Primary Central Nervous System Lymphoma: Three Cases and Review of the Literature

PRİMER SANTRAL SİNİR SİSTEMİ LENFOMASI: ÜÇ OLGU VE LİTERATÜRÜN GÖZDEN GEÇİRİLMESİ

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Summary

Primary central nervous system lymphoma (PCNSL) is defined as lymphoma limited to the cranial-spinal axis without systemic disease. The rising incidence of this tumor has made improved treatment a priority. We followed three cases with PCNSL (AIDS non-related) by radiotherapy (40-46 Gray). Additionally two cases received chemotherapy (CHOP). Patients died 10, 14, and 16 months after the diagnosis. These three cases were reported and the treatment of PCNSL was discussed here by the recent literature.

Key Words: Radiotherapy, Chemotherapy, Primary central nervous system lymphoma

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Özet

Primer santral sinir sistemi lenfoması (PSSSL) sistemik tutulum olmayan ve kranial-spinal bölgede sınırlı kalan lenfomayı belirtir. Bu tümörün artan görülme sıklığı tedavisini öncelikli hale getirmiştir. Primer santral sinir sistemi lenfoma tanısı ile takip ettiğimiz (AIDS ile ilişkili olmayan) üç olguya radyoterapi uyguladık. İki olguya ilave olarak kemoterapi verdik (CHOP). Olgular tanıdan sonra 10, 14 ve 16. aylarda öldüler. Burada PSSSL'lı üç olgu rapor edildi ve PSSSL tedavisi ile ilgili literature tartışıldı.

Anahtar Kelimeler: Radyoterapi, Kemoterapi, Primer merkezi sinir sistemi lenfoması

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Primary central nervous system lymphoma (PCNSL) is a non-Hodgkin's lymphoma, usually of B cell type, arising within and confined to the central nervous system (CNS) (1). This tumor primarily arises in brain tissue as a single or multi-focal lesion. However, the rest of the CNS can be involved as well, including the cerebrospinal fluid (CSF), the orbit, and rarely the spinal cord parenchyma. This disease occurs with marked increased frequency among immunocompromised patients; however, its incidence has risen dramatically in the past 20 to 30 years in the immunocompetent population. There is no obvious explanation for this change. PCNSL is frequently a disease of elderly patients with a median age at onset of 60 years, which can make therapy particularly challenging.

Chemotherapy, particularly high dose methotrexate, is recognized as the initial treatment for this disease. The addition of high dose methotrexate-based regimens to cranial irradiation has produced a substantial improvement over the 12- to 18- month median survival achieved with whole-brain radiotherapy (WBRT) alone. While cranial irradiation often ameliorated symptoms and caused disease regression, tumor usually recurred and 5-year survival was less than 5% (2). Combined modality treatment increased the median survival to about 40 months, but it often caused delayed neurotoxicity. Chemotherapy alone is being explored as an alternative treatment, not only to improve disease control, but also to minimize some of the neurologic sequelae that are observed when these agents are combined with cranial irradiation. A single randomized phase III trial has been conducted in this disease, but it was terminated before completion because of poor patient accrual. However, a substantial body of experience has been collected on the basis of serial phase II studies that have elucidated some of the critical therapeutic challenges of PCNSL; which these will be summarized here, by mentioning three cases whom we treated with WBRT in GATA from 1998 to 1999. Three cases were reported and the treatment of PCNSL was discussed here by the recent literature.

Cases

Case 1

A 53-year old female patient was operated with the clinical diagnosis of brain metastases and was registered after the histologic examination revealed a high-grade diffuse large cell primary brain lymphoma in 1999 (Figure 1). She was HIV negative and performance status was ECOG 2. After this excisional biopsy WBRT was applied

with Co-60 therapy machine, by giving 2 Gy daily doses to a total of 46 Gy. Neurological symptoms of the patient were dissipated after the completion of radiotherapy. Three cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy was applied to patient. No serious toxicities were seen related to WBRT or chemotherapy. Unfortunately the patient died due to infection ten months after the diagnosis.

Case 2

A 20-year old male patient who was diagnosed as primary brain lymphoma radiologically (Figure 2) was registered in our department in 1998. He was HIV (-) and performance status was ECOG 1. Total of 40 Gy was given to the whole brain with 2 Gy daily doses by Co-60 therapy machine. After completion of radiotherapy neurological symptoms were dissolved and partial response were seen in the cranial lesion. The patient refused chemotherapy. Disease progressed four months after WBRT. He died 14 months after the diagnosis.

Case 3

A 46-year old male patient with primary brain lymphoma confirmed with excisional biopsy (high grade diffuse large cell) was registered in our department (Figure 3). He was HIV negative and performance status was ECOG 2. Forty six Grays WBRT was applied with Co-60 therapy machine. Neurological symptoms lasted one more month after radiotherapy but completely dissolved. Three cycles of CHOP chemotherapy was given and no serious toxicity was observed. The patient died due to primary disease progression 16 months after the diagnosis.

Discussion

Three multicentral trials have now been completed in patients with PCNSL, to examine the standard chemotherapeutic regimen of CHOP in the treatment of systemic non-Hodgkin's lymphoma. Two studies were similar in their design and consisted of giving approximately three cycles of CHOP before the administration of WBRT (3, 4). The median survivals were 16 months and 9.5 months in these studies, identical to cranial irradiation alone. Significant chemotherapeutic toxicity was observed in at least one trial. The third trial was a phase III study in which the patients were randomized to WBRT alone or radiation therapy (XRT) followed by six cycles of CHOP (5). Survival in both groups were identical.

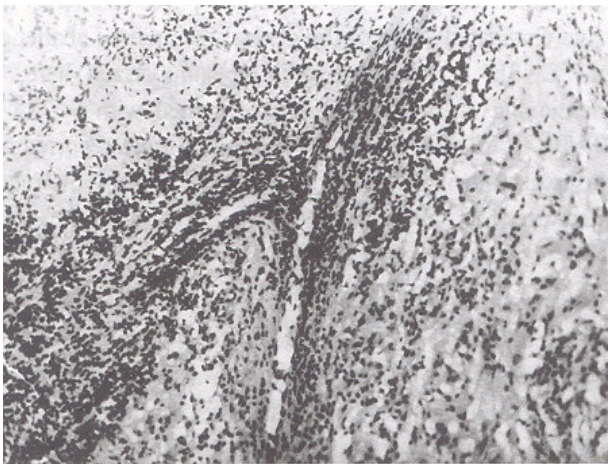

Figure 1. Diffuse atypical lymphocyte infiltration around vascular area in glial tissue (HEx100).

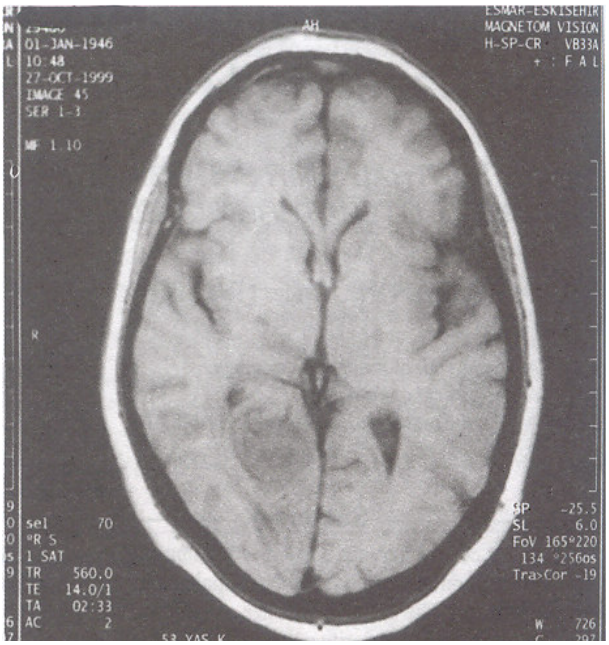

Figure 2. MR of the 20 year old patient.

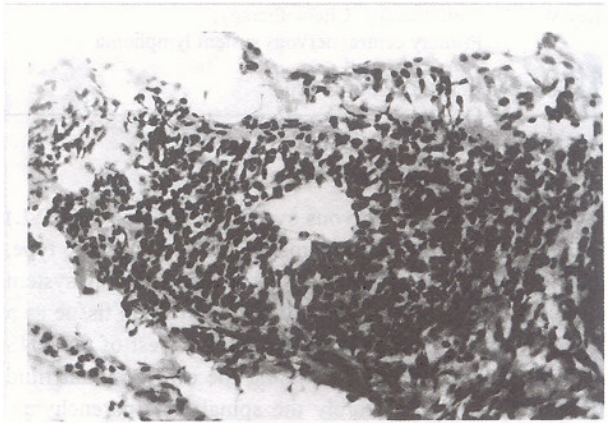

Figure 3. Atypical lymphocytes that were caused concentric enlargement through the vessel wall are infiltrating vessel wall under the endothelium (HEx400).

Despite the absence of an impact on survival, many patients had an initial response to CHOP, with shrinkage of the lesions seen on magnetic resonance imaging (MRI) and computed tomographic (CT) scans. However, before the planned regimen of CHOP could be completed, many developed tumor progression in other areas of the brain that initially did not appear to be involved on MRI. A number of patients developed leptomeningeal spread as well. This experience demonstrates the importance of the blood-brain barrier in effective treatment for PCNSL. Areas of bulky disease as seen on MRI or CT scans have a grossly impaired blood-brain barrier; this is why the lesions are evident after the administration of contrast. Cyclophosphamide, doxorubicin, and vincristine are incapable of penetrating an intact blood-brain barrier but can reach areas of bulky disease when the barrier is disrupted. These agents could penetrate into the initial lesions and kill the lymphoma cells that they could reach; tumor shrinkage was then appreciated on neuro-imaging. However, PCNSL is a widely and diffusely infiltrative disease. There are many areas of brain which cannot be observed on MRI scans. Consequently, these areas have tumor that exists behind an intact blood-brain barrier, which these chemotherapeutic agents are unable to penetrate. In these areas, tumor can grow and develop into a mass that is subsequently appreciated on MRI. When CHOP was used before XRT, tumor progression most commonly occurred between the second and the third cycles of CHOP. These three studies clearly define the importance of using agents that are effective against non-Hodgkin's lymphoma and can penetrate through the blood-brain barrier. It is also clear from these studies that CHOP and comparable regimens have no role in the treatment of PCNSL (6).

High-dose methotrexate has emerged as the most important drug for the treatment of PCNSL. Two large retrospective studies have convincingly demonstrated that methotrexate is the single most active agent for PCNSL (7, 8). PCNSL patients at Memorial Sloan-Kettering Cancer Center were treated with systemic, 1 g/m^2, and intra-Ommaya methotrexate followed by XRT and high-dose cytarabine. A recent analysis of this original cohort confirms, a cause-specific median survival of 42 months, with a 22% 5-year survival; this is a significant improvement over XRT alone (9). Age greater than 60 years was a poor prognostic factor for response and survival. Others have confirmed that age and performance status are important prognostic factors, regardless of treatment type (2-4, 7, 8, 10). The patients reported here were at 20, 46 and 53 ages and their performance status were between ECOG 1-2. All of our patients were HIV negative and their survival after the diagnosis were 10, 14, and 16 months.

Effective treatment for systemic non-Hodgkin's lymphoma requires combination chemotherapy. Consequently, new regimens for PCNSL are combining multiple agents that can penetrate the blood-brain barrier. In a study, five cycles of high-dose methotrexate (3.5 g/m^2), vincristine, and procarbazine before cranial XRT were given to patients (10). Vincristine cannot pass an intact blood-brain barrier, but both highdose methotrexate and procarbazine can. Despite a relatively old population with a median age of 65, the median survival was 60 months. In an intergroup trial with Radiation Therapy Oncology Group and Southwest Oncology group, similar regimen with a lower dose of methotrexate (2.5 g/m^2) was used and a median survival of 30 months was achieved (11). This is the first multicentral trial to demonstrate an improved outcome over XRT alone.

Although most studies have focused on pre-radiation chemotherapy, the question of adjoint chemotherapy in patients who have completed WBRT and not received prior chemotherapy often arises. It is unknown whether adjoint chemotherapy is equivalent to pre-radiation drug, but preliminary data suggest it is superior to XRT alone. Chamberlain and Levin[13] applied procarbazine, lomustine, and vincristine (PVC) followed by WBRT, and achieved a 41-month median survival in 16 patients. Therefore, four to six cycles of PVC after WBRT has been completed are reasonable in patients who have received no prior chemotherapy.

We have not observed any tretment-related neurotoxicity in our cases. The prolonged survival seen with combined modality regimens has led to greater appreciation of treatment-induced late neurologic toxicity. Liang et al (14) noted a high incidence of late toxicity in survivors treated with CHOP and intrathecal methotrexate plus WBRT. Long-term follow-up of their original cohort of patients reveals that almost 100% of patients over the age of 60 at diagnosis suffered significant late sequelae within 4 years of treatment, whereas only 30% of younger patients had similar problems after a 7.5-year latency (9). McAllister et al reported no delayed neurotoxicity with intra-arterial therapy (15). However, the procedure is associated with acute toxicities and requires a skilled team to administer. Furthermore, their experimental work clearly demonstrated damage of normal brain structures when chemotherapy follows blood-brain barrier disruption (16).

These issues led to an exploration of systemic chemotherapy alone as effective treatment for PCNSL. Glass et al. (17) reported long-term survival in a few patients treated with high-dose methotrexate alone. Some investigators have treated elderly patients with a multiagent chemotherapeutic regimen (10, 18, 19). The response rate was greater than 90% with most patients having a complete response. Abrey et al found the median survival for

patients over the age of 60 as 33 months, which was identical to the 32-month median survival of older patients receiving identical chemotherapy plus XRT (10). This approach is clearly superior than the median survival of 7.1 months for XRT alone in a comparable age group (2). Importantly, none of the patients treated with chemotherapy alone, developed neurotoxicity. Similar results were observed in 14 patients treated by Sandor et al (20) with a high-dose methotrexate-based regimen without XRT. These preliminary data suggest that good disease control can be achieved with chemotherapy alone.

However, therapeutic advances are still essential. Although older patients had the same survival whether XRT followed chemotherapy or not, their causes of death were different. Those who received XRT died of neurotoxicity, whereas those treated with chemotherapy alone died of tumor progression. Clearly, XRT contributes to tumor control, but with serious toxicities when administered as 45 Gy to the whole brain. Further studies should be performed to optimize the radiotherapy dose.

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