

Clinical Response Following Adjuvant Temozolomide in a Patient with Primary Cerebral Lymphoma

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Abstract. A 69-year-old female patient was treated for primary CNS-lymphoma (PCNSL) starting from August 2002. As her general condition allowed no high-dose methotrexate (MTX) therapy, radiotherapy was administered as a first-line treatment. CSF involvement could be managed by intrathecal Ara-C. Her general condition and cognitive status stabilized, but did not improve for 3 months. Therefore, oral chemotherapy with Temozolomide 200mg/m² was initiated. After two courses, which were tolerated without any problems, the patient's Karnofsky performance index had improved from 40% to 50%, the Mini-Mental Status rose from 16 to 27/30. The CSF-cell count was elevated again to 23 cells/μl without signs of meningeal relapse. Unfortunately, the patient died unexpectedly from suspected pulmonary embolism. We conclude that adjuvant Temozolomide chemotherapy can improve the general condition and cognition in patients with PCNSL even when the general condition is poor. Long-term effects and neurotoxicity remain to be analysed in prospective trials, as well as the efficacy in leptomeningeal disease.

For unknown reasons, primary CNS-lymphoma (PCNSL) has been diagnosed in a growing number of immuno-competent patients during recent years (1). The prognosis of these patients, when treated with radiotherapy alone or combined with conventional-dose chemotherapy, is comparable with that of glioblastoma patients (2-4). Only with the introduction of chemotherapy based upon high-dose intravenous methotrexate (HD-MTX), did the median survival improve considerably (5-7). The use of HD-MTX, however, is restricted by both acute and

delayed toxicity that may prevent its use, especially in elderly patients (8-10). Therefore, this treatment option can not be offered to a considerable number of patients.

Temozolomide (TMZ) is an alkylating substance with good enteral resorption, bioavailability and CSF-penetration. Because of its good tolerance and considerable efficacy, TMZ is already widely used in the therapy of malignant gliomas and metastases of systemic cancer (11). Only a few reports exist on the use of TMZ in relapsing (12) and newly-diagnosed PCNSL (13,14).

We report, here, on a 69-year-old female patient with PCNSL, whose cognition and general condition improved considerably after two courses of adjuvant oral Temozolomide chemotherapy.

Case Report

A 69-year-old woman experienced a decline of cognitive and general performance, starting from March 2002. In April, a left-sided hemiparesis was interpreted as cerebral ischemia. During rehabilitation therapy, a progressive disturbance of orientation and short-time memory was recognized. In July, the patient was referred to our hospital because of suspected encephalitis. At this stage, she was somnolent with only short periods of reduced communication, disoriented in time and place and incompletely oriented for her personal dates. The neurological examination showed a mild left-sided hemiparesis, but no other focal signs. The Mini-Mental Status was 13/30, the Karnofsky performance score 20%.

The transversal T1-weighted MRI (Figure 1) showed gadolinium enhancement in the basal ganglia on the right side and of the splenium of the corpus callosum as well as in the peritrigonal white matter on both sides, consistent with cerebral lymphoma. The CSF-cell count was elevated to 46 cells/μl, CSF-protein was 2.808 mg/l, lactate 2.3 mmol/l. Local synthesis of IgM was 75%. The cytocentrifuged and air-dried preparations from the CSF were stained with May-Grünwald-Giemsa. They presented predominately small

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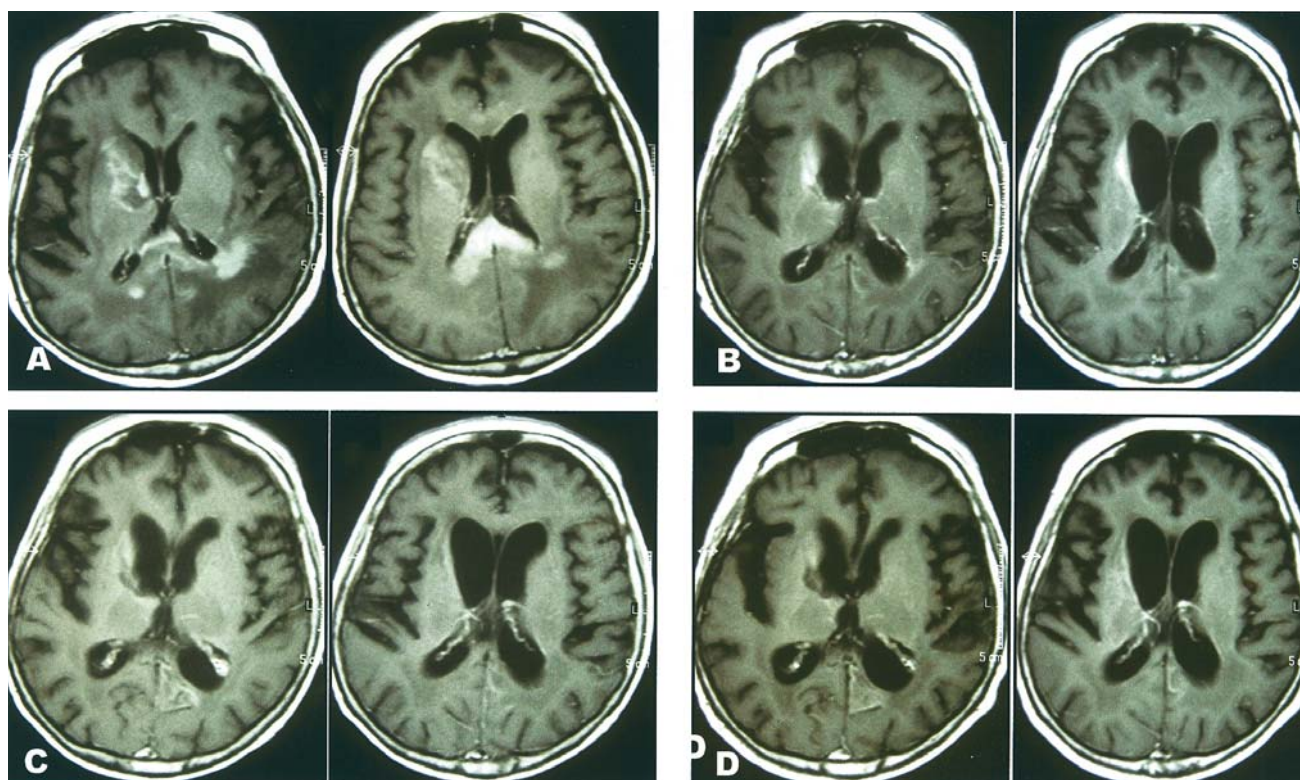


Figure 1. Transversal T1 (TR 429, TE 12)-weighted MRI. A: Gadolinium-enhanced tumor in the basal ganglia, splenium of the corpus callosum and around the peritrigonal white matter before therapy (July 2002). B: Regressive enhancement after one month of therapy with cortisone (August 2002). C: Only slight enhancement in the basal ganglia three months after treatment with cortisone and radiation therapy (October 2002). D: The finding remains stable two months after onset of chemotherapy with Temozolomide (January 2003).

lymphocytes and few monocytes. In addition to these background cells, a population of large, atypical lymphoid cells was intermingled, which were characterized by abundant pale basophilic cytoplasm and enlarged nuclei with prominent nuclear membrane irregularities and nuclear lobulations. The cytomorphological features combined with the CD20-positive immunophenotype were diagnostic for an intermediate grade large B-cell lymphoma (Figure 2).

In view of these results, the diagnosis of a cerebral lymphoma was accepted in our interdisciplinary tumor conference and brain biopsy considered unnecessary. No systemic manifestation was found by abdominal and thoracic CT, bone marrow aspirate and split-lamp examination of the eyes, leading to the diagnosis of a primary CNS lymphoma.

After administration of systemic high-dose cortisone, the patient's vigilance improved markedly. Because of myocardial infarction 3 months previously and a Karnofsky performance score of only 40%, no high-dose methotrexate therapy was administered. The CSF could be cleared from lymphoma cells with 4 times 80mg Ara-C intrathecally. The

patient underwent whole-brain radiation with 30 Gy in 10 fractions. During this therapy, her general condition and vigilance stabilized. The contrast medium enhancement in the MRI examination, especially in the basal ganglia and peritrigonally, regressed remarkably. Only a slight remnant enhancement in the basal ganglia on the right side was detectable. At discharge from the first clinical treatment in August 2002, she could walk for 10 meters with help, had only discrete hemiparesis and was oriented for her personal dates, but not in time and place. The Mini-Mental Status was 15/30.

At readmissions in October and November 2002, the patient's general condition was unchanged. In the Mini-Mental Status she still achieved not more than 16/30 points. Also the neuroradiological findings remained stable. In view of the lack of further improvement, an oral chemotherapy with Temozolomide was initiated with the informed consent of the patient's carer. A daily dose 200mg/m² was administered (320 mg total), but the course was restricted to four instead of the usual five days because of the patient's bad general condition. Two courses were given in an

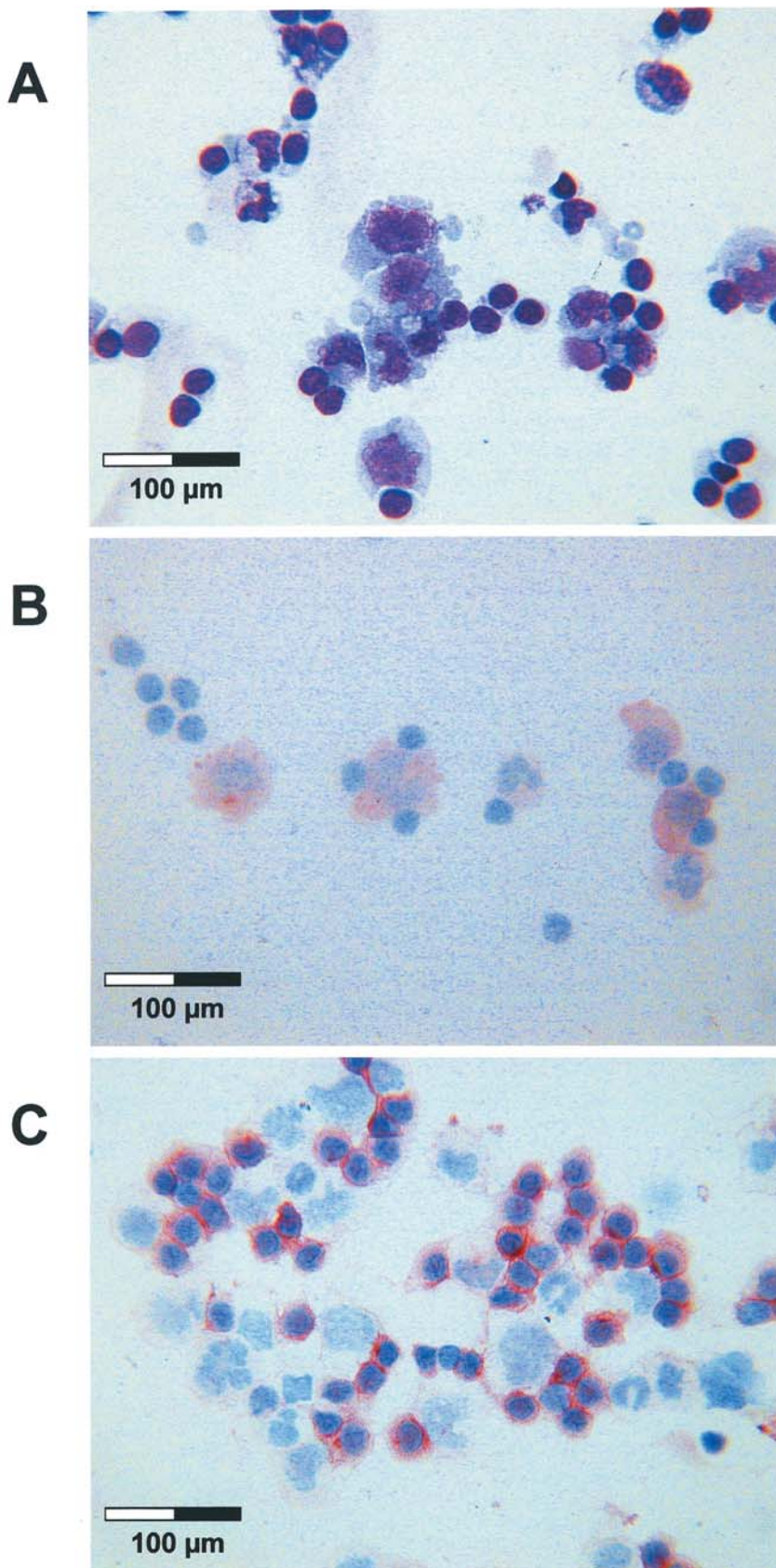


Figure 2. Large lymphoma cells with atypically lobulated nuclei in a background population of small lymphocytes (A; MGG, x 400). In contrast to the reactive small T-lymphocytes, the lymphoma cells are CD20-positive (B) and CD2-negative (C; APAAP, red labelling, x 400).

ambulant setting in November and December 2002 and tolerated without any complications. In January 2003, she was readmitted in markedly improved general and cognitive condition. She still lived in a nursing home and was dependent on help for daily activities. However, she could walk more than 30 meters without help. The Karnofsky performance status was estimated at 50%. Orientation was still not complete, but the Mini-Mental Status had improved to 27/30 points. Cranial MRI showed no signs of relapse. The CSF-cell count was elevated again to 23 cells/ μ l with some atypical, but no clearly malignant, cells. Therefore, one course of 80mg Ara-C was given intrathecally. The patient was discharged in stable condition and the next course of chemotherapy envisaged.

Unfortunately, the patient died unexpectedly at home shortly before the next course of chemotherapy without clinical signs of solid or meningeal relapse. Autopsy could not be achieved. Because of dyspnoea on the day before, pulmonary embolism was suspected as the cause of death.

Discussion

Primary central nervous system lymphoma (PCNSL) is characterized by rapid proliferation, frequent CSF involvement and early relapse (15). The overall survival could be improved markedly by the introduction of HD-MTX (5-7). There are, however, important limitations to the use of HD-MTX: chronic central nervous toxicity may lead to severely disabling encephalopathy in up to 30% of patients (9,10). As the combination of radiotherapy and chemotherapy increases the risk of chronic CNS toxicity, especially in elderly patients, some groups prefer to treat these patients with chemotherapy alone in first-line therapy (16). In addition, HD-MTX is also associated with considerable acute systemic toxicity affecting renal, cardiac and hematological functions, which endanger especially elderly patients with significant comorbidity (8). Therefore, both acute systemic and delayed CNS toxicity are substantial limitations to the recent developments in the treatment of PCNSL, especially in patients of older age. Moreover, HD-MTX treatment failed to be as effective as expected, at least in one series (17). Thus, there is a need for an alternative chemotherapy that is both efficient and well-tolerated in elderly patients.

The patient reported here improved after only two courses of Temozolomide chemotherapy, both in terms of general condition and cognitive functions. While her clinical status had remained largely unchanged for three months after radiotherapy, her independence on the ward and cognitive functions improved markedly after the onset of chemotherapy. No toxic side-effects were seen, despite the initial poor Karnofsky performance status of only 40%. The clinical course and the observations of the general

practitioner in care do not indicate that the tumor itself or treatment-related toxicity were the reason for death. As the patient complained about dyspnea on the previous day, repeated pulmonary embolism appears to be the most probable cause of death.

Good response to Temozolomide chemotherapy has already been reported in three patients with first-line therapy (13,14) and at relapse (12). Our report on the use of Temozolomide in an adjuvant setting after whole-brain radiation underlines previous reports that TMZ: i) is efficient in PCNSL, ii) can be tolerated by patients with reduced general condition, and iii) may improve both general condition and cognition in PCNSL patients. The clinical course in our patient indicates that the relevant improvement was associated with the application of TMZ chemotherapy. The clinical course and cytopathological examination were not suspicious of CSF relapse. The new elevation of the CSF-cell count, however, indicates that continuous CSF-monitoring was important and that the efficacy of TMZ on leptomeningeal seeding should be analysed thoroughly.

In conclusion, our experience is in line with other reports and indicates that TMZ chemotherapy can be administered safely and seems to be efficient in elderly patients who are not eligible for HD-MTX therapy. Long-term efficacy and delayed toxicity have yet to be evaluated in prospective studies, as well as the role and sequence of a combination of TMZ with radiotherapy.

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