

# Delayed Neurotoxicity in Primary Central Nervous System Lymphoma

Antonio M. P. Omuro, MD; Leah S. Ben-Porat, MS; Katherine S. Panageas, DrPH; Amy K. Kim, BA; Denise D. Correa, PhD; Joachim Yahalom, MD; Lisa M. DeAngelis, MD; Lauren E. Abrey, MD

**Background:** Treatment for primary central nervous system lymphoma (PCNSL) with chemotherapy and radiotherapy has resulted in improved survival, but some patients develop neurologic deterioration that represents a treatment-related toxic effect. This delayed neurotoxicity has been poorly defined in the literature, and the underlying mechanisms are unknown.

**Objective:** To describe the clinical findings, time course, and pathophysiologic mechanisms associated with neurotoxicity in an attempt to generate hypotheses for future studies that address prevention and treatment of this complication of successful PCNSL therapy.

**Design:** Retrospective review.

**Setting:** Department of Neurology, Memorial Sloan-Kettering Cancer Center.

**Patients:** One hundred eighty-five patients treated for PCNSL, including 43 who developed neurotoxicity.

**Main Outcome Measures:** Potential risk factors, clinical course, and neuropsychological, neuroimaging, and histologic findings.

**Results:** The 5-year cumulative incidence of neurotoxicity was 24%; this incidence increases over time. Neurotoxicity presented as a rapidly progressive subcortical dementia characterized by psychomotor slowing, executive and memory dysfunction, behavioral changes, gait ataxia, and incontinence. Imaging findings revealed diffuse white matter disease and cortical-subcortical atrophy. Available autopsy data showed white matter damage with gliosis, thickening of small vessels, and demyelination. Statistical analyses were performed, accounting for death as a competing risk. Older age ( $P=.01$ ), mental status changes at diagnosis ( $P=.04$ ), female sex ( $P=.05$ ), and radiotherapy ( $P<.001$ ) predicted neurotoxicity on univariate analysis, but only radiotherapy remained significant in the multivariate setting.

**Conclusion:** These findings suggest that the core pathophysiologic mechanism is the interruption of frontal-subcortical circuits mediated by radiation damage, possibly caused by progressive microvascular alterations, loss of oligodendrocyte progenitors, or oxidative stress.

*Arch Neurol.* 2005;62:1595-1600

#### Author Affiliations:

Departments of Neurology (Drs Omuro, Correa, DeAngelis, and Abrey and Ms Kim), Epidemiology and Biostatistics (Ms Ben-Porat and Dr Panageas), and Radiation Oncology (Dr Yahalom), Memorial Sloan-Kettering Cancer Center, New York, NY.

**P** RIMARY CENTRAL NERVOUS system lymphoma (PCNSL) is a non-Hodgkin lymphoma that arises within the brain, spinal cord, or eyes in the absence of systemic disease. Treatment often includes whole-brain radiotherapy and chemotherapy, which achieve a median survival of 30 to 60 months and occasional cures. However, following treatment, some patients develop neurologic deterioration in the absence of tumor recurrence. This delayed treatment-related toxic effect has a clinical and radiographic picture that most closely resembles a diffuse leukoencephalopathy.

The pathophysiologic mechanisms underlying the development of neurotoxicity are poorly understood. It has

been suggested that the combination of chemotherapy and radiotherapy is synergistic in producing the damage based on in vitro and animal model studies,<sup>1,2</sup> but direct evidence is lacking in humans.

Several clinical trials on PCNSL have reported neurotoxicity as a consequence of therapy.<sup>3-6</sup> When a combination of whole-brain radiotherapy and chemotherapy is used, the incidence ranges from 20% to 30% of patients. However, interpretation of these data has been limited by small sample sizes, immature data, varying statistical analysis, and lack of a uniform definition of neurotoxicity. Treatment-related neurotoxicity may describe a wide spectrum of neurologic conditions, ranging from asymptomatic white matter changes on neuroimaging studies

**Table 1. Characteristics of All 183 Patients With PCNSL**

Characteristic	Finding
Age at diagnosis of PCNSL, median (range), y	60 (20-89)
Karnofsky performance status score at diagnosis of PCNSL, median (range)	70 (10-100)
Follow-up of survivors, median (range), y	3.6 (0.1-12.9)
Overall survival, median (95% CI), y	2.9 (2.3-3.6)
Patients who developed neurotoxicity, No.	43
Survival after neurotoxicity onset, median (95% CI), y	1.8 (1-2.3)

Abbreviations: CI, confidence interval; PCNSL, primary central nervous system lymphoma.

to severe dementia. Many studies do not make a distinction between acute and delayed toxicity, and a detailed description of clinical features and outcomes associated with neurotoxicity is not available in the literature. The objective of our study was to describe the clinical findings, time course, and pathophysiologic mechanisms associated with neurotoxicity in an attempt to generate hypotheses for future studies that address prevention and treatment of this complication of successful PCNSL therapy.

## METHODS

We reviewed our PCNSL database for all patients seen at the Department of Neurology of Memorial Sloan-Kettering Cancer Center between 1985 and 2000. In this database, neurotoxicity was defined clinically as neurologic deterioration following treatment for PCNSL that was not caused by tumor recurrence or another identifiable cause. Patients with neurotoxicity were assessed for potential risk factors and outcomes and compared with patients who had PCNSL without neurotoxicity.

Time to neurotoxicity was calculated from the date of initial treatment to the date of neurotoxicity or last follow-up. Typically, the Kaplan-Meier method is used to calculate survival or incidence probabilities. However, a large number of patients die of PCNSL before developing neurotoxicity. Therefore, when estimating the incidence of neurotoxicity, we accounted for death as a competing risk.<sup>7</sup> The estimates of the incidence of neurotoxicity for various groups were compared using a modified  $\chi^2$  test.<sup>8</sup> Potential risk factors assessed included age, sex, history of lymphoma, positive cerebrospinal fluid cytologic test results, meningeal enhancement on magnetic resonance imaging, presence of mental status changes or seizures at diagnosis, number of lesions, abnormal creatinine clearance, ocular involvement, Karnofsky scale performance status, cranial radiotherapy, radiotherapy dose, and chemotherapy.

The medical records of patients with neurotoxicity were reviewed to characterize the clinical syndrome. Prevalence of symptoms and severity over time were assessed. For recording these changes, neurologic assessments closest to the dates of neurotoxicity onset and 6 months, 1 year, and 2 years after neurotoxicity onset were reviewed. Symptoms were divided into 4 categories, cognitive, psychiatric, motor, and autonomic, and were rated as severe, moderate, mild, or absent. Progression for a given category of symptom was defined as change of at least 1 degree in severity during the observed period. Reports of magnetic resonance imaging performed at diagnosis and during follow-up for neurotoxicity were reviewed. When films were

available, the degree of leukoencephalopathy observed on fluid-attenuated inversion recovery or T2-weighted images was rated per the Fazekas scale.<sup>9</sup> Autopsy findings, when available, were also reviewed.

## RESULTS

One hundred ninety-four patients with PCNSL were seen in our institution from May 1985 to October 2000. Eleven patients were excluded owing to lack of information regarding treatment date or follow-up status; therefore, 183 patients were included in the analysis. The median age was 60 years; there were 103 men (**Table 1** and **Table 2**). Treatment for PCNSL included whole-brain radiotherapy in 129 patients (70%) and high-dose methotrexate-based regimens in 152 patients (83%). The median overall survival was 2.9 years (95% confidence interval [CI], 2.3-3.6 years), and the median follow-up of survivors was 3.6 years (range, 0.1-12.9 years).

Neurotoxicity developed in 43 patients. The cumulative incidence of neurotoxicity was 5% (95% CI, 3%-10%) at 6 months, 18% (95% CI, 13%-32%) at 2 years, and 24% (95% CI, 18%-32%) at 5 years (**Figure 1**). Figure 1 also shows the incidence of death without neurotoxicity and the incidence of either event. At 2 years, the probability of either event (neurotoxicity or death without neurotoxicity) was 50%. This was made up of an 18% probability of developing neurotoxicity and a 32% probability of death before development of neurotoxicity. All deaths before neurotoxicity were due to tumor progression. The probability of either event was 16% (95% CI, 11%-21%) at 6 months and 77% (95% CI, 70%-84%) at 5 years. The median overall survival for patients who developed neurotoxicity was 1.8 years (95% CI, 1.0-2.3) from the onset of neurotoxicity.

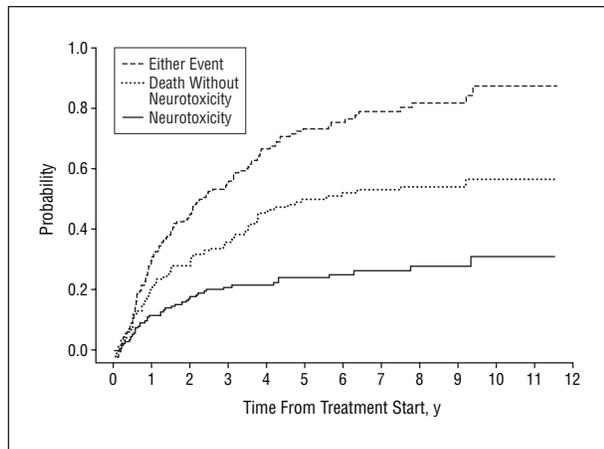
Univariate analysis of the incidence of neurotoxicity by potential risk factors showed that age of 60 years or older (**Figure 2**,  $P=.01$ ), female sex ( $P=.05$ ), presence of mental status abnormalities at PCNSL diagnosis ( $P=.04$ ), and cranial radiotherapy ( $P<.001$ ) were statistically significant risk factors for the development of neurotoxicity (Table 2). In the multivariate analysis, only radiotherapy remained a significant risk factor.

Medical records from 30 of the 43 patients with neurotoxicity contained sufficient information to evaluate the clinical course of neurotoxicity. The prevalence of symptoms 1 month after treatment for PCNSL (considered new baseline neurologic status), at neurotoxicity diagnosis, and at 6 months, 1 year, and 2 years after diagnosis of neurotoxicity is given in **Table 3**. One month after the end of treatment, 59% of patients had mild or moderate cognitive impairment, which was thought to represent the residual effects of tumor or acute toxicity. However, all patients subsequently developed some degree of cognitive impairment, which was the symptom that led to the diagnosis of neurotoxicity in all of them. Frequent complaints were decreased attention, slowness, apathy, and memory difficulties; these symptoms were often subtle and difficult to recognize, but patients' conditions deteriorated over time and most patients eventually fulfilled criteria for overt dementia. Eight patients underwent com-

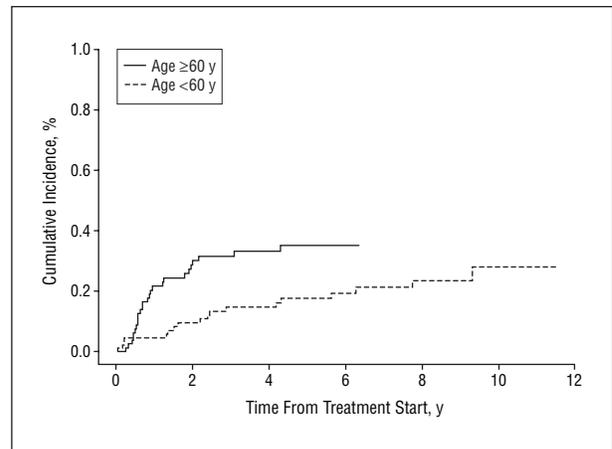
**Table 2. Risk Factor Univariate Analysis (N = 183)**

Variable	Total No. of Patients	No. of Patients With Neurotoxicity	2-Year Incidence, % (95% CI)	5-Year Incidence, % (95% CI)	P Value
Age, y					
<60	95	17	8 (4-16)	16 (13-19)	.01
≥60	88	26	28 (20-40)	33 (27-40)	
Sex					
Male	103	19	16 (10-25)	18 (15-22)	.05
Female	80	24	20 (13-31)	32 (26-39)	
CSF positivity					
Positive or suspicious	56	16	18 (10-32)	26 (21-33)	.82
Reactive or negative	100	23	20 (13-30)	25 (21-30)	
Unknown	27				
Mental status changes					
Yes	107	30	22 (15-32)	31 (26-36)	.04
No	76	13	11 (6-22)	15 (12-18)	
No. of lesions					
0 or 1	120	29	18 (12-27)	24 (20-28)	.93
≥2	48	11	17 (9-33)	23 (18-31)	
Unknown	15				
Ocular involvement					
Yes	34	8	18 (8-37)	25 (18-35)	.50
No	124	31	20 (14-29)	26 (22-30)	
Unknown	25				
Karnofsky performance status score at start of treatment					
≤70	87	19	21 (14-32)	25 (20-30)	.67
>70	80	19	11 (6-21)	21 (17-26)	
Unknown	16				
Radiation therapy					
Yes	129	42	24 (16-31)	30 (26-35)	<.001
No	54	1	0	5 (3-7)	
Radiotherapy dose, cGy					
360-4100	49	16	22 (13-38)	29 (16-41)	.07
4140-5940	63	21	22 (14-36)	31 (19-43)	
Radiotherapy plus chemotherapy					
Yes	111	37	25 (18-35)	30 (19-46)	.65
No	18	5	24 (10-59)	31 (26-36)	

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid.



**Figure 1.** Incidence of neurotoxicity, death, and either neurotoxicity or death (either event).



**Figure 2.** The incidence of neurotoxicity stratified by age, showing that although older patients are at a significantly higher risk, the development of neurotoxicity is also a concern in long-term survivors younger than 60 years.

plete neuropsychological evaluation, which revealed impaired psychomotor speed, executive function, and memory abilities; a detailed description of neuropsychological findings was reported elsewhere.<sup>10</sup>

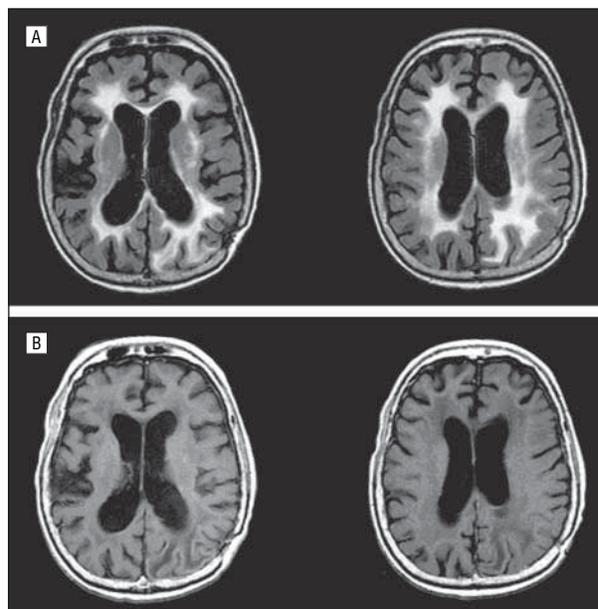
Psychiatric symptoms, characterized by personality changes, aggressiveness, psychotic symptoms, and episodes of delirium, were present in 40% of patients at neurotoxicity onset. These symptoms did not seem to progress

**Table 3. Prevalence of Symptoms 1 Month After End of Treatment (Baseline), at Diagnosis of Neurotoxicity, and at 6 Months, 1 Year, and More Than 2 Years From Diagnosis of Neurotoxicity**

Symptoms	Prevalence, % (n = 30)				
	Baseline	At Neurotoxicity	6 mo	1 y	>2 y
<b>Cognitive</b>					
Absent	38	0	0	0	0
Mild	52	75	60	63	33
Moderate	7	18	15	31	22
Severe	3	7	25	6	44
<b>Psychiatric</b>					
Absent	79	61	58	69	50
Mild	17	29	26	25	28
Moderate	0	4	5	6	0
Severe	4	7	11	0	22
<b>Motor</b>					
Absent	52	25	32	25	11
Mild	34	43	26	31	22
Moderate	14	21	32	25	17
Severe	0	10	11	19	50
<b>Autonomic</b>					
Absent	86	71	74	50	50
Mild	14	25	16	31	11
Moderate	0	4	10	13	17
Severe	0	0	0	6	22
Median Karnofsky performance status score	90	70	60	60	50

over time, reflecting a response to neuroleptics or development of severe apathy that obscured other symptoms.

Motor and autonomic features developed after cognitive difficulties became apparent. Mild or moderate motor symptoms were present in 48% of patients at baseline assessment, mostly due to lateralized weakness corresponding to the prior tumor location. As neurotoxicity symptoms progressed, all patients developed a stereotypic gait disturbance characterized by small shuffling steps, widened base, difficult turns, and postural instability. These symptoms progressed over months to years, and patients eventually became bed or wheelchair bound. At 2-year follow-up, 67% of the patients assessed had moderate or severe gait disturbance. Difficulty with swallowing and pseudobulbar symptoms developed in some patients, requiring gastrostomy. Autonomic symptoms represented by urinary and subsequently fecal incontinence were seen in advanced disease and resembled a frontal-type autonomic dysfunction. At 2-year follow-up, incontinence was present in 50% of patients, and there was no response to the use of anticholinergic medications. As a result of neurologic deterioration, the median Karnofsky performance status score decreased from 90 one month after completing PCNSL treatment to 50 two years later. All patients eventually required nursing care, and most died of causes related to neurotoxicity. Five patients with neurotoxicity underwent autopsy, and the details were reported elsewhere.<sup>11</sup> Findings included diffuse thickening of small



**Figure 3.** Magnetic resonance image from a 70-year-old patient with neurotoxicity. The original tumor was located in the left parieto-occipital region. Fluid-attenuated inversion recovery sequences show diffuse white matter changes and brain atrophy (A). T1 postgadolinium images (B) confirm the absence of tumor recurrence.

vessels in the deep white matter as well as white matter gliosis, spongiosis, and widespread myelin and axonal loss in all patients. No tumor was identified in any patient.

Neuroimaging revealed that all patients with neurotoxicity had progressive diffuse white matter changes and cortical-subcortical brain atrophy, with diffuse ventriculomegaly in addition to variable degrees of encephalomalacia corresponding to the location of the previous tumor (**Figure 3**). Only 12 patients had films available for review and rating of white matter changes. At a median of 4 years after neurotoxicity onset, 4 patients had grade 4 or 5 white matter changes, 5 had grade 3, and 2 patients had grade 1 or 2. In some patients, the white matter changes were asymmetrical, with more severe abnormalities corresponding to previous tumor location or radiotherapy boost. White matter changes progressed in all patients throughout follow-up.

Hydrocephalus was a frequently associated radiographic feature, and 12 patients had a ventriculoperitoneal shunt placed to treat normal pressure hydrocephalus, which may be a component of neurotoxicity. Four patients had transient, mild improvement that was insufficient to change the symptom score according to our classification; all these patients' conditions continued to deteriorate clinically.

#### COMMENT

The present study provides the first comprehensive description, to our knowledge, of the neurologic consequences associated with successful combined modality treatment for PCNSL. Although a few reports that focus on the incidence of neurotoxicity are available, interpretation of results has been limited by small sample size, short follow-up, and varying definitions of neurotoxicity.<sup>3,10,12,13</sup>

In our series, neurotoxicity presented as a stereotypical and progressive dementia, developing after a variable delay from the end of treatment. Cognitive dysfunction was seen early in the syndrome and was followed by motor and, eventually, autonomic symptoms. The resulting clinical picture resembles other diseases categorized as subcortical dementias, particularly subcortical arteriosclerotic encephalopathy (Binswanger disease),<sup>14</sup> cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, and normal pressure hydrocephalus.<sup>15</sup> Through various mechanisms, these diseases disrupt parallel circuits from the frontal cortex to the basal ganglia and corresponding thalamocortical connections.<sup>16,17</sup> In our patients, a ventriculoperitoneal shunt failed to produce a consistent and sustained benefit, suggesting that the observed ventricular dilation is primarily *ex vacuo* and that normal pressure hydrocephalus plays a minor role, if any. Conversely, radiotherapy was the only significant risk factor that led to neurotoxicity, suggesting that radiation-induced injury is the primary pathophysiologic process.

Extensive studies<sup>18</sup> have detailed the timing and radiobiological parameters concerning radiotherapy-induced brain injury, but little is known about the cellular and biochemical pathophysiologic features. Radiation-induced central nervous system damage has been divided into 3 forms: acute, early delayed, and late delayed. The acute and early delayed forms usually produce transient deficits and probably involve a different pathogenesis compared with the late-delayed reactions, which are irreversible. Leukoencephalopathy is a late-delayed reaction, but some of our patients developed symptoms and signs within months of completing treatment, suggesting that a long latency is not necessary for permanent damage to occur.

Vascular injury is a well-described feature of radiation-induced central nervous system damage. Studies in humans and animal models have demonstrated that radiation induces vessel wall thickening, vessel dilation, nuclear enlargement in endothelial cells, and necrosis. These are features of radionecrosis that, only recently have been recognized as important in treatment-related leukoencephalopathy.<sup>11</sup> An argument against the vascular hypothesis for radiotherapy-induced leukoencephalopathy is that the gray matter is relatively spared by radiation effects, despite its vulnerability to ischemia.<sup>19,20</sup> However, the predilection for white matter injury is consistent with the vascular hypothesis because our patients developed a syndrome similar to Binswanger disease in which microvascular alterations that affect the blood flow in medullary arterioles lead to loss of oligodendrocytes, myelin, and axons in the deep white matter.<sup>14</sup> These findings are identical to those seen in our patients at autopsy.<sup>11</sup>

One of the hallmarks of neurotoxicity is the ongoing and cumulative damage manifested clinically as a delayed and progressive encephalopathy. Continued injury to vessels or other parenchymal elements must occur to explain the delay in presentation and the progression over time. Suggested mechanisms include depletion of glial progenitor cells and perpetuation of oxidative stress induced by radiation.<sup>18</sup> Radiation may diminish the reproductive capacity of oligodendrocyte precursors such as O-2A, disrupting the normal turnover of

myelin.<sup>21</sup> This progressive demyelination may take months to cause symptoms, contributing to the latency in onset of neurotoxicity and its progressive nature.

Radiotherapy causes tissue injury by generating intracellular free radicals. A study<sup>18</sup> that examined the expression of Hmox1, a surrogate marker of oxidative stress, after spinal cord irradiation in animal models showed that overexpression of Hmox1 could be detected after a delay of 5 months and that it anticipated the development of radiotherapy-induced myelopathy. These data suggest that persistent oxidative stress triggered by radiotherapy may be a determining factor in the delayed and progressive character of neurotoxicity.

Based on these pathogenetic theories, several strategies of treatment for radiotherapy-induced brain injury have been proposed, including hyperbaric oxygen, amifostine, anticoagulation, vitamin E, and other antioxidants.<sup>22-25</sup> However, available studies are limited to a small series of patients, most notably in the setting of radionecrosis developing after focal radiotherapy. Therefore, to date, no effective treatment has been defined.

The role played by chemotherapy in the genesis of neurotoxicity has been difficult to ascertain. Most PCNSL regimens include known neurotoxic drugs, such as methotrexate and cytarabine. Chronic, permanent methotrexate-related neurotoxicity has been described in children undergoing treatment for leukemia or sarcomas in the absence of central nervous system disease or cranial irradiation.<sup>26,27</sup> Pathologic findings are similar to those associated with radiotherapy-induced neurotoxicity.<sup>26</sup> However, those children all developed acute, severe deficits at onset and remained stable or improved over time, unlike our patients, who had a delay in onset and deteriorated. This suggests that chemotherapy-related toxicity is a different entity from radiotherapy-related toxicity; this is consistent with the fact that only 1 of our patients treated with chemotherapy alone developed neurotoxicity. Furthermore, the addition of chemotherapy to radiotherapy did not increase the risk of developing neurotoxicity in this study.

The role of preexisting conditions, such as prior vascular disease or degenerative conditions, is difficult to establish because patients were not evaluated before PCNSL diagnosis. The PCNSL cells infiltrate brain parenchyma widely, which may render these patients more susceptible to other injuries.<sup>28</sup> The presence of mental status changes at tumor diagnosis was a significant univariate risk factor for neurotoxicity and may be a surrogate marker for severity or extent of tumor damage that could enhance patients' vulnerability to subsequent neurotoxicity. Moreover, the finding that older age is a risk factor suggests that age-related alterations in the brain microenvironment may be critical to the pathogenesis of neurotoxicity.

The present study is limited by its retrospective nature. The diagnosis of neurotoxicity was based on clinically significant cognitive dysfunction, and mild cases may have been missed. In fact, mild cognitive impairment is a frequent finding in patients treated for PCNSL.<sup>10,29</sup> A prospective study is needed to ascertain whether these minor symptoms are part of the spectrum of delayed neurotoxicity or whether they represent a nonprogressive consequence of

direct tumor damage or treatment-related acute toxicity. Regardless, our study demonstrates that delayed neurotoxicity following treatment for PCNSL is a progressive syndrome with a well-defined and fatal clinical course, characterized by neurologic dysfunction that goes beyond cognitive symptoms. Treatment of neurotoxicity is ineffective, so prevention is essential. There are 2 potential approaches to decrease the incidence of neurotoxicity. One is the development of more effective chemotherapy regimens that eliminate or defer radiotherapy, which has been the current trend in recent PCNSL trials.<sup>30-33</sup> A second possible approach is interrupting the chain of biochemical and cellular events that precedes the clinical manifestations of neurotoxicity. The delay in development of symptoms provides a potential therapeutic window for neuroprotective strategies that aim to decrease the vascular damage and oxidative stress in patients at risk. Other investigational venues include extrapolating prevention and symptomatic treatment for vascular dementia and regeneration therapies such as oligodendrocyte progenitor cell-associated remyelination.<sup>34</sup>

Accepted for Publication: May 9, 2005.

Correspondence: Lauren E. Abrey, MD, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021 (abreyl@mskcc.org).

Author Contributions: Study concept and design: Omuro and Abrey. Acquisition of data: Omuro, Kim, and Abrey. Analysis and interpretation of data: Omuro, Ben-Porat, Panageas, Correa, Yahalom, DeAngelis, and Abrey. Drafting of the manuscript: Omuro, Ben-Porat, Panageas, Kim, and Abrey. Critical revision of the manuscript for important intellectual content: Omuro, Ben-Porat, Panageas, Correa, Yahalom, DeAngelis, and Abrey. Statistical analysis: Ben-Porat and Panageas. Obtained funding: DeAngelis. Administrative, technical, and material support: Kim and Yahalom. Study supervision: Correa, DeAngelis, and Abrey.

## REFERENCES

- Mullen PJ, Kernan WJ, Schunior A, et al. Interactions of steroid, methotrexate, and radiation determine neurotoxicity in an animal model to study therapy for childhood leukemia. *Pediatr Res*. 1994;35:171-178.
- van der Kogel AJ, Sissingh HA. Effects of intrathecal methotrexate and cytosine arabinoside on the radiation tolerance of the rat spinal cord. *Radiother Oncol*. 1985;4:239-251.
- Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. *J Clin Oncol*. 1998;16:859-863.
- Abrey LE, Yahalom J, DeAngelis LM. Treatment for primary CNS lymphoma: the next step. *J Clin Oncol*. 2000;18:3144-3150.
- Poortmans PMP, Kluin-Nelemans HC, Haaxma-Reiche H, et al. High-dose methotrexate-based chemotherapy followed by consolidating radiotherapy in non-AIDS-related primary central nervous system lymphoma: European Organization for Research and Treatment of Cancer Lymphoma Group Phase II Trial 20962. *J Clin Oncol*. 2003;21:4483-4488.
- Harder H, Holtel H, Bromberg JEC, et al. Cognitive status and quality of life after treatment for primary CNS lymphoma. *Neurology*. 2004;62:544-547.
- Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;16:1141-1154.
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496-509.
- Fazekas F, Chawluk JB, Alavi A, et al. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol*. 1987;149:351-356.
- Correa DD, DeAngelis LM, Shi W, et al. Cognitive functions in survivors of primary central nervous system lymphoma. *Neurology*. 2004;62:548-555.
- Lai R, Abrey LE, Rosenblum MK, DeAngelis LM. Treatment-induced leukoencephalopathy in primary CNS lymphoma: a clinical and autopsy study. *Neurology*. 2004;62:451-456.
- Blay JY, Conroy T, Chevreau C, et al. High-dose methotrexate for the treatment of primary cerebral lymphomas: analysis of survival and late neurologic toxicity in a retrospective series. *J Clin Oncol*. 1998;16:864-871.
- Wassenberg MW, Bromberg JE, Witkamp TD, et al. White matter lesions and encephalopathy in patients treated for primary central nervous system lymphoma. *J Neurooncol*. 2001;52:73-80.
- Roman GC, Erkinjuntti T, Wallin A, et al. Subcortical ischaemic vascular dementia. *Lancet Neurol*. 2002;1:426-436.
- Hebb AO, Cusimano MD. Idiopathic normal pressure hydrocephalus: a systematic review of diagnosis and outcome. *Neurosurgery*. 2001;49:1166-1184.
- Cummings JL. Frontal-subcortical circuits and human behavior. *Arch Neurol*. 1993;50:873-880.
- Tullberg M, Fletcher E, DeCarli C, et al. White matter lesions impair frontal lobe function regardless of their location. *Neurology*. 2004;63:246-253.
- Tofilon PJ, Fike JR. The radioresponse of the central nervous system: a dynamic process. *Radiat Res*. 2000;153:357-370.
- Steen RG, Spence D, Wu S, et al. Effect of therapeutic ionizing radiation on the human brain. *Ann Neurol*. 2001;50:787-795.
- Mulhern RK, Reddick WE, Palmer SL, et al. Neurocognitive deficits in medulloblastoma survivors and white matter loss. *Ann Neurol*. 1999;46:834-841.
- van der Maazen RW, Kleiboer BJ, Verhagen I, van der Kogel AJ. Repair capacity of adult rat glial progenitor cells determined by an in vitro clonogenic assay after in vitro or in vivo fractionated irradiation. *Int J Radiat Biol*. 1993;63:661-666.
- Glantz MJ, Burger PC, Friedman AH, et al. Treatment of radiation-induced nervous system injury with heparin and warfarin. *Neurology*. 1994;44:2020-2027.
- Hulshof MC, Stark NM, van der Kleij A, et al. Hyperbaric oxygen therapy for cognitive disorders after irradiation of the brain. *Strahlenther Onkol*. 2002;178:192-198.
- Nieder C, Andratschke NH, Wiedenmann N, Molls M. Prevention of radiation-induced central nervous system toxicity: a role for amifostine? *Anticancer Res*. 2004;24:3803-3809.
- Chan AS, Cheung MC, Law SC, Chan JH. Phase II study of alpha-tocopherol in improving the cognitive function of patients with temporal lobe radionecrosis. *Cancer*. 2004;100:398-404.
- Allen JC, Rosen G, Mehta BM, Horten B. Leukoencephalopathy following high-dose iv methotrexate chemotherapy with leucovorin rescue. *Cancer Treat Rep*. 1980;64:1261-1273.
- Bleyer WA. Neurologic sequelae of methotrexate and ionizing radiation: a new classification. *Cancer Treat Rep*. 1981;65(suppl 1):89-98.
- Lai R, Rosenblum MK, DeAngelis LM. Primary CNS lymphoma: a whole-brain disease? *Neurology*. 2002;59:1557-1562.
- O'Neill BP. Neurocognitive outcomes in primary CNS lymphoma (PCNSL). *Neurology*. 2004;62:532-533.
- Hoang-Xuan K, Taillandier L, Chinot O, et al. Chemotherapy alone as initial treatment for primary CNS lymphoma in patients older than 60 years: a multicenter phase II study (26952) of the European Organization for Research and Treatment of Cancer Brain Tumor Group. *J Clin Oncol*. 2003;21:2726-2731.
- Pels H, Schmidt-Wolf IGH, Glasmacher A, et al. Primary central nervous system lymphoma: results of a pilot and phase II study of systemic and intraventricular chemotherapy with deferred radiotherapy. *J Clin Oncol*. 2003;21:4489-4495.
- Batchelor T, Carson K, O'Neill A, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. *J Clin Oncol*. 2003;21:1044-1049.
- Herrlinger U, Schabet M, Brugger W, et al. German Cancer Society Neuro-Oncology Working Group NOA-03 multicenter trial of single-agent high-dose methotrexate for primary central nervous system lymphoma. *Ann Neurol*. 2002;51:247-252.
- Goldman S. Glia as neural progenitor cells. *Trends Neurosci*. 2003;26:590-596.