard treatment relapse and generally succumb to their disease (24-26). There is no standard approach for such patients. Generally, those who relapse after chemoradiotherapy require second-line chemotherapy and radiotherapy if possible. Median survival for responders is about a year (49). The most frequently used agents are cytarabine, procarbazine, vincristine, cisplatin, temozolomide or re-induction with high-dose MTX (50). In those who were initially treated without radiotherapy, WBRT may yield a median survival of 11-19 months (51).

New drugs and treatment options

High-dose chemotherapy with autologous peripheral blood stem cell transplantation (PBSCT) is an interesting therapeutic option in patients younger than 60 or 65 years with overall survival over 60% at four years (52, 53). This strategy is effective even in relapsed/refractory patients (54). Since the median age of PCNSL patients is above 60 years, PBSCT is feasible only in a subset of patients. Although intensive chemotherapy protocols followed by PBSCT have shown promising results, the numbers of patients included in the studies are still insufficient to make conclusions at this time point.

Another interesting approach in the treatment is a reversible blood-brain barrier disruption (BBBD) by intra-arterial infusion of hypertonic manitol followed by intra-arterial chemotherapy. Initial results are encouraging with acceptable toxicity (55). However, this strategy is invasive and requires adequate expertise.

Temozolomide is an oral alkylating agent that permeates the BBB. It is well tolerated and may used in older patients alone (56) or in combination with MTX (57) or rituximab (58).

Rituximab is a monoclonal anti-CD20 antibody that was recently established as a new standard treatment of B-cell NHL in addition to chemotherapy. Unfortunately, due to insufficient permeability through BBB, results of intravenously administered rituximab in PCNSL are poor (5). Interestingly, patients with leptomeningeal lymphoma treated with intraventricular rituximab had good, but transient response (59).

Topotecan, intravenous topoisomerase I inhibitor, has been shown to be active in relapsed patients with PCNSL (60). However, progression is frequent and early with significant myelotoxicity.

CONCLUSION

Treatment of patients with PCNSL is still undefined and unsatisfactory especially in the elderly. Younger patients with a good performance status may be offered different treatment modalities based on high-dose MTX with our without radiotherapy. These patients can be cured in about 60% of cases. In contrast, older patients, who comprise the majority of this patient population, have dismal prognosis due to excessive toxicity that compromises intensive chemoradiotherapy. Novel agents are needed to improve the prognosis of these patients.

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