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Age-Adjusted Chemotherapy for Primary Central-Nervous System Lymphoma

A Pilot Study

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Patients with primary central-nervous-system lymphoma (PCNSL) are treated with chemotherapy and cranial irradiation, which increase the risk of late neurotoxicity. The aim of this phase II trial was to investigate whether chemotherapy alone could induce durable remissions. Thirty non-immunocompromised patients were enrolled in two treatment groups, according to age. Patients in group A (< 65 years; $n = 17$) received carmustine, vincristine, dexamethasone, high-dose methotrexate and high-dose cytarabine. Patients in group B (> 65 years: $n = 13$) were treated with carmustine, vincristine, dexamethasone and high-dose cytarabine. Both groups received intrathecal treatment. Radiotherapy was reserved for patients with stable or progressive disease. The overall response rate in group A was 65% (complete response 35%; partial response 29%) and in group B, 61% (complete response 23%; partial response 38%), but only 6 remissions were maintained without irradiation. In all, there were five treatment-related deaths. Responses were induced, but were mostly of short duration, and the treatment was associated with profound toxicity.

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Although primary CNS lymphoma is a rare disease, its incidence is described as having increased threefold among immunocompetent individuals between 1973 and 1984, an increase that could not be explained through better diagnostic techniques alone (1–3). Primary central-nervous-system lymphoma (PCNSL) is often multicentric and diffusely infiltrating, and recurrence often involves the primary tumor site or other sites in the brain and/or the neural axis (3–5). Recurrence is seldom seen outside the CNS. The prognosis of PCNSL remains poor, the estimated median survival time being less than 3 months, with symptomatic treatment. Although treatment with cranial irradiation and corticosteroids can lead to rapid responses, these are often of short duration, translating into median survival times of 12–18 months (5–8). The Radiation Therapy Oncology Group (RTOG) conducted a phase II trial, demonstrating that, despite the intensification of irradiation (with whole brain irradiation to 40 Gy and a 20 Gy boost to tumor-involved sites), 70% of the patients failed to respond in irradiated sites and of these, 90% failed within the 60 Gy region. Median survival was 11.6 months and 28% of the patients were alive 2 years later, showing that radiotherapy alone, even when used with optimal fields and doses, yields poor results and is seldom curative (9, 10).

An improved outcome has been demonstrated when various cytotoxic drugs are combined with radiotherapy, but the efficacy of the drugs is dependent on their ability to cross the blood–brain barrier (BBB) (11). Ott et al. showed that, within 5 weeks of the start of treatment, tumor-associated BBB permeability decreased to a level found in the normal brain, thereby limiting the effect of further conventional chemotherapy (12). This phenomenon was confirmed in a trial by O'Neill et al., in which CHOP combined with radiotherapy and postirradiation high-dose cytarabine did not produce better results than radiotherapy alone (13, 14). On the other hand, by using drugs that do pass the BBB, an improved outcome has been obtained. By sequencing high-dose methotrexate (MTX), high-dose cytarabine and radiotherapy, DeAngelis et al. reported a median survival time of 42.5 months in 31 previously untreated patients (11, 15). Subsequently, a meta-analysis, including more than 1000 patients with PCNSL in 40 published series, confirmed this finding and summarized

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that median survival was increased when combination therapy was used (from 16 months' survival in patients treated with radiotherapy to 29 months in patients treated with chemotherapy and radiotherapy) (6).

However, cranial irradiation, particularly in combination with systemic and intrathecal chemotherapy and in the elderly, could lead to neurologic sequelae (16). The mechanism is likely mediated by vascular changes, resulting in ischemia and hypoxia in the hippocampus, a region important in memory and learning (17, 18). Late neurologic complications, particularly in the elderly, are a common problem and are associated with a poor survival prognosis, despite the cerebral lymphoma being in remission (19, 20). After treatment with MTX, cranial radiotherapy and high-dose cytarabine, nearly 80% of the 1-year survivors over 60 years of age developed progressive leucoencephalopathy (15).

A few studies have been performed in which systemic chemotherapy (i.e. high-dose MTX) has been administered and radiotherapy has been reserved for recurrence or progression. One study, performed by McAllister et al. using MTX-based, BBB disruption, resulted in a median survival time of 40.7 months and no evidence of cognitive loss at follow-up (21). Two other clinical trials used systemic chemotherapy as a single modality. Of the 8 patients included in the first trial, 7 responded and 2 are alive without lymphoma at 10 and 47 months, respectively (22).

In the second trial, Sandor et al. treated 14 patients with high-dose MTX (8.4 g/m^2), thiotepa and vincristine (MTV), which produced a 100% response rate and a projected, minimum, median survival of 40 months (23). Thus, both trials indicated that chemotherapy used as a single modality could induce long-term remissions.

To investigate this possibility, we treated 10 patients during 1997 with high-dose methotrexate, thiotepa and vincristine intravenously (i.v.), along with intrathecal (i.t.) cytarabine and methotrexate. This combination of drugs was active against PCNSL, but the toxicity, above all the renal and gastrointestinal toxicity, was considered unacceptable. On the basis of these observations, a modified protocol was introduced in the Nordic countries as a phase II study. Here, a distinction was made regarding patient age. We decided to treat patients younger than 65 years with chemotherapy based on MTX, but as compared with the pilot study, in a reduced dose. Patients older than 65 years were treated with a regimen based on high-dose cytarabine, with the assumption that elderly patients would be more prone to immediate toxic reactions, such as nephrotoxicity, after high-dose MTX. The protocol was approved by the lymphoma groups in the four Nordic countries.

The aim of the present study was therefore to test the hypothesis that chemotherapy alone can induce durable remissions in patients with PCNSL.

MATERIAL AND METHODS

Patients

Between February 1997 and May 1999, 30 patients aged 31–75 years, with a diagnosis of large-cell lymphoma involving the central nervous system and with no evidence of systemic disease, were enrolled. They were all previously untreated, with the exception of one patient who had received systemic chemotherapy (CHOP) earlier. The eligibility criteria for patients included performance status 0–2, normal renal function, no need for anti-inflammatory drugs and no immunosuppression (including organ transplantation and HIV infection). The protocol prescribed a staging procedure including computed tomography (CT) or magnetic resonance imaging (MRI) of the brain and spinal cord, a lumbar puncture, a stereotactic biopsy if cytology from the cerebrospinal fluid (CSF) was negative, an ophthalmologic examination, including slit-lamp, a neurologic examination, including 'mini-mental-state examination' and a test of creatinine clearance. The study was approved by the Ethics Committees of the four Nordic countries. All the patients were informed about the study and gave their consent to participate.

Treatments

All patients had placement of an Ommaya or Rickham reservoir, through which those who had involvement of the CSF received five doses of i.t. treatment during the first cycle, cytarabine (50 mg) on days 6, 13 and 19 and MTX (12.5 mg) on days 9 and 16. In subsequent cycles, and if no involvement of the CSF was found at diagnosis, the patients received cytarabine (50 mg) i.t. on days 6 and 18 and MTX (12.5 mg) i.t. on day 12.

For systemic treatment, the patients were divided into two groups according to age. The two different schedules are presented in Fig. 1.

Patients less than 65 years of age (group A) received carmustine 100 mg/m^2 and vincristine 1.4 mg/m^2 intravenously on day 1, dexamethasone 20 mg × 1 orally on days 1–5 and methotrexate 1600 mg/m^2 i.v. as a 2-h bolus on day 2, followed by a continuous infusion of MTX 4400 mg/m^2 for 22 h. Leucovorin rescue was started 12 h after the MTX infusion was completed. Serum MTX was analyzed at hours 12, 24, 36 and 48, and then daily until the concentration was less than 0.05 μmol/l. The CSF concentration of MTX was analyzed at the end of the MTX infusion and after another 12 h. A new cycle was started on day 22 (Fig. 1).

Granulocyte-colony-stimulating factor (G-CSF) was added for granulocyte nadirs of $\leq 1 \times 10^9$/l that lasted for 3 to 7 days. The dose of MTX was reduced in subsequent cycles for grades 2 and 3 mucositis and for more than a 20% reduction of creatinine clearance. Systemic MTX was omitted for grades 3–4 hepatologic toxicity that lasted more than one week.

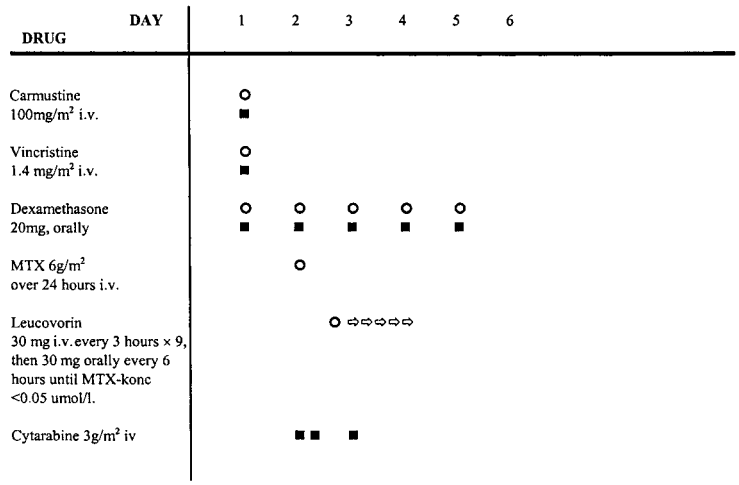

Fig. 1. Treatment regimen. Group A (○) and group B (■). Abbreviations: i.v. = intravenously; MTX = methotrexate.

A new CT or MRI scan and/or CSF cytology was performed after two cycles of chemotherapy. Patients who achieved a complete or a partial response (CR/PR) were scheduled to receive further chemotherapy. Patients with progressive (PD) or stable disease (SD) were recommended to receive whole brain radiotherapy (WBRT), mostly 40 Gy in 2 Gy fractions (Fig. 2).

Patients older than 65 years (group B) received the same schedule with the exception that cytarabine 3 g/m^2 i.v., given twice on day 2 and once on day 3, replaced methotrexate. (Fig. 1) Adjustment of dosage was dealt with as in group A and the second cycle was started on day 29. After the second cycle, a CT or MRI evaluation was performed. Patients with CR were scheduled to receive another cycle of chemotherapy and patients with PR, SD or PD were recommended to undergo WBRT treatment (Fig. 3).

Follow-up

Patients were evaluated for the degree of toxicity according to the World Health Organization (WHO) recommendations and for response to treatment. After the completion of therapy, there was no standardized time for follow-up in the protocol, but clinical and radiologic evaluations every third month along with a 'mini-mental-state examination' were recommended.

The primary endpoints were response and toxicity. Secondary endpoints were overall survival and time-to-treatment failure.

Statistics

Patient survival data were analyzed using the estimation method of Kaplan and Meier (24). Survival duration was measured from the date of diagnosis to the date of death or the last follow-up. For the responders, time-to-treatment failure was calculated from the date of diagnosis to the date of progression.

RESULTS

Five toxic deaths were reported after enrolment of 30 patients. It was therefore decided to stop any further inclusions, in order to analyze the efficacy and safety of the protocol.

Patient characteristics

Group A comprised 17 patients and group B 13 patients. The diagnosis was established after histologic (n = 28) or cytologic (CSF) examination (n = 1), with the exception of one patient, who achieved a prompt PR after treatment with steroids. Here, neither a histologic nor a cytologic diagnosis could be made, but inclusion was based upon a characteristic radiographic appearance, as well as a prompt response to steroid treatment. The remaining 29 patients were diagnosed as having large-cell lymphoma: 25 of B-lymphocyte origin, 1 of T-lymphocyte origin and in 3 patients immunophenotyping was not performed. Multiple lesions were seen in CT or MRI scans in 10 patients and a single lesion was seen in 19 patients. No radiographic abnormality was seen in one patient and the diagnosis was

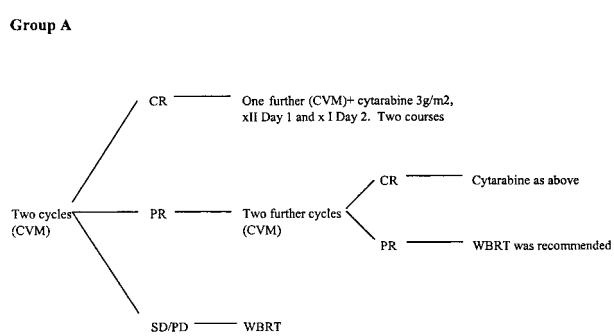

Fig. 2. Treatment plan, group A. Abbreviations: CVM = carmustine, vincristine, methotrexate; CR = complete response; PR = partial response; SD/PD = stable or progressive disease; WBRT = whole-brain radiation therapy.

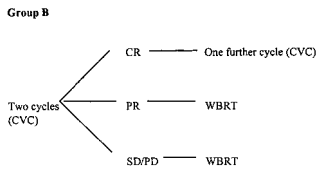

Fig. 3. Treatment plan, group B. Abbreviations: CVC = carmustine, vincristine, cytarabine; CR = complete response; PR = partial response; SD/PD = stable or progressive disease; WBRT = whole brain radiation therapy.

made on CSF cytology only. Five patients (17%) had detectable lymphoma cells in the CSF and none of the 30 patients had ocular involvement. One patient had involvement of a lymph node in the left groin, but in no other patient was there evidence of disease outside the CNS.

Group A comprised 10 men and 7 women, median age 58 years (range 31–71) and group B comprised 8 men and 5 women, median age of 70 years (range 63–75).

Response, survival and toxicity

Patients' characteristics, response to treatment and outcome are summarized in Table 1.

Group A. Six patients (35%) achieved a CR and 5 (29%) patients achieved a PR, for an overall response rate of 65%. One patient died of treatment-related septicemia (*E. coli*) and another died of an unknown cause after the first cycle. Four patients (23%) had SD/PD after two courses of chemotherapy.

The overall results of therapy for group A are presented in Fig. 4 and Table 1. Eleven (65%) patients responded to chemotherapy, but during follow-up 7 patients relapsed. Six of the 7 patients received radiotherapy and one patient received radiotherapy owing to having a PR only. Bearing in mind the primary aim of the protocol, only 3 out of 17 patients remained progression-free after chemotherapy alone. The median overall survival has not yet been reached at a median follow-up among survivors of 14 months (Fig. 5) and the median time-to-treatment failure (TTF) by responders is 18 months. Fifty-eight cycles of MTX were administered; 77% of the patients suffered from hematologic toxicity (WHO grade 3–4), but gastrointestinal and neurologic toxicities were minimal and not dose-limiting. Twenty courses of cytarabine were administered in this group. In all, 10 patients received full treatment according to the protocol.

Group B. Three patients (23%) reached a CR and 5 patients (38%) reached a PR at the first response assessment, for an overall response rate of 61%. Three patients died after the first cycle of chemotherapy, of neutropenia and infection in two cases and of unknown causes in the third case. Two patients received WBRT, as only SD/PD was achieved.

Six patients are progression-free at follow-up, 3 after chemotherapy alone and 3 after radiochemotherapy. The follow-up is summarized in the Table and in Fig. 6. The median overall survival in this group was 15.1 months and the TTF by responders has not been reached after a median follow-up of 9 months (Fig. 5).

Twenty-seven courses of cytarabine were administered in group B, with three treatment-related deaths. All 13 patients in the group suffered from hematologic toxicity (WHO grade 3–4). Hepatic, renal and neurologic toxicities were minimal and not therapy-limiting.

The MTX concentration in the CSF was analyzed at the end of MTX infusion and after another 12 h. Fourteen samples from 4 different patients were obtained, resulting in a median concentration of 2.83 μmol/l (range 1.5–6.1) at 0 h and a median concentration of 0.69 μmol/l (range 0.49–1.29) at 12 h.

DISCUSSION

The aim of our study was to investigate whether chemotherapy alone could induce durable remissions in patients with PCNSL, with an acceptable level of toxicity. Our data demonstrate that remissions were indeed obtained, but at the cost of severe toxicity. Since older patients are assumed to be more vulnerable to toxicity from chemotherapy, the protocol was divided into two treatment arms, according to age. Still, the hematologic toxicity was especially profound in both groups. In all,

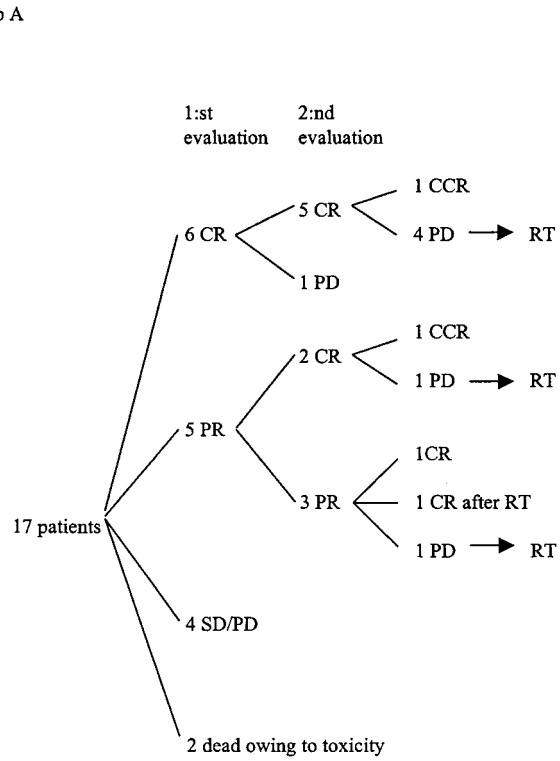

Fig. 4. Response evaluation, group A. Abbreviations: CR = complete response; CCR = continuous complete response; PR = partial response; SD = stable disease; PD = progressive disease; RT = radiotherapy.

Table 1

Patient characteristics and response to treatment

Patient no.	Age	Pathology	CSF-cytol.	Multiple or solid lesion	Response at first follow-up	RT at initial treatment	RT at relapse	Survival (months)	Remarks
Group A									
1	59	LCL-B	Pos.	Multiple	CR	No	–	6+	Alive without lymphoma
2	56	LCL	Neg.	Multiple	CR	No	Yes	18+	Alive with lymphoma
3	69	LCL-B	Neg.	Solid	CR	No	Yes	11+	Alive with lymphoma
4	63	LCL-B	Neg	Solid	CR	No	Yes	18	Died with lymphoma
5	50	LCL-B	Neg.	Solid	CR	No	No	4	Died with lymphoma
6	58	LCL-B	Neg.	Multiple	CR	No	Yes	31+	Alive with lymphoma
7	51	LCL-B	Pos.	Solid	–	No	–	2	Died of sepsis after the first cycle
8	59	LCL-B	Neg.	Solid	–	No	–	3	Died after the first cycle
9	64	LCL	Neg.	Solid	PR	Yes	–	25+	Alive without lymphoma
10	36	LCL-B	Neg.	Solid	PR	No	–	17+	Alive without lymphoma
11	31	LCL-B	Neg	Multiple	PR	No	–	31+	Alive without lymphoma
12	57	LCL-B	Neg.	Solid	PR	No	Yes	8+	Alive without lymphoma
13	57	LCL-B	Neg.	Solid	PR	No	Yes	5+	Alive with lymphoma
14	53	LCL-B	Pos.	Solid	SD/PD	Yes	–	6+	Alive with lymphoma
15	45	LCL-B	Pos.	Multiple	SD/PD	Yes	–	6	Died with lymphoma
16	71	LCL-T	Neg.	Solid	SD/PD	No	–	5	Change of therapy due to toxicity Died with lymphoma
17	58	LCL-B	Neg.	Solid	SD/PD	Yes	–	2	Died with lymphoma
Group B									
1	74	?	Neg.	Solid	CR	No	–	4+	Alive without lymphoma
2	70	LCL-B	Neg.	Multiple	CR	No	Yes	15	Died with lymphoma
3	70	LCL-B	Neg.	Solid	CR	No	–	5+	Alive without lymphoma
4	69	LCL-B	Neg.	Solid	PR	Yes	–	22+	Alive without lymphoma
5	67	LCL-B	Neg.	Multiple	PR	Yes	–	14+	Alive without lymphoma
6	67	LCL	Neg.	Multiple	PR	No	–	18+	Alive without lymphoma
7	63	LCL-B	Pos.	Normal	PR	Yes	–	8+	Change of therapy due to toxicity Alive with lymphoma
8	75	LCL-B	Neg.	Multiple	PR	Yes	–	9+	Change of therapy due to toxicity Alive without lymphoma
9	74	LCL-B	Neg.	Solid	–	No	–	1	Died after the first cycle
10	69	LCL-B	Neg.	Solid	–	No	–	4	Died of infection after the first cycle
11	73	LCL-B	Neg.	Solid	–	No	–	–	Died of infection after the first cycle
12	64	LCL-B	Neg.	Multiple	SD/PD	Yes	–	6	Died with lymphoma
13	68	LCL-B	Neg.	Solid	SD/PD	Yes	–	5	Died with lymphoma

Abbreviations: CSF = cerebrospinal fluid; cytol. = cytology; LCL-B = large-cell lymphoma of B-cell origin; LCL-T = large-cell lymphoma of T-cell origin; CR = complete response, PR = partial response, SD/PD = stable or progressive disease.

there were five treatment-related deaths, three of which were related to infection in the neutropenic phase. Renal toxicity was also a dose-limiting factor in group A. Toxicity was a much greater problem than in the trial performed by Sandor et al. (23). There may be several reasons for this: first, a new dose-intensive protocol was used and the patients in our trial were treated at a large number of different centres, in four different countries, compared with Sandor's single-centre study. Secondly, the combination with BCNU may have contributed to the hematologic toxicity, as the point of maximal myelosuppression from the carmustine would occur just at the time when the next cycle was being administered. Third, elderly patients were included in group A, despite the inclusion criteria.

A response rate of 65% and 61% for groups A and B, respectively, and a median overall survival rate of 15 months in group B were obtained. The median overall survival in group A has not yet been reached. These results seem to be inferior to the results obtained in other reports, using chemotherapy as a sole treatment for PCNSL, which can be explained by the high number of early deaths and the fact that 4 patients in group A and 2 patients in group B did not achieve a response at all. The inferior response rate, as compared to that found by Sandor et al. (23), may, apart from different doses of methotrexate and the incorporation of carmustine instead of thiotepa, also rest upon differences in patient selection. Of the 6 patients who did not respond to treatment, 5 received cranial irradiation, resulting in the survival of one patient at 5.5 months and the deaths of the remaining 4 patients during or shortly after the completion of radiotherapy, indicating resistant disease from the beginning. Even though the number of

patients was small, radiotherapy in this setting seems to be of limited value and the prognosis is dismal.

In spite of the aims of the present study, 12 of the 19 patients who initially responded to chemotherapy received radiotherapy at some point, because of reaching a PR only (4 patients) or owing to relapse (7 patients). One patient received radiotherapy owing to toxicity from chemotherapy. Only 3 patients in group A and 3 in group B remained progression-free, with a short follow-up, after chemotherapy alone. These results may indicate that chemotherapy as a single modality and given as in the present protocol yields a low rate of complete remissions and that these remissions are often of short duration. We also found that the response evaluation with CT or MRI is associated with uncertainty and in our experience it is, even with MRI, difficult to distinguish edema from tumor.

MTX distribution in CSF was determined at 0 and 24 h after the administration of i.v. MTX. In all, 14 samples were obtained. Though the number of samples is small, they all demonstrated therapeutic MTX levels (1 μmol/l)

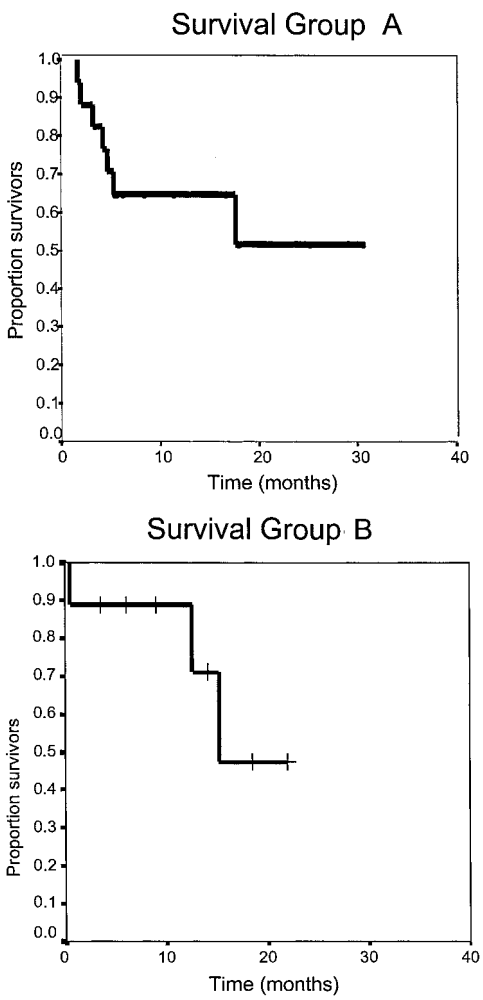

Fig. 5. Kaplan-Meier plot for overall survival, group A and group B.

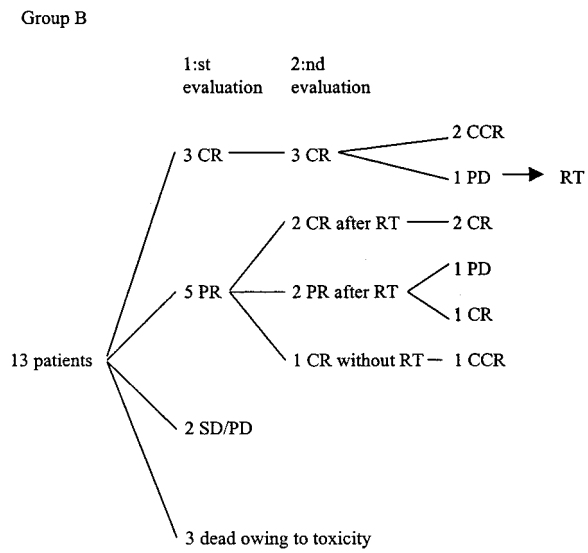

Fig. 6. Response evaluation, group B. Abbreviations: CR = complete response; CCR = continuous complete response; PR = partial response; SD = stable disease; PD = progressive disease; RT = radiotherapy.

(25, 26) at 0 h, but not at 24 h. The importance of this finding is not clear, since it has been suggested that, to yield optimal results, the duration of exposure to suprathreshold concentrations of MTX is more important than the peak levels (25). However, it has been suggested that prolonged intrathecal therapy in combination with subsequent radiotherapy increases the risk of neurotoxicity (16, 23). Therefore, in view of the finding of therapeutic concentrations in CSF after the MTX infusion, it seems reasonable to decrease the number of i.t. treatments in future protocols.

According to the protocol, a 'mini-mental-state examination' was recommended every third month. In view of the low number of non-irradiated patients in continuous CR, an analysis of these data seems to be of limited value.

In conclusion, this new protocol for the treatment of PCNSL, introduced in a multicenter setting, did result in the induction of responses, but often of short duration and at the cost of severe toxicity.

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