Cognitive Performance and Magnetic Resonance Imaging Findings After High-Dose Systemic and Intraventricular Chemotherapy for Primary Central Nervous System Lymphoma

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Background: Long-term neurotoxicity is a frequent complication of combined radiotherapy and chemotherapy in patients with primary central nervous system lymphoma. Treatment protocols without radiotherapy have been implemented to avoid this; however, little detailed neuropsychologic and neuroradiologic data exist to assess the frequency of long-term treatment sequelae in this patient group.

Objective: To determine whether a polychemotherapy regimen based on high-dose methotrexate results in cognitive impairment and/or changes detectable by magnetic resonance imaging of the brain during long-term follow-up.

Patients and Methods: Twenty patients with histologically proven primary central nervous system lymphoma were treated with a novel chemotherapy protocol that included systemic and intraventricular administration of methotrexate and cytarabine (ara-C). Standardized neuropsychologic testing and magnetic resonance imaging investigations were performed prior to therapy and prospectively during a median follow-up period of 36 months (range, 21-69 months).

Results: Ten patients achieved durable remissions without relapse for more than 1 year after completion of chemotherapy. There was no gross cognitive decline in any of these patients during the follow-up period. In contrast, magnetic resonance imaging revealed therapy-induced white matter changes in 5 of these patients.

Conclusions: We conclude that chemotherapy alone is associated with a low risk of long-term neurotoxicity in primary central nervous system lymphoma. Methotrexate-induced white matter lesions detectable on magnetic resonance imaging are not inevitably associated with significant cognitive decline.

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Primary central nervous system lymphoma (PCNSL) is a malignant brain tumor sensitive to both radiotherapy and chemotherapy. While radiotherapy alone results in a median survival of only 12 to 18 months, a median survival of more than 40 months has been achieved with combined radiotherapy and chemotherapy. High-dose chemotherapy protocols that include methotrexate are similarly effective in terms of tumor response and extension of survival. In view of the greater proportion of long-term survivors, long-term treatment toxicity becomes increasingly relevant.

Both irradiation and methotrexate are known to be potentially neurotoxic. Combined therapy may cause severe leukencephalopathy and deep brain atrophy, resulting in a dementing illness. This complication typically occurs from 4 months to several years after treatment. The incidence of severe neurotoxic events ranges from 8% to 50% in different series and is particularly high in the older population. In a study by Abrey et al, neurotoxicity occurred in more than 80% of the patients older than 60 years. Besell et al reported that 5 (62%) of 8 patients older than 60 years developed dementia after a combined polychemotherapy-radiotherapy regimen.

A major goal in introducing treatment regimens using chemotherapy without irradiation is to prevent late neurotoxic effects. To effectively control tumor growth, chemotherapy protocols are necessarily “aggressive,” eg, using high-dose systemic methotrexate alone or in combination with other compounds, and using intraventricular or intra-arterial administration of methotrexate. The safety of these regimens with respect to neurotoxicity is, thus, not a priori. Hence, it is instru-
mental to assess long-term neurotoxic sequelae and their effects on cognitive performance by standardized, validated methods that include neuropsychologic testing in addition to magnetic resonance imaging (MRI) of the brain. However, the availability of comprehensive neuropsychologic data is limited to a single institution’s experience with intra-arterial chemotherapy after blood-brain barrier disruption.13 Those authors concluded that no cognitive decline was detectable in any of the 31 patients examined. Sandor et al4 reported the results of a neuropsychologic assessment of 7 of 14 patients treated according to an intravenous polychemotherapy protocol: 2 of these patients experienced severe cognitive deterioration after treatment. Guha-Thakurta et al5 presented detailed data on a quality-of-life assessment of patients after intravenous methotrexate monotherapy. In other studies,3,14,15 neurotoxicity was assessed only by means of clinical impression or by rough measures, such as the Mini-Mental State Examination or by a Karnofsky Performance Score. Consequently, the extent of cognitive deficits that result from different treatment regimens remains unclear. This holds particularly true for more subtle neuropsychologic deficits, which are expected to be more frequent than severe dementia.7 Therefore, we have included longitudinal neuropsychologic testing in a series of 20 patients treated with a novel polychemotherapy regimen that included high-dose systemic methotrexate. Additionally, standardized MRI investigations were performed to document possible treatment sequelae, since high-dose methotrexate administered to patients with sarcomas reportedly had resulted in periventricular white matter changes detectable on MRI.16,17 So far, it is not clear whether these changes invariably led to neuropsychologic dysfunction.

**METHODS**

**PATIENTS AND TREATMENT**

Between September 1995 and September 1998, 20 consecutive patients (human immunodeficiency virus negative) with histologically proven PCNSL were treated with a novel chemotherapy protocol consisting of combined intravenous and intraventricular administration of methotrexate and cytarabine in combination with intravenous application of vinca-alkaloids and alkylating agents. The chemotherapy protocol is presented in Table 1. The results of the trial with respect to treatment response (70%), median time to treatment failure (20.5 months), and median overall survival (54 months) have been published in detail.18

**NEUROPSYCHOLOGIC ASSESSMENT**

Patients underwent a standardized neuropsychologic test battery, comprising tests of attention, verbal memory, visual retention, word fluency, and visuoconstruction. The tests were chosen because of their known sensitivity to nonspecific changes in cognitive function that would be expected to result from treatment-related white matter disease. The neuropsychologic examinations were performed prior to treatment or immediately after its initiation and at 4 months, 12 months, and at the most recent follow-up. The following psychometric tests were used:
• Number Connection Test\textsuperscript{19}: Test of attention. This test is analogous to the Trail Making Test Part A, in which the subject has to connect numbered circles, and the time for completion is analyzed. For patients older than 60 years, a special version for elderly subjects\textsuperscript{20} was used.

• Controlled Written Word Association\textsuperscript{21}: Test of word fluency. The subject has to write as many words as possible that begin with the letters L, P, and S (or K/L/P in a parallel version) within 1 minute for each letter. The parameter used for analysis was the number of correctly produced words.

• Verbal Learning and Memory Test\textsuperscript{22}: Test of verbal memory. This is a word-list learning task analogous to the Rey Auditory Verbal Learning Test. A 15-item word list has to be learned during 5 learning trials and recalled after an interference list and a 30-minute delay. Both learning (sum of correct items in the first 5 trials) and recall (loss of learned items in delayed recall) were analyzed.

• Benton Visual Retention Test\textsuperscript{23}: Test of visual retention. Ten items with a 3-figure design format are presented for 10 seconds, and the subjects must recall the figure immediately by drawing it. The parameter used for analysis was the number of correctly reproduced items.

• Block Design Test\textsuperscript{24}: Test of visuconstruction. The subject has to reproduce 2-dimensional colored designs using colored blocks. The parameter used for analysis was the raw value according to the Wechsler Adult Intelligence Scale.

To prevent training effects, parallel test forms were used in repeated testing if available (Controlled Written Word Association, Verbal Learning and Memory Test, and Benton Visual Retention Test).

**STATISTICAL ANALYSIS**

All raw values were transformed into standard values according to normative test data of healthy controls that consider age and education. In healthy controls, standard values have a mean ± SD of 100 ± 10, yielding a normal range of 90 to 110. As an indicator for overall cognitive performance, a summary score was computed by calculating the arithmetic mean of the standard values of the 6 evaluated test parameters. Changes in test performance between results at 4 months and at the most recent follow-up were analyzed by calculating reliable change indices for each test score in every patient. This is an established procedure to test for the significance of individual changes by comparing them with the extent of changes expected to occur in a healthy control population.\textsuperscript{25} Analogous to Hermann et al.,\textsuperscript{25} a 90% change score confidence interval was computed by multiplying the SE of differences (SE\textsubscript{D}) by ± 1.64. The SE\textsubscript{D} was derived from the SE of measurement (SE = [1 – r\textsubscript{xx}]\textsuperscript{1/2}) by the formula \(SE\textsubscript{D} = (2(SE))^{1/2}\). In this equation, r\textsubscript{xx} are the published retest reliability indices of the tests. The difference between 2 individual test scores was considered significant if its value exceeded the borders of this confidence interval. Given only statistical variation, one would expect only 5% of differences outside this confidence interval in both directions. Binomial tests were applied to compare the number of observed differences with the number of expected differences.

**MAGNETIC RESONANCE IMAGING**

Each patient was studied by MRI within 72 hours prior to initiation of therapy, after the second chemotherapy cycle, and after completion of therapy. Magnetic resonance imaging follow-up was done every 4 months within the first year after therapy and every 6 months thereafter. Magnetic resonance imaging was performed on a 0.5-T (Gyroscan T5; Philips Medical Systems, Best, the Netherlands) or a 1.5-T scanner (Gyroscan ACS-NT; Philips Medical Systems). All MRI studies were carried out using a standardized protocol that included sagittal T1-weighted spin echo (slice thickness, 5 mm; interslice gap, 0.5 mm), axial T2-weighted fast spin echo (5 mm; 1 mm), coronal fluid-attenuated inversion recovery (5 mm; 1 mm), and axial T1-weighted spin echo (5 mm; 1 mm) before and following gadolinium injection. If contrast enhancement was observed on the axial slices, additional sagittal and coronal T1-weighted spin-echo images were acquired.

**RESULTS**

**PATIENT CHARACTERISTICS**

Of the 20 patients treated, 2 died of treatment-related complications (sepsis with multiorgan failure related to myelosuppression in both cases), 4 showed progressive disease, and 14 achieved either complete (n = 12) or partial (n = 2) remissions.\textsuperscript{16} Ten of these patients achieved durable remissions without relapse for more than 1 year after completion of chemotherapy (6 women, 4 men; median age, 60 years [range, 27-67 years]). In these patients, the development of cognitive performance could be evaluated with regard to potential neurotoxicity. In the 4 patients who experienced relapses within 1 year after completion of treatment, cognitive deficits resulting from the relapse itself could not be distinguished from treatment-induced deficits. Therefore, cognitive deficits in these patients could not be directly attributed to treatment-related neurotoxicity. However, neuropsychologic tests were carried out in these patients as well.

**NEUROPSYCHOLOGIC ASSESSMENT**

Follow-up of the 10 patients with long-term survival and without relapse ranged from 21 to 69 months (median, 36 months; mean, 43 months) after diagnosis. Prior to therapy, 5 of them showed cognitive impairment, 2 could not be tested (global aphasia in one, noncooperation in the other), and 3 showed normal cognitive function. The neuropsychologic summary scores of these 10 patients during follow-up are shown in Figure 1. In 4 of 5 patients with cognitive impairment at the initial examination, improvement was found 4 months after therapy, resulting in a normal summary score for 3 of them. In 1 patient, this improvement resulted from recovery of a verbal memory deficit; in the remaining 3 patients, there was a recovery of basic attentional functions, which affected their performance on more than 1 test. Patients with normal cognitive function prior to therapy showed preserved cognitive function 4 months after therapy and thereafter, ie, there were no significant changes in the summary score during the entire follow-up period. At the most recent follow-up, the summary scores ranged from 86 to 109, with a median value of 94. Although patients older than 60 years tended to have lower test scores, the overall development of the neuropsychologic scores during follow-up was identical in patients younger and older than 60 years.

Figure 2 shows the individual performance changes for single test scores between examinations at 4 months
and at the most recent follow-up, as judged by the Reliable Change Indices. For each of the 56 comparisons (6 test scores for 10 patients were compared; there were 4 missing values), the number of improvements, stable scores, and deteriorations are given. In total, there were 10 improvements and 4 deteriorations. The number of observed deteriorations did not significantly exceed the number of expected deteriorations (binomial test, $P=.33$), whereas the number of improvements did ($P<.001$). This analysis was also carried out separately for the 5 patients who were older than 60 years. In 28 comparisons (2 missing values), there were 3 deteriorations, which did not exceed the number of expected deteriorations significantly ($P=.17$), and 5 improvements, which exceeded the number of expected improvements ($P=.004$). No patient experienced a decline in more than 1 test score subsequent to therapy.

Neuropsychologic test results in 4 patients who relapsed within 1 year after therapy are of note: a 37-year-old woman re-treated with combined chemotherapy, resulting in complete remission, showed good cognitive function at her most recent follow-up (summary score, 100). Two other patients (aged 59 and 67 years), who had received either whole brain radiotherapy or chemotherapy plus ocular radiotherapy at relapse, developed dementia thereafter. Persistent impairment of cognitive function (summary score, 76 at most recent follow-up) was observed in a 62-year-old woman who had received combined chemotherapy at relapse and who had experienced serious tumor complications, including intracerebral and panventricular hemorrhage at initial examination.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging revealed white matter changes that developed during therapy in 4 of 10 patients (aged 67, 65, 62, and 51 years) (Figure 3). In one of them (aged 67 years), these changes were detectable after the third chemotherapy cycle but substantially decreased in size until completion of therapy, resulting in a few persistent periventricular white matter spots. This patient showed moderate improvement in cognitive function (summary score, 88 at most recent follow-up, 84 at initial examination). In the other 3 patients, confluent widespread white matter changes partly involving subcortical U fibers were progressive until the end of therapy and remained stable thereafter. In all of them, the overall cognitive function was within the normal range at the most recent follow-up (summary score, 94, 95, and 97, respectively). In another patient (aged 68 years), white matter lesions were already detectable prior to therapy (most likely representing microangiopathic changes) and showed progression with therapy. This patient showed severe cognitive dysfunction at initial examination (summary score, 73) and ongoing improvement after therapy (summary score, 86 at most recent follow-up).
This study evaluated cognitive function and treatment-induced white matter changes on MRI in patients receiving intravenous and intraventricular polychemotherapy for PCNSL. Long-term survival without relapse, defined as durable remission for more than 1 year after completion of therapy, was achieved in half of the patients treated. In this subgroup, sensitive test procedures did not reveal any evidence of cognitive decline attributable to therapy-related neurotoxicity. Initially, successful treatment of PCNSL often resulted in significant improvement of cognitive function. As cognitive impairment is one of the most frequent clinical features of PCNSL, cognitive improvement with successful therapy is to be expected. Hence, to determine treatment-induced neurotoxicity, long-term cognitive performance has to be compared with the patients’ performance after completion of therapy and not with pretreatment performance. Four months after completion of therapy, neither acute adverse treatment effects nor long-term neurotoxicity are to be expected. Comparison between the patients’ cognitive performance 4 months after completion of therapy and at the most recent follow-up showed either preserved function or ongoing recovery of primary impaired functions subsequent to therapy. This also applied to 5 patients older than 60 years who belonged to a group at high risk for developing neurotoxicity. Two years after diagnosis (minimum follow-up, 21 months), none of these 5 patients showed cognitive decline. Our findings are in sharp contrast with published long-term observations in patients after combination therapy for PCNSL. One study reported that 6 of 10 patients older than 60 years who had received combined radiotherapy and chemotherapy were demented 24 months after diagnosis.

In the present series, cognitive function was significantly impaired after irradiation in 2 of 4 patients who experienced early relapses and in a third patient in this group who had tumor-related brain hemorrhage at the initial examination. In these patients, an unequivocal evaluation of chemotherapy-related neurotoxicity was not possible since the relapse itself or its treatment could have led to substantial cognitive impairment.

Somewhat unexpectedly, MRI demonstrated white matter changes in 5 of the 10 long-term survivors. The temporal relationship between polychemotherapy and the development of MRI changes strongly suggests that the white matter changes were treatment induced. Strikingly, none of these patients experienced overall cognitive decline during a follow-up period of at least 16 months after the appearance of white matter changes. Therefore, methotrexate-induced leukoencephalopathy detectable by MRI does not inevitably lead to gross cognitive dysfunction. Further follow-up has to show whether there might be future deterioration of cognitive performance in these patients.

The occurrence of clinical asymptomatic white matter changes in patients treated with chemotherapy for PCNSL has recently been reported. In one study, 2 of 37 patients treated with systemic high-dose methotrexate showed changes classified as “clinically asymptomatic leukoencephalopathy.” In our series, white matter changes seemed to be more frequent (5 of 10 patients). Nine patients in another series who received systemic high-dose methotrexate were found to have persisting white matter lesions in “close proximity to the original enhancing masses” on MRI. The demyelinating effect of the brain lymphoma itself was discussed from an etiological viewpoint by the authors. In contrast to this, the white matter changes found in our series were more widespread and most probably represented a treatment-induced leukoencephalopathy.

Two mechanisms may contribute to the frequent occurrence of widespread white matter lesions in our series: first, methotrexate reaches cytotoxic concentrations in the CSF and probably in brain parenchyma when administered in high systemic doses. White matter seems to be particularly sensitive to high-dose systemic methotrexate, and clinically asymptomatic or symptomatic white matter lesions have been reported in young patients treated with high-dose or ultrahigh-dose methotrexate therapy. Second, in this study, methotrexate was also given intraventricularly on days 1 to 4 via an Ommaya reservoir, with single doses of 3 mg/d. Intraventricular methotrexate penetrates only a few millimeters into the surrounding parenchyma. Presumably, the periventricular white matter was exposed to a particularly high concentration of methotrexate in the patients in this study.

We conclude that the risk of long-term neurotoxicity in patients treated with combined intravenous and intraventricular therapy is increased in patients older than 60 years who are treated for PCNSL. Further follow-up has to show whether there might be future deterioration of cognitive performance in these patients.
intraventricular chemotherapy that includes methotrexate and cytarabine is low. Accordingly, this treatment regimen seems to be more favorable than combined radiotherapy and chemotherapy protocols, which have a known high risk of severe neurotoxicity, particularly in older patients. However, at present, a reliable prediction of the risk of long-term neurotoxicity is not possible because of the small number of patients examined. In light of the ongoing debate on treatment in PCNSL, the inclusion of appropriate assessments of cognitive function appears indispensable in any controlled clinical trial that compares different treatment modalities.

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