Long-Term Survival Following Radiotherapy and Cytarabine Chemotherapy for Sporadic Primary Central Nervous System Lymphoma

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Purpose: To analyze the long-term results following whole brain radiotherapy (WBRT) with sequential intrathecal (i.th.) cytosine arabinoside (Ara-C) ± intravenous (i.v.) Ara-C in patients with primary central nervous system lymphoma (PCNSL).
Patients and Methods: 14 patients were treated between July 1987 and August 1995. All had sporadic PCNSL with proven histology of high-grade CNS lymphoma (twelve diffuse large-cell B-lymphomas, one lymphoblastic lymphoma, one large T-cell lymphoma). Patients were treated with two to four cycles of induction chemotherapy (40 mg/m^2 Ara-C i.th.), four patients received additional Ara-C i.v. (150 mg/m^2, d1–4). WBRT was administered using 1.8-Gy fractions. Intrathecal chemotherapy was planned afterwards in 4-week intervals for 6 months. Posttreatment neurocognitive evaluations were performed in two long-term survivors.
Results: Two of four patients who received i.v. and i.th. induction chemotherapy showed progressive disease, and irradiation was started immediately. Six of 14 patients received 50.4 Gy WBRT, four patients had WBRT up to 39.6 Gy followed by a 10.8-Gy boost. Five patients died early during therapy either due to a decline of the general medical condition or progressive disease. Median survival was 41 months (95% confidence interval: 6–79 months), survival at 3 and 5 years was 59% and 42%, respectively. Six patients survived for 3 years, two younger patients are still alive (> 12 years). They show only slightly impaired neurocognitive functions without clinical relevance.
Conclusion: This WBRT-based protocol with i.th. meningeal prophylaxis using Ara-C ± i.v. Ara-C yields substantial long-term survival with moderate toxicity. The value of i.v. chemotherapy is currently being investigated in prospective studies.

Key Words: Primary CNS lymphoma · Whole brain radiotherapy · Cytosine arabinoside

Langzeitüberleben von Patienten mit malignem zerebralem Lymphom nach kombinierter Radiotherapie und Ara-C-Gabe

Ziel: Analyse der Langzeitergebnisse von Patienten mit primären ZNS-Lymphomen nach Ganzhirnbestrahlung (WBRT) mit intrathekaler (i.th.) ± intravenöser (i.v.) Cytosinarabinosid-(Ara-C-)Gabe.
Patienten und Methodik: 14 Patienten wurden zwischen Juli 1987 und August 1995 behandelt. Alle Patienten hatten ein histologisch gesichertes hochgradig malignes ZNS-Lymphom (zwölf diffuse großzellige B-Zell-Lymphome, ein lymphoblastisches Lymphom, ein anaplastisches Ki1-Lymphom). Die Induktionstherapie bestand aus zwei bis vier Zyklen i.th. Ara-C-Gabe (40 mg/m^2), vier Patienten erhielten parallel eine i.v. Ara-C-Applikation (150 mg/m^2, d1–4). Anschließend erfolgte eine WBRT mit 50,4 Gy (1,8 Gy/Fraktion) bzw. WBRT bis 39,6 Gy, gefolgt von kleinvolumiger Dosiserhöhung in der Lymphomregion bis 50 Gy. Die Behandlung wurde dann mit i.th. Ara-C-Chemotherapie in 4-wöchigen Intervallen fortgesetzt. Bei zwei langzeitüberlebenden Patienten wurden posttherapeutische neurokognitive Funktionsprüfungen durchgeführt.
Ergebnisse: Vier Patienten erhielten i.v. und i.th. Induktionschemotherapie; zwei von ihnen zeigten eine Progression und wurden unverzüglich der Strahlentherapie zugeführt. Sechs von 14 Patienten erhielten 50,4 Gy als WBRT, vier Patienten erhielten

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nach 39,6 Gy WBRT einen Boost mit 10,8 Gy. Fünf Frühtodesfälle während der Therapie waren auf eine Verschlechterung des Allgemeinzustandes oder Krankheitsprogression zurückzuführen, ein Patient verstarb interkurrent an einer Pneumonie. Das mediane Überleben betrug 41 Monate (95%-Konfidenzintervall: 6–79 Monate), die Überlebenswahrscheinlichkeit nach 3 und 5 Jahren lag bei 59% und 42%. Sechs Patienten lebten länger als 3 Jahre, zwei jüngere Patienten leben noch (> 12 Jahre). Beide zeigen nur leichte Einschränkungen der neurokognitiven Fähigkeiten ohne klinische Relevanz.
Schlussfolgerung: Mit einer kombinierten Radiochemotherapie kann in diesem Patientenkollektiv Langzeitüberleben mit moderater Toxizität erzielt werden. Die Wertigkeit der i.v. Chemotherapie wird derzeit prospektiv untersucht.

Schlüsselwörter: Primäres ZNS-Lymphom · Ganzhirnbestrahlung · Cytosinarabinosid

Introduction

Primary sporadic central nervous system lymphoma (PCNSL) is a rare neoplasm, but the incidence has increased significantly within the past 2 decades [14]. Brain lymphomas are, according to their clinical behavior, aggressive and morphologically in the vast majority diffuse polymorphous large-cell lymphomas, though other B-cell subtypes and rare lymphomas such as Ki1 lymphomas of T-cell origin have been described [10, 24, 29].

Whole brain radiotherapy (WBRT) in combination with corticosteroids alone was the mainstay of therapy for patients with primary brain lymphoma for a long time. However, even with radiotherapy up to high total tumor doses of 50–60 Gy, local control rates and survival are poor [27]. In the RTOG 8315 study, local cerebral relapses were observed in 61% of patients with PCNSL and negative cerebrospinal fluid (CSF) cytology within a limited follow-up time. Patients received 40 Gy WBRT followed by 20 Gy boost to the contrast-enhancing lesions plus a 2-cm margin given with 1.8 Gy per fraction, five fractions per week [35, 36]. Murray et al. [34] found 21 survivors out of 693 PCNSL patients with a follow-up > 5 years, mainly treated with radiotherapy alone in the period between 1964 and 1984. In a more recent review, survival at 5 years was estimated to be 17% after WBRT with total doses > 40 Gy [41].

Leptomeningeal involvement was found in considerable percentages between 10–42% of patients with primary cerebral lymphomas at the time of diagnosis in several large series [2, 8, 34, 41]. The study by Balmaceda et al. [2] with a high proportion of CSF examinations at the start of therapy as well as at the time of recurrence showed that leptomeningeal relapse, with 41%, was quite common and that meningeal recurrence was reduced in patients who received treatment that included the leptomeninges. A high risk of meningeal relapse was also found in other series, but with lower proportion of CSF examinations at diagnosis [13, 38].

We report the long-term results of thoroughly staged PCNSL patients receiving intrathecal (i.th.) cytosine arabinoside (Ara-C) as prophylactic treatment for leptomeningeal lymphoma spread before and after high-dose WBRT with or without intravenous (i.v.) systemic Ara-C administration prior to radiotherapy.

Patients and Methods

All patients were recruited between July 1987 and August 1995 at the Department of Radiotherapy, University Clinic Essen, Germany, according to protocol guidelines initially planned for a randomized multicenter study. In one treatment arm, patients should receive combined i.v. and i.th. Ara-C induction chemotherapy prior to WBRT followed by i.th. Ara-C. Patients in the other treatment arm were planned to receive i.th. Ara-C and WBRT alone. Only patients with histologically proven PCNSL without systemic manifestations and a Karnofsky index ≥ 40% were included. Patients with CSF positive for lymphoma cells were eligible.

All were immunocompetent and had no clinical evidence of HIV infection nor did they test HIV-1-positive. Patients were randomized centrally to initial treatment with i.v. and i.th. versus i.th. chemotherapy alone. Due to slow patient entry and with seven of eight patients being from the same institution, the randomization was terminated in December 1989. At that time, four patients had been randomized to i.v./i.th. Ara-C induction chemotherapy. Afterwards, patients were treated according to protocol guidelines as a monocentric prospective study on i.th. Ara-C and WBRT alone. All patients had given written informed consent.

Staging Procedures

All patients had contrast-enhanced CT scans of the brain. Original histology after resection (n = 5) or stereotactic biopsy (n = 9) was reexamined in 1996. Among the 14 patients, twelve diffuse large-cell B-lymphomas were diagnosed, one lymphoblastic B-cell lymphoma, and one anaplastic large-cell Ki1 lymphoma. All tumors were reviewed at the Department of Neuropathology (K.S.) or diagnosed at the German Lymph-Node Registry in Kiel (H.-H.W.). The Ki1 lymphoma showed expression of CD30 and, furthermore, partial expression of the T-cell antigen CD3 as well as ALK1. Immunohistochemical stainings for B-cell-associated antigens remained negative.

Further investigations included cytospin evaluation of CSF, ophthalmologic examination (split lamp), CT of thoracic and abdominal organs, complete blood cell counts, lactate dehydrogenase (LDH), immunoelectrophoresis and protein electrophoresis, and bone marrow biopsy.

Treatment Schedule

Meningeal prophylaxis with Ara-C was given i.th. (40 mg/m^2, administered either via lumbar puncture or Ommaya reservoir) 5 days and 1 day before the start of WBRT. The clinical target volume (CTV) comprised the whole neurocranium extended to the inferior border of the second cervical vertebra. The posterior half of the orbit was included in the CTV. A safety margin of 0.5 cm was added for setup uncertainties (planning target volume, PTV). Two isocentric opposing lateral fields were used to cover the entire PTV. Critical structures were shielded with individual blocks. All patients were treated daily with megavolt irradiation using either a ^{60}Co source or a linear accelerator. The dose was prescribed at isocenter depth. Fraction size was 1.8 Gy. The planned total dose was 50.4 Gy. In accordance with other reports [15], WBRT was limited to a dose of 39.6 Gy during the later study period. Thereafter, irradiation of the tumor region was continued with shrinking portals (boost), which enclosed the macroscopic tumor region plus a safety margin of 2 cm. Nevertheless, a total dose of 50.4 Gy for the boost volume was planned.

Following WBRT, chemotherapy was continued i.th. (40 mg/m^2) every 4 weeks for up to six cycles.

Those patients, who were randomized to systemic i.v. Ara-C, were planned to additionally receive four cycles of Ara-C (150 mg/m^2 i.v., d1–4, q3wk) before the start of WBRT on day 56.

Follow-Up

After treatment completion, a routine follow-up including physical examination and contrast CT or MRI, respectively, was performed. Long-term survivors were followed up with neuropsychologic testing. Global intellectual functions were assessed with subtests of the Adult Wechsler Intelligence Scale. Memory was assessed with age-scaled scores for logical memory and paired associate learning. Working memory, attention, and concentration were evaluated with the Wechsler Digit Span Test. Visual memory was tested with the Benton Visual Retention Test, attentional function with the Trail Making Test. Perceptual discrimination and information-processing abilities were tested with a Divided Attention Test [4]. These tests were completed with an adapted version of a Thurstone Cognitive Ability Test [28, 30].

Statistical Analysis

All statistics were done using the SAS software package (SAS Inc., Calgary, Canada). Follow-up and survival were calculated from the time of first diagnosis to the date of this evaluation (September 1, 2001). Survival estimates were calculated according to the Kaplan-Meier method. Intercurrent deaths or patients who were lost to follow-up were censored.

Results

Between July 1987 and August 1995, 14 patients were treated according to protocol guidelines. Five more patients with PCNSL were treated during the same time interval with WBRT alone. These patients were not eligible for this study due to limited Karnofsky index. They received 50 Gy WBRT (two patients), 40 Gy WBRT plus a 10-Gy boost (two patients), and 56 Gy (WBRT, one patient), respectively. Median survival was 3 months, all patients died within 1 year.

Table 1. Patient characteristics. CR: complete remission; F: female; KPS: Karnofsky performance scale; M: male; na: not available; NED: no evidence of disease; PD loc: progressive disease locally; PD sys: systemic progressive disease; PR: partial remission.

Tabelle 1. Patientencharakteristik. CR: komplette Remission; F: weiblich; KPS: Karnofsky performance scale; M: männlich; na: nicht untersucht; NED: kein Anhalt für Rezidiv; PD loc: lokale Krankheitsprogression; PD sys: systemische Krankheitsprogression; PR: partielle Remission.

Pat. no.	Sex	Age (years)	KPS (%)	Surgical procedure	Histology	Radiotherapy dose (Gy)	Post-radiotherapy Ara-C (cycles)	Initial response to treatment chemo-/radiotherapy)	Survival (months)	Time to disease progression (months)
1	F	44	100	Resection	Diffuse large-cell B-lymphoma	50.4	1	CR	24	Intercurrent death
2	M	20	90	Resection	Ki1 lymphoma	50.4	2	CR	146+	NED
3	M	29	90	Biopsy	Diffuse large-cell B-lymphoma	50.4	4	CR	162+	NED
4	F	63	90	Biopsy	Diffuse large-cell B-lymphoma	50.0	5	CR	41	40
5	F	65	90	Biopsy	Diffuse large-cell B-lymphoma	50.0	3	CR	65	na
6	M	66	90	Biopsy	Regressive malignant lymphoma	49.8	–	PD sys	2	2
7	M	38	80	Biopsy	Diffuse large-cell B-lymphoma	50.4	2	CR	39	39
8	F	64	80	Biopsy	Regressive malignant lymphoma	50.0	2	CR	47	43
9	F	73	80	Resection	Diffuse large-cell B-lymphoma	24.0	–	PR	2	Intercurrent death
10	M	56	50	Resection	Diffuse large-cell B-lymphoma	30.6	–	na	1	Intercurrent death
11	F	57	50	Resection	Diffuse large-cell B-lymphoma	50.0	6	CR	79	78
12	F	59	50	Biopsy	Diffuse large-cell B-lymphoma	23.4	–	PD loc	3	1
13	F	75	50	Biopsy	Diffuse large-cell B-lymphoma	50.0	1	PD loc	3	3
14	M	53	40	Biopsy	Diffuse large-cell B-lymphoma	39.6	–	PR	3	3

Patient characteristics of the study cohort are shown in Table 1. Median follow-up was 129 months (range 69–166 months). Four patients received i.v. and i.th. induction chemotherapy with Ara-C. Two of these patients showed intracerebral tumor progression after one and two cycles, respectively, and passed over to WBRT. The other two completed the planned four cycles. Acute toxicity of i.v. Ara-C was low, one episode of leukocytopenia grade IV was observed during eleven chemotherapy cycles.

All patients received i.th. Ara-C according to protocol guidelines and proceeded to radiotherapy. Ten patients received the planned total tumor dose of 50.4 Gy, six patients had WBRT up to 50.4 Gy, four patients had WBRT up to 39.6 Gy and received a boost of 10.8 Gy in the macroscopic tumor region.

Radiotherapy was stopped in four patients (between 23.4–39.6 Gy). In two patients, treatment disruption was necessary due to deterioration of their general medical condition (in one patient proven to be related to tumor progression). Furthermore, one patient developed a severe pneumonia and died subsequently (see Table 1, patient no. 9), one other patient (no. 10) died following a status epilepticus.

Nine patients received at least one cycle i.th. Ara-C after completion of WBRT (three patients had two cycles each, four patients had three or more cycles). During the first 3 months after WBRT, two early deaths were observed: one patient (no. 6) had a pronounced systemic disease progression as diagnosed by CT, for the other (no. 13) a decline in general condition was reported by the private practitioner, but the patient did not return to this center.

The median survival of the entire cohort was 41 months (95% confidence interval [CI]: 6–79 months, Figure 1). The survival rates at 2 and 3 years were 59% (95% CI: 31–87%), and at 5 years 42% (95% CI: 14–70%), respectively. In those patients, who received i.th. chemotherapy alone, median survival amounted to 39 months (95% CI: 3–65 months) with survival rates at 2 and 3 years of 51% (95% CI: 33–69%) and 38% (95% CI: 21–55%). The median time to progression in this patient group was 13.5 months (95% CI: 2–43 months).

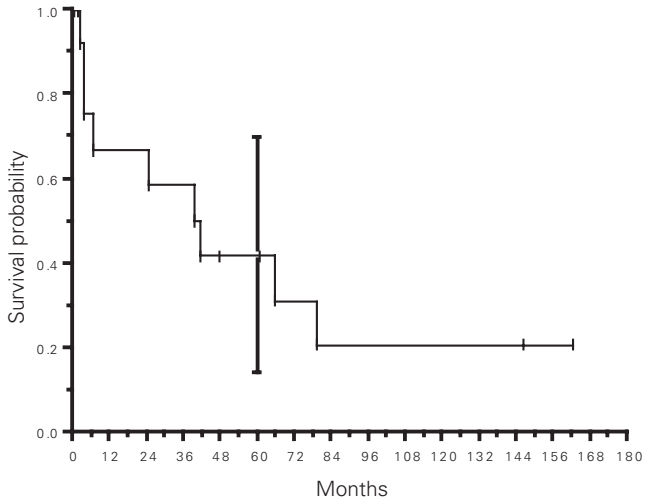

Figure 1. Overall survival (the bar presents the 95% confidence interval, tick marks represent censored events).

Abbildung 1. . Gesamtüberleben (der Balken zeigt das 95%-Konfidenzintervall, Striche markieren zensierte Ereignisse).

Despite the small number of patients, exploratory multivariate analysis with the factors age, Karnofsky index, sex, and i.v. Ara-C revealed age as the most important prognostic factor ($p = 0.02$).

Eight patients survived for 2 years, six patients died between 24 and 79 months, two patients are still alive.

Causes of Death

Progressive disease leading to death was observed in three cases during or early after completion of therapy, one of these patients had generalized disease manifestations at autopsy. Six late deaths were noted, 23–79 months after therapy. Four patients died intercurrently or without known disease-specific cause, the two others had documented disease relapse. In one patient (no. 8), ocular disease was the first site of relapse (43 months after therapy), followed by meningeal and cerebral involvement. The other patient (no. 4) had recurrent disease in the basal ganglia (41 months after therapy).

Neurocognitive Toxicity

Six patients survived for 3 years and were evaluable for late complications. Four patients maintained their pretreatment social and professional activities with a stable performance scale, until two of these suffered from recurrent disease. The other two patients from the long-term survivors experienced severe late neurologic complications. One patient (no. 5), being 65 years old at the time of diagnosis with a Karnofsky index of 90%, developed dementia and ataxia 17 months after therapy. She had WBRT up to 50.4 Gy combined with i.th. Ara-C before and after radiotherapy. Despite the need for custodial care, she survived the following 4 years. Another patient (no. 11) experienced bilateral visual loss at 20 (right eye) and 24 months (left eye) after therapy. She was 63 years old at the time of diagnosis and had four cycles of i.v. chemotherapy as well as pre- and post-radiotherapy i.th. Ara-C and WBRT with 50.4 Gy. Visual acuity was restrained to dark and light only (right eye) and finger counting (left eye). She later developed urinary incontinence and, finally, somnolence, but survived for 79 months. Unfortunately, CT scans were not available.

Formal neurocognitive testing was performed on two patients who survived for > 12 years (nos. 2 and 3). Both were < 30 years at the time of diagnosis. Both received WBRT with 50.4 Gy, i.th. Ara-C pre- and post-radiotherapy; one of them additionally received four cycles of i.v. induction chemotherapy. MRI scans showed no signs of leukoencephalopathy nor signs of local recurrence. Both patients are fully working. One

complained of memory difficulties and needed written notes during his daily routine and professional activity (no. 2). This patient who had the T-cell lymphoma showed impairments concerning verbal learning, visual reproduction, and memory (34.5 percentile). The speed of information processing was reduced (34 percentile). Nevertheless, the neurocognitive impairments were of slight to intermediate degree (average: > 50 percentile, speech-free I.Q.: 87). The other patient (no. 3) achieved completely normal results in all tests (visual reproduction and memory: 86.4 percentile, information processing: 46 percentile, speech-free I.Q.: 107). This patient had a large-cell B-lymphoma. Both patients could fully compensate treatment-related impairments, and daily activities of social and professional life were not affected by late neurologic toxicities.

Discussion

Studies on induction chemotherapy containing blood-brain barrier-crossing drugs, i.e., high-dose methotrexate (MTX), followed by WBRT with or without post-radiotherapy i.v. Ara-C repeatedly achieved long-term survival rates of > 40% at 3 years and > 25% at 5 years [1, 5, 7, 9, 20, 46]. Established patient-dependent prognostic factors like age and perfomance status [8, 13, 23, 31, 36, 41, 42, 45] can profoundly influence the treatment results and may even dominate differences in efficacy between alternative treatment options. However, a large exploratory retrospective study by Blay et al. [8] showed a survival improvement after treatment with high-dose MTX-based regimens in addition to radiotherapy. This was supported by a literature review of Reni et al. [41], who found that high-dose MTX and additional i.th. chemotherapy were independent prognostic factors in multivariate analysis.

The present study with i.th. Ara-C with or without pre-radiotherapy i.v. Ara-C showed efficacy and achieved favorable results with survival rates of 59% at 3 years and 42% at 5 years, respectively. The response rate to induction i.v. Ara-C, however, seems to be worse than those observed with modern high-dose MTX-based regimens [11, 12, 18, 37, 42]. One of the long-term survivors in our series had a PCNSL of T-cell origin, which due to its rarity is much less well defined than B-cell lymphomas. Gijtenbeek et al. [19] discussed two patients, who both achieved complete response after MTX, WBRT, and high-dose Ara-C but relapsed early and died. Here, we report a patient in whom the anaplastic grade was initially confirmed and who is cured after follow-up of 12 years.

The ultimate aim of treatment optimization for primary cerebral lymphoma is to increase the chance of long-term survival without severe neurocognitive side effects. Data on neurologic functioning of long-term PCNSL survivors after radiotherapy without chemotherapy are sparse. Corry et al. [13] reported on four out of 33 patients who died with dementia after radiotherapy alone. More detailed data are available from prospective studies on radiochemotherapy for PCNSL. Abrey et al. [1] reported a very high incidence of late neurologic toxicity after pre-radiotherapy MTX followed by WBRT and high-dose Ara-C. Age was a major risk factor for treatment-related neurotoxicity with cumulative risks of 60% and 100% at 2 and 5 years for patients > 60 years. O'Neill et al. [38] observed higher incidences of neuromotor toxicity in patients > 60 years after CHOP and WBRT followed by Ara-C-based combination chemotherapy. Shibamoto et al. [47] treated ten patients with WBRT followed by CHOP. Two patients developed brain necrosis and two became bedridden without signs of tumor recurrence. Blay et al. [8] reported on twelve of 221 patients after radiotherapy with or without chemotherapy who experienced late neurotoxicity. All had dementia, more than one half of them gait disturbances. Multivariate analysis revealed that chemotherapy after irradation increased the risk of late neurotoxicity significantly in comparison to irradiation alone or chemotherapy followed by irradiation. In a recent investigation [43], patients treated solely with a high-dose MTX-containing regimen were prospectively followed up with formal neuropsychologic assessment. Despite the renunciation of radiotherapy, the two oldest out of 14 patients developed severe leukoencephalopathy. In patients who were treated with CHOD/BVAM followed by WBRT, dementia occurred in five (62%) of eight patients being ≥ 60 years [5]. Herrlinger et al. [25] examined 15 patients who received combined-modality treatment (twelve patients) or radiotherapy alone (three patients). The patients with WBRT alone (age 70–81 years) had severe neuropsychologic deficits with the need for intensive nursing care. Following combined-modality therapy, seven patients (58%) had severe neuropsychologic deficits requiring continuous support in daily life. The experiences from the present study agree with the aforementioned reports, that long-term survivors from PCNSL > 60 years have a considerable risk of late neurologic toxicity after regimens with WBRT to doses ≥ 40 Gy. The question whether i.th. Ara-C increases the risk of late neurologic damage in comparison with radiotherapy alone cannot be answered satisfactorily due to the low number of long-term survivors. The risk of developing bilateral blindness, as observed in one patient, is rather low after irradiation alone up to 50.4 Gy with conventional fractionation [22, 36, 40, 44], and therefore an additional toxicity of Ara-C has to be suspected. It is crucial to discriminate neurologic side effects from late recurrences during follow-up. The latency times to expression of neurologic side effects are in the range of 24–30 months for older patients and may take > 5 years in patients < 60 years [1, 8, 48]. In order to reduce the risk of neurotoxicity for protocols containing full-dose radiotherapy, studies have been started with chemotherapy alone. The rates of complete remissions, observed in several studies with high-dose MTX-containing regimens alone are in the range of 60–90% with a rather low risk of late neurotoxicity after chemotherapy alone, especially in older patients [11, 12, 18, 37, 42]. However, long-term tumor control rates are not completely satisfying with 13–53%. An ongoing phase II trial of high-dose MTX with deferred radiotherapy has been compromised by a disease progression rate of 28% (4/14 patients) [3].

A German multicenter study (NOA-3) has been closed early, because high-dose MTX alone was not able to induce the expected rate of complete remissions [26].

We agree, that future strategies should aim at optimized chemotherapy and a more selective use of radiotherapy depending on certain patient and tumor risk factors. In order to clarify the role of WBRT in PCNSL, the Neuro-Oncologic Working Party of the German Cancer Society has set up a phase III study on high-dose MTX with or without WBRT after complete remission. However, it remains unclear whether it is justified to reserve WBRT for patients with overt recurrence after complete response to initial chemotherapy. As, especially in younger patients, toxicity of radiotherapy is mild, moderate doses of radiotherapy might optimize the therapeutic benefit in PCNSL patients with complete response to chemotherapy, as it has been recently demonstrated in extracerebral lymphomas [17, 21, 33, 39]. Up to now, intrathecal chemotherapy has not found a defined role in the primary treatment of PCNSL [16]. This is in part due to the increased risk of severe neurotoxicity, especially when combined with WBRT, and the lack of a prospective assessment of its survival effect. According to the present investigation, good long-term results can be obtained with schedules primarily based on WBRT with additional meningeal prophylaxis using i.th. Ara-C. The proven efficacy and moderate toxicity of radiotherapy in younger patients should guarantee radiotherapy a firm place in modern multimodal treatment protocols for PCNSL.

References

1. Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. J Clin Oncol 1998;16:859–63.
2. Balmaceda C, Gaynor JJ, Sun M, et al. Leptomeningeal tumor in primary central nervous system lymphoma: recognition, significance, and implications. Ann Neurol 1995;38:202–9.
3. Batchelor TT, Hochberg F, O'Neill A, et al. The treatment of primary central nervous system lymphoma (PCNSL) with methotrexate and deferred radiotherapy: NABTT 96-07. Proc Am Soc Clin Oncol 2000;19:616.abstract.
4. Becker M, Sturm W, Willmes K, et al. Normierungsstudie zur Aufmerksamkeitstestbatterie (TAP) von Zimmermann und Fimm. Z Neuropsychol 1996: 7:3–15.
5. Bessell EM, Graus F, Lopez-Guillermo A, et al. CHOD/BVAM regimen plus radiotherapy in patients with primary CNS non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 2001;50:457–64.
6. Bessel EM, Graus F, Punt JAG, et al. Primary non-Hodgkin's lymphoma of the CNS treated with BVM or CHOD/BVAM chemotherapy before radiotherapy. J Clin Oncol 1996;14:945–54.
7. Blay JY, Bouhour D, Carrie C, et al. The C5R Protocol: a regimen of high-dose chemotherapy and radiotherapy in primary cerebral non-Hodgkin's lymphoma of patients with no known cause of immunosuppression. Blood 1995;86:2922–9.
8. 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 study. J Clin Oncol 1998;16: 864–71.
9. Brada M, Hjiyiannakis D, Hines F, et al. Short intense primary chemotherapy and radiotherapy in sporadic primary CNS lymphoma. Int J Radiat Oncol Biol Phys 1998;40:1157–62.
10. Braus DF, Schwechheimer K, Müller-Hermelink HK, et al. Primary cerebral malignant non-Hodgkin's lymphomas: a retrospective clinical study. J Neurol 1992;239:117–24.
11. Cheng AL, Yeh KH, Uen WC, et al. Systemic chemotherapy alone for patients with non-acquired immunodeficiency syndrome-related central nervous system lymphoma. Cancer 1998;82:1946–51.
12. Cher L, Glass J, Harsh GR, et al. Therapy of primary CNS lymphoma with methotrexate-based chemotherapy and deffered radiotherapy: preliminary results. Neurology 1996;46:1757–9.
13. Corry J, Smith JG, Wirth A, et al. Primary central nervous system lymphoma: age and performance status are more important than treatment modality. Int J Radiat Oncol Biol Phys 1998;41:615–20.
14. Cote TR, Manns A, Hardy CR, et al. Epidemiology of brain lymphoma among people with or without acquired immunodeficiency syndrome. J Natl Cancer Inst 1996;88:675–9.
15. DeAngelis LM, Yahalom J, Heinemann MH, et al. Primary CNS lymphoma: combined treatment with chemotherapy and radiotherapy. Neurology 1990;40:80–6.
16. Ferreri AJM, Reni M, Villa E. Therapeutic management of primary central nervous system lymphoma: lessons from prospective trials. Ann Oncol 2000;11:927–37.
17. Frank C, Zierhut D, Schulz-Ertner D, et al. Centroblastic-centrocytic non-Hodgkin's lymphoma stage I--III: patterns of failure following radiotherapy. Strahlenther Onkol 2001;177:597–603.
18. Freilich RJ, Delattre JY, Monjour A, et al. Chemotherapy without radiation therapy as initial treatment for primary CNS lymphoma in older patients. Neurology 1996;46:435–9.
19. Gijtenbeek J, Rosenblum MK, DeAngelis LM. Primary central nervous system T-cell lymphoma. Neurology 2001;57:716–8.
20. Glass J, Gruber, ML, Cher L, et al. Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma: long-term outcome. J Neurosurg 1994;81:188–95.
21. Glick JH, Kim K, Earle J, et al. An ECOG randomized phase III trial of CHOP vs CHOP + radiotherapy for intermediate grade early stage non-Hodgkin's lymphoma. Proc Am Soc Clin Oncol 1996;15:411.abstract.
22. Gordon, KB, Char DH, Sagerman RH. Late effects of radiation on the eye and ocular adnexa. Int J Radiat Oncol Biol Phys 1995;32:1123–40.
23. Grangier C, Coucke P, Croisille P, et al. Primary cerebral lymphoma. A retrospective study of 27 cases. Strahlenther Onkol 1994;170:206–12.
24. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84:1361–92.
25. Herrlinger U, Schabet M, Brugger W, et al. Primary central nervous system lymphoma 1991--1997. Outcome and late adverse effects after combined modality treatment. Cancer 2001;91:130–5.
26. 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;51:247–52.
27. Hetzel-Sesterheim M, Schnabel K, Nestle U, et al. Primary cerebral non-Hodgkin's lymphoma. Results or radiotherapy. Strahlenther Onokol 1996; 172:198–204.
28. Horn W. Leistungsprüfungssystem, 2. Aufl. Göttingen: Hogrefe, 1983 (http: //www.testzentrale.de).
29. Jellinger KA, Paulus W. Primary central nervous system lymphomas – an update. J Cancer Res Clin Oncol 1992;119:7–27.
30. Kvaal SA, Wygonik E, Spanos A, et al. A revalidation of the Thurstone Test of Mental Alertness as a brief measure of intelligence through comparison with the Wechsler Adult Intelligence Scale-III. Psychol Rep 2001;88: 581–6.
31. Lachance DH, Brizel DM, Gockerman JP, et al. Cyclophosphamide, doxorubicin, vincristine, and prednisone for primary central nervous system lymphoma: short duration response and multifocal intracerebral recurrence preceding radiotherapy. Neurology 1994;44:1721–7.
32. Laperriere NJ, Cerezo L, Milosevic MF, et al. Primary lymphoma of brain: results of management of a modern cohort with radiation therapy. Radiother Oncol 1997;43:247–52.
33. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998;339:21–6.
34. Murray K, Kun L, Cox J. Primary malignant lymphoma of the central nervous system. J Neurosurg 1986;65:600–7.

35. Nelson DF. Radiotherapy in the treatment of primary central nervous system lymphoma (PCNSL). J Neurooncol 1999;43:241–7.
36. Nelson DF, Martz KL, Bonner H, et al. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. Int J Radiat Oncol Biol Phys 1992;23:9–17.
37. Neuwelt EA, Goldman DL, Dahlborg SA, et al. Primary CNS lymphoma treated with osmotic blood-brain barrier disruption: prolonged survival and preservation of cognitive function. J Clin Oncol 1991;9:1580–90.
38. O'Neill BP, O'Fallon JR, Earle JD, et al. Primary central nervous system non-Hodgkin's lymphoma: survival advantages with combined initial therapy? Int J Radiat Oncol Biol Phys 1995;33:663–73.
39. Ott M, Schmidberger H, Wormann B, et al. Involved-field irradiation in combination with total-body irradiation (TBI) does not increase short-term toxicity compared to TBI alone in patients with advanced-stage low-grade non-Hodgkin lymphoma. Strahlenther Onkol 2002;178:245–51.
40. Parsons JT, Bova FJ, Fitzgerald CR, et al. Radiation optic neuropathy after megavoltage external-beam irradiation: analysis of time-dose factors. Int J Radiat Oncol Biol Phys 1994;30:755–63.
41. Reni M, Ferreri AJM, Garancini MP, et al. Therapeutic management of primary central nervous system lymphoma in immunocompetent patients: results of a critical review of the literature. Ann Oncol 1997;8:227–34.
42. Reni M, Ferreri AJM, Guha-Thakurta N, et al. Clinical relevance of consolidation radiothearpy and other main therapeutic issues in primary central nervous system lymphomas treated with upfront high-dose methotrexate. Int J Radiat Oncol Biol Phys 2001;51:419–25.
43. Sandor V, Stark-Vancs V, Pearson D, et al. Phase II trial of chemotherapy alone for primary CNS and intraocular lymphoma. J Clin Oncol 1998;16: 3000–6.
44. Schultheiss TE, Kun LE, Ang KK, et al. Radiation response of the central nervous system. Int J Radiat Oncol Biol Phys 1995;31:1093–112.
45. Schultz C, Scott C, Sherman W, et al. Preirradiation chemotherapy with cyclophosphamide, doxorubicin, vincristine, and dexamethasone for primary CNS lymphomas: initial report of Radiation Therapy Oncology Group protocol 88-06. J Clin Oncol 1996;14:556–64.
46. Schwegler N. Preradiotherapy chemotherapy in primary CNS lymphomas: progress? Strahlenther Onkol 1997;173:117–8.
47. Shibamoto Y, Tsutsui K, Dodo Y, et al. Improved survival rate in primary intracranial lymphoma treated by high-dose radiation and systemic vincristine-doxorubicin-cyclophosphamide-prednisolone chemotherapy. Cancer 1990;65:1907–12.
48. Sminia P, Oldenburger F, Slotman BJ, et al. Re-irradiation of the human spinal cord. Strahlenther Onkol 2002;178:453–6.

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