Early complete response during chemotherapy predicts favorable outcome in patients with primary CNS lymphoma

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In primary central nervous system lymphoma (PCNSL), 2 international prognostic scores have been developed to estimate the outcome according to certain “prognostic groups”. However, these scores do not predict the individual course of a single patient under therapy. In this analysis, we addressed the question of whether early tumor remission in patients still under therapy, according to magnetic resonance imaging (MRI) criteria, helps to predict long-term outcome. Eighty-eight patients treated with 6 polychemotherapy cycles within a pilot/phase II trial underwent MRI scanning within 72 hours prior to initiation of therapy, after the second chemotherapy cycle, and after completion of chemotherapy. Response was assessed by contrast-enhanced MRI of the brain according to the Macdonald criteria. Median follow-up was 42 months (range, 0–124 months). Patients achieving a complete radiographic response after 2 courses of chemotherapy (n = 18) had a significantly longer median overall survival (OS) (not reached) and median time-to-treatment failure (TTF) (not reached) than patients with complete response (CR) after termination of treatment but with only a partial response after the second cycle (n = 24) (OS: 55 months; TTF: 32 months) (P < .01). Early complete tumor response assessed by MRI after the second of six scheduled chemotherapy cycles was highly predictive for both OS and TTF in patients with PCNSL treated in this series.

Keywords: chemotherapy, primary CNS lymphoma, prognosis.

Primary central nervous system lymphomas (PCNSLs) are highly malignant non-Hodgkin’s B-cell lymphomas restricted to the CNS. Prognosis of these tumors has been poor. However, combination chemotherapy and radiotherapy has extended median survival times up to 60 months.

It has been proposed that treatment response and survival depend on different prognostic factors. Validated prognostic factors are useful for stratification of patients in randomized trials and their knowledge is essential for critical comparison of treatment results within clinical trials. Moreover, attribution of patients to different risk groups may lead to more sophisticated and risk-tailored therapeutic strategies.

The 2 most important independent prognostic factors identified for PCNSL in immunocompetent individuals are age and performance status. Moreover, an elevated lactate dehydrogenase serum level, high protein concentration of the cerebrospinal fluid (CSF), and involvement of deep structures of the brain have been proposed to be independently associated with a worse
survival in a retrospective analysis and were included in a prognostic score suggested by the International Extranodal Lymphoma Study Group (IELSG).\textsuperscript{5} The Memorial Sloan-Kettering Cancer Centre (MSKCC) prognostic score\textsuperscript{6} comprises only age (<=50 years or older) and clinical performance status (Karnofsky performance score [KPS]<70 or above).

In this analysis, we addressed the question of whether early tumor remission, according to MRI criteria, in patients still under therapy would help to predict long-term outcome and would thereby provide a tool for early modification of therapy according to radiologic response. This question has not been addressed yet in PCNSL, whereas early decrease of tumor size assessed by MRI could be shown to be predictive for a good final response in other malignancies such as breast cancer.\textsuperscript{7,8} In systemic aggressive lymphomas early response assessment after 2–3 chemotherapy cycles with fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) has been shown to be as reliable as definite response assessment at the end of therapy.\textsuperscript{9} Progression-free and OS can be predicted with this method in systemic high-grade non-Hodgkin lymphoma.\textsuperscript{10}

We retrospectively analyzed tumor response assessed by MRI after 2 and after 6 courses of chemotherapy in a series of 88 immunocompetent patients with primary CNS lymphoma treated with 6 cycles of a combined systemic and intraventricular chemotherapy as previously published.\textsuperscript{11}

**Methods**

**Patients and Treatment**

Eighty-eight immunocompetent patients have been treated within a pilot/phase II trial evaluating a systemic and intraventricular chemotherapy ("Bonn protocol") after systemic lymphoma manifestation had been excluded by comprehensive staging according to the study protocol and in line with international guidelines.\textsuperscript{12} This included slit lamp examination as well as CSF analysis with cytopathology for leptomeningeal tumor involvement. Patients were immunocompetent and all gave written informed consent prior to inclusion in the study. The study has been approved by the local ethics committee. Treatment was based on systemic high-dose methotrexate and high-dose cytarabine in addition to vinca-alkaloids, alkylating agents, and dexamethasone. In addition, intraventricular application of methotrexate, cytarabine, and prednisolone via Ommaya reservoir was part of each therapy cycle.\textsuperscript{11}

**MRI**

Each patient underwent an MRI scan within 72 hours prior to initiation of therapy, after the second chemotherapy cycle, and after completion of chemotherapy. MRI was performed on a 0.5 T (Gyrosan T5) or a 1.5 T scanner (Gyrosan ACS-NT, Philips Medical Systems). All patients were studied with a standardized protocol including sagittal T1-weighted spin echo (slice thickness of 5 mm/interslice gap of 0.5 mm), axial T2-weighted fast spin echo (5/1), coronal FLAIR (5/1), and axial T1-weighted spin echo (5/1) before and following Gd-DTPA injection. If contrast enhancement was observed on the axial slices, sagittal and coronal T1-weighted spin echo sequences followed.

**MRI Response Evaluation**

According to the study protocol, response was assessed by contrast enhanced MRI of the brain after the second and sixth chemotherapy cycles. Complete response was defined as disappearance of all enhancing lesions on MRI of the brain in patients being off steroids, partial response (PR) as a reduction of enhancing tumor volume by more than 50%, progressive disease (PD) as increase of tumor volume of more than 25% or occurrence of new lesions and stable disease (SD) as any other situation.\textsuperscript{12} Treatment failure was defined as PD or SD, relapse after initial response, death, or discontinuation of chemotherapy due to any cause. All patients were observed every 4 months within the first year after therapy and every 6 months thereafter. Follow-up consisted of neurologic examination, MRI, CSF examination, and ophthalmologic evaluation.

For this analysis, only responding patients were considered and divided into 3 MRI response categories: Response category 1: patients with a radiographic CR after the second treatment cycle; 2: patients with a PR after the second treatment cycle and a CR after termination of treatment; 3: patients with a PR after the second and sixth cycles.

The predefined primary endpoint of the formal therapy trial was time-to-treatment failure (TTF), which was defined as time from onset of treatment to disease progression or relapse, death from any cause, discontinuation of treatment as a result of any cause, or last date of follow-up. A secondary endpoint of the trial and the endpoint in this analysis with respect to radiological response was OS. OS was calculated from the date of histological diagnosis to death or date of last follow-up. Relapse or progression was defined as growth or regrowth of tumor at any site within or outside the CNS. TTF and OS were estimated by the Kaplan–Meier method. Log-rank tests were used to compare TTF and OS between patient groups.

Two common prognostic scores, the prognostic scoring system for primary CNS lymphomas established by the IELSG\textsuperscript{5} and the MSKCC prognostic score\textsuperscript{6} were used to verify that patients outcome according to different MRI response categories was not influenced by established prognostic factors. Using Pearson’s chi-square test the distribution to the prognostic classes was tested.

**Results**

**Patient Characteristics**

Eighty-eight patients from 4 centers were accrued. Median follow-up was 42 months (range, 0–124
months), median age was 62 years (range, 26–75 years), and the median KPS was 70 (range, 20–100). Further characteristics of patients, surgical procedures, and neuropathology are listed in Table 1. Results of CSF analysis were documented in 78 patients with detection of lymphoma cells within the CSF in 7 of those (9%). Though ocular involvement has been found in 4/86 patients (5%) at relapse, ocular lymphoma could not be detected in any of the patients of this series at presentation despite thorough ophthalmological investigation.

**Treatment Response**

In 4 of 88 patients, response to chemotherapy could not be determined because of complete tumor resection before chemotherapy (n = 2) and because of treatment termination after 1 cycle due to the patient’s (n = 1) or participating center’s decision (n = 1, protocol violation). Therefore, 84 of 88 patients were assessable for response. After completion of therapy 46 patients (54%) achieved CR, 12 (15%) PR and 14 (17%) progressed under therapy. In 5 (6%) of 84 patients therapy had to be discontinued due to severe treatment-related complications. Seven (8%) of 88 patients suffered treatment-related early death. In the analysis presented here, only patients of MRI response category 1–3, as defined above, were evaluable. Of these 53 patients, 42 (79%) achieved a CR after completion of therapy; 11 (21%) achieved a PR. Five responding patients from the study population had to be excluded from the analysis due to missing MRI data after the second treatment course.

**MRI Response Evaluation**

Eighteen patients showed a CR after the second treatment cycle (response category 1), 24 patients achieved a PR after the second cycle but CR after completion of treatment (response category 2). Eleven had a PR after the second cycle and after completion of treatment as well (response category 3).

**Prognostic Impact of MRI Response Assessment**

Median TTF was not reached for patients of response category 1. In contrast, patients of response category 2 had a median TTF of 32 months. This difference was statistically significant (P < .01) (see Fig. 1). Median TTF of patients of response category 3 was 10 months. The difference between groups 2 and 3 was not statistically significant.

Median OS was not reached for patients of response category 1. For both, response category 2 and 3 median OS was 55 months each. The difference of OS between patients of category 1 and 2 was not statistically significant (P < .01).

Patients of each response category were assigned to an individual prognostic score, both according to the IELSG and the MSKCC prognostic model. The IELSG score could be obtained for 37 of 53 evaluable patients; for 16 patients documentation of parameters necessary to assign patients to this prognostic score was incomplete. The MSKCC-prognostic score could be assigned to 48 of 53 patients. The chi-square test was used to compare the distribution of the prognostic scores between the MRI classes. No difference in distribution
between the prognostic groups was found for patients of MRI response categories 1–3 (IELSG $P = .72$; MSKCC $P = .11$). The distribution of MSKCC prognostic scores to patients of different MRI response categories is shown in Table 2. No correlation between the presence or absence of leptomeningeal disease as detected by CSF cytology could be demonstrated, probably due to the low percentage of positive cases.

### Discussion

Reliable prognostic factors and scores are useful for comparison of treatment results in clinical trials. Two analyses have resulted in prognostic scores in PCNSL: the IELSG Score\(^5\) and the MSKCC prognostic score.\(^6\) While both prognostic models are useful in defining stratification criteria for clinical trials, for comparison of treatment results and for an outcome estimate within a certain “prognostic group,” they are not able to predict the individual course of a single given patient while under therapy. Treatment protocols of patients with PCNSL are demanding and harbor the risk of therapy-related immediate\(^1\),\(^2\),\(^3\) and late\(^4\),\(^5\) toxicity. The role of high-dose chemotherapy regimens\(^1\),\(^5\),\(^6\) and of complex multimodal regimens\(^7\) is currently evaluated. Therefore, it is desirable to identify non-responders to conventional therapy at an early stage of treatment in order to potentially escalate treatment strategies early.

MRI is the standard neuroimaging method of treatment response evaluation in PCNSL.\(^8\) However, assessment of early treatment response with MRI does not allow early prediction of outcome in high-grade glioma.\(^9\) In contrast, early change of breast cancer tumor size, assessed by MRI measurements has been shown to be highly predictive for the final response.\(^7\),\(^8\)

In osteosarcoma increase of tumor volume assessed by MRI could be shown to correlate with poor survival, whereas MRI was not helpful in the early identification of good responders.\(^1\)\(^9\) In systemic aggressive non-Hodgkin lymphoma, MRI is not the standard imaging technique; however, early interim FDG-PET could be shown to be an independent predictor of progression-free and OS in this tumor entity.\(^1\)\(^0\)

The present analysis demonstrates that early CR of PCNSL after 2 treatment courses of an MTX-based polychemotherapy is a strong and independent prognostic factor. In case of incomplete response, the chance of cure was low in this series. However, even complete responders after termination of therapy, but with only a PR after 2 cycles of therapy harbored an equally high risk of early tumor recurrence, such that the OS of these patients was not superior to those with partial tumor remission after the completion of treatment.

It has to be taken into account that this is a retrospective analysis on a limited number of patients treated with a homogeneous regimen and with 1 modality only, that is chemotherapy. However, it may be concluded that patients without an early CR to MTX-based polychemotherapy without radiotherapy, even if having reached CR after completion of treatment, have to be monitored closely after treatment for possible early relapse. While Table 2 suggests a non-significant trend for patients with good prognosis according to the MSKCC prognostic score to experience a durable remission after the completion of treatment.

### References


