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PRIMARY MALIGNANT LYMPHOMA OF THE BRAIN

A report of 24 cases from the Norwegian Radium Hospital

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Between 1975 and 1987, 24 patients with primary central nervous system lymphoma were seen and treated at the Norwegian Radium Hospital. The overall median survival was 24 months. Patients with poor performance status (WHO 3–4) had a median survival of 3 months whereas patients with good performacne status (WHO 0–2) had a median survival of 40 months ($p < 0.0001$). Patients who were not steroid-dependent after operation had a better survival than those patients who were steroid-dependent ($p = 0.02$). Nine patients were still living without evidence of disease at last follow-up, 18–130 months after the initial treatment.

Primary central nervous system lymphoma (PCNSL) accounts for approximately 1% of all intracranial neoplasms and represents about 2% of the extranodal lymphomas (1–7). The tumor has a characteristic albeit non-diagnostic appearance on computed tomography (8–10) and occurs with increased frequency in patients with hereditary and acquired immune deficiency states, including transplanted patients and AIDS victims (11–15). The incidence reported in earlier literature may have been underestimated due to the similarity to undifferentiated metastatic tumours and lack of the monoclonal immunoglobulin detection system now available (16–24). The registered incidence of PCNSL slowly increased between 1960 and 1980. In the 5-year interval between 1980 and 1984, however, the incidence was about 3 times as high as in any previous 5-year interval (10). This increase cannot be accounted for by changes in nosology, referral pattern or use of new diagnostic tools or by increased physician awareness. Nor does AIDS or other forms or immuno-suppression seem to explain the registered increased incidence.

Long-term survival is rare in PCNSL and the median survival has been reported to be only 6–12 months (10, 25). Radiation therapy has been the main therapy to date. Prompt initial response is often noted clinically and radiographically.

However, most patients eventually get recurrence within CNS (26, 27). Combination chemotherapy following surgery and radiotherapy seems to improve the survival rate (28, 29).

In the current report a material of PCNSL is analysed with regard to treatment, failure pattern and prognosis.

Material and Methods

From 1975 to 1987, 24 cases of primary non-Hodgkin's lymphoma of the central nervous system were seen and treated at the Norwegian Radium Hospital. There were 11 females and 13 males and their age ranged from 16 to 74 years (mean 57 years). The patients were evaluated to rule out systemic disease at the time of presentation. This evaluation included blood chemistry, bone marrow aspirate and biopsy, liver and spleen radionuclide scan, chest x-ray, bipedal lymphangiography and, after 1982, computerized tomography of the abdomen. The pre-operative

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evaluation consisted of radionuclide brain scanning (until 1982) and computerized tomography of the brain (after 1982).

CT scan yielded the diagnosis of cerebral tumour in 20 patients. In 17 of these patients a solitary tumour was found. Radionuclide brain scan yielded the diagnosis of cerebral tumour in 5 patients treated before 1983. Two of these patients had solitary tumour. In none of the patients were signs of lymphoma found outside the CNS.

All patients has some type of surgery. In 4 patients the tumour was macroscopically totally removed, in one patient a stereotactic biopsy was performed and in the remainder a non-radical tumour resection was performed. All tissue specimens were reviewed by one pathologist.

All patients had high-grade non-Hodgkin's malignant lymphomas (Table) as judged by light microscopy. For immunohistochemical evaluation, dewaxed serial sections from the routinely formaldehyde and glutaraldehyde-fixed material were subjected to paired immunofluoresence staining for Ig heavy and light chains (the immunological reagents and methods have been described in detail previously) (30, 31), or stained with monoclonal antibodies to leukocyte common antigen (CD45, Dacopatts, Denmark), B-lymphocytes (MB1, Eurodiagnostics BV, Holland) or T-lymphocytes (MT1, Eurodiagnostics BV, Holland) using the alkaline phosphatase-anti alkaline phosphatase (APAAP) technique (32).

Eleven patients (cases 5, 8, 9, 10, 11, 13, 15, 17, 20, 21, 24) had B-cell lymphomas verified by monoclonality. Eight patients (cases 2, 3, 6, 14, 16, 18, 19, 23) were positive for leukocyte common antigen but negative for MB1, MT1 or Ig. Based on light microscopy, however, they are most likely to have had centroblastic (B-cell) lymphomas. Lack of staining for MB1 and MT1 may be due to the fixation in which flutaraldehyde is added for electron microscopical purposes (31). One patient (case 22) had a lymphoblastic lymphoma consisting of predominantly immature T-cells (convoluted type). Due to poor histologic material four cases (No. 1, 4, 7, 12) were unclassifiable. No patients had undergone organ transplantation or received long-term immuno-suppressive therapy. No patients had multiple opportunistic infections consistent with a diagnosis of AIDS. The clinical data are summarized in the Table.

All patients were treated with external megavoltage whole brain irradiation via parallel opposed fields. The midplane dose was usually about 40 Gy, given in 20 fractions with 5 treatments per week.

Various chemotherapeutic regimens were used: a) CHOP (cyclophosphamide 750 mg/m^2 i.v., vincristine 2 mg i.v., doxorubicin 25 mg/m^2, prednisone 50 mg × 2 orally for 5 days), b) PCV (160 mg lomustine orally, 2 mg vincristine i.v., procarbazine 50 mg × 3 orally for one week), c) high-dose methotrexate (1–3, 2 g i.v. followed by leucovorin rescue), d) 12 mg methotrexate intrathecally and e) 160 mg intracarotid carmustine. Nine patients received chemotherapy as part of the initial treatment while 5 patients received chemotherapy at recurrence. The treatment regimens for the different patients are shown in the Table.

Survival was calculated with the Kaplan-Meier method. Test of statistical significance were computed with the log-rank test (Mantel-Haenszel). Survival rates were calculated from the date of the surgical procedure.

Results

Survival from admission was 70% and 50% at one and two years respectively (Fig. 1). The median survival was 24 months (range 3 months to 130 months). At last follow-up, 9 patients were still alive and disease-free at 130, 93, 61, 44, 35, 34, 33 and 18 months respectively.

Survival was significantly longer for 17 patients who on admission had WHO performance status 0–2 compared to 7 patients with a performance status 3–4 ($p < 0.0001$) (Fig. 2). Survival for 9 patients who received chemotherapy as a supplement to irradiation was longer compared to 15 patients who received radiation therapy only ($p = 0.07$) (Fig. 3). Two of the 9 patients who received chemotherapy

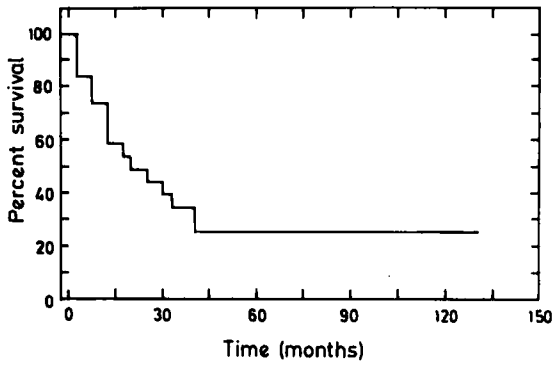

Fig. 1. Survival of the 24 patients with primary CNS lymphoma treated at the Norwegian Radium Hospital between 1975 and 1987.

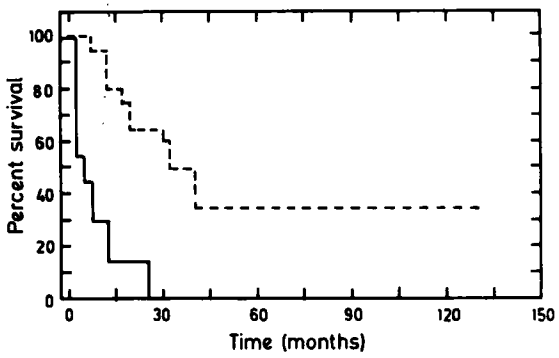

Fig. 2. Survival curves for 17 patients with performance status WHO 0–2 (- - -) compared to 7 patients with WHO performance status 3–4 (——).

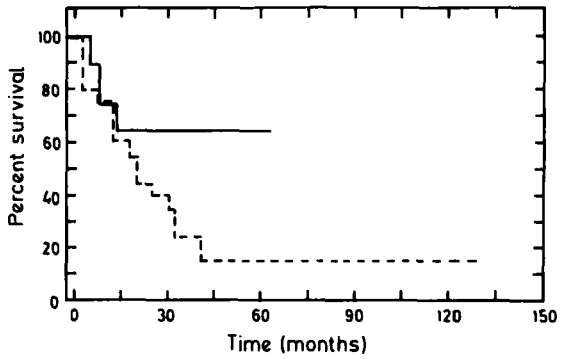

Fig. 3. Survival in 9 patients who received chemotherapy as a supplement to irradiation (——) compared to 15 patients who received only irradiation (- - -).

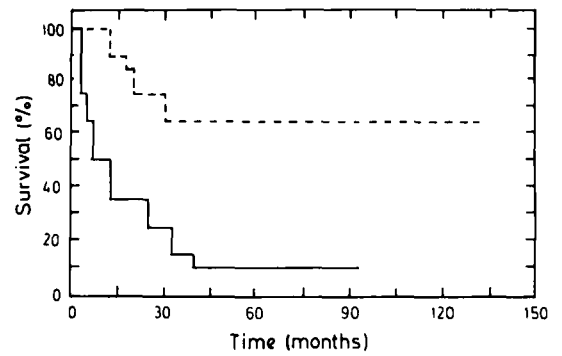

Fig. 4. Survival curves in 12 patients who were steroid dependent after operation (——) compared to 12 patients who were off steroid medication (- - -).

had WHO performance status 3–4, whereas 5 of the 15 patients who received radiation only had WHO performance status of 3–4. Survival was slightly longer for 17 patients who received a tumour dose of 40 Gy or more compared with 4 patients who received a lower dose. Three of the 4 patients who received small radiation doses had WHO performance status 3–4. Twelve of the patients were steroid-dependent after operation and these patients had a significantly shorter survival ($p = 0.02$) than patients who did not need steroids (Fig. 4). No significant difference in survival was seen between males and females, between patients over or under 60 years of age or between patients with duration of symptoms longer or shorter than 4 months. Due to small number of patients in the subgroups a multivariate survival analysis was not performed.

Three patients developed dementia after treatment and 6 patients complained of marked fatigue which persisted for several years after treatment. In none of our patients were ocular manifestations seen, but a routine slit-lamp examination was not performed.

Discussion

The median survival of 24 months observed in the present study compares favourably with other studies which report a median survival between 6 and 13 months with incidental long-term survivors (10, 28, 29). Many factors may influence the survival rate. A solitary intracranial lesion, good initial performance status, favourable histology, may thus be positively associated with the survival while multiple or periventricular/meningeal lesions and predisposing immuno-suppression may be negatively associated (10, 24).

Nineteen of the 24 patients in the present study has solitary intracranial lesions (17 monitored by CT scan and 2 by radionuclide scan). This is in contrast to several other studies which report a higher proportion of multicentricity (10, 29). The reason for this discrepancy is not possible to assess.

Radionuclide brain scan using $^{99}Tc^{m}$ pertechnetate or glucoheptonate labelled with $^{99}Tc^{m}$ is a simple non-invasive method for demonstration of a defect blood–brain barrier (33). After introduction of CT and MR with better anatomical resolution, radionuclide brain scans were done infrequently. However, other radionuclide scanning methods like positron emission tomograpy (PET) have become important to monitor therapy response (34).

The median survival of the patients with solitary lesion in the present study was 32 months, whereas all patients with multiple intracranial lesions and subependymal contrast enhancing lesions were dead before 8 months, except one patient who lived 2 years. Similar findings were reported by Hochberg & Douglas (10) who in their study found a median survival of 9 months in 16 patients with multiple lesions, whereas 11 of 33 patients with solitary lesions survived more than two years.

Seventeen patients had a good initital performance status, WHO 0–2, and a far better outcome than the remaining 7 patients who had marked neurological deficits before treatment (Fig. 2). The association between performance status and survival has also been shown for patients with glial cell tumours. In several of the reported series, this association has been stronger than the association between histology or age and survival (10, 35).

Although univariate analysis suggested that combination of chemotherapy and irradiation might prolong survival (Fig. 3), no conclusions can be drawn from this retrospective study. The number of patients in the subgroups was very small making a multivariate survival analysis impossible or highly questionable and the study was not randomized.

Admitting the imperfections of a retrospective study and the possible interrelation of multiple prognostic factors, the study suggested that steroid dependency after operation may be negatively associated with survival (Fig. 4).

A unique feature of PCNSL is the sensitivity to corticosteroids. There are numerous reports of complete disappearance of these lesions on CT scan, as well as rare long clinical remissions, after systemic administration of corticosteroids (10, 36). One of our patients (case 21) had a

Table

Case No.	Year	Age/Sex	Dur. months	Loc.	Hist.	Signs		Surg.	Rad. (Gy)			Chemotherapy			Survival months	Cause of death
									WB	B	S	i.v.	i.t.	i.a.		
1	1975	54/F	3	L.F	UC	ND		R	40						9	DNK
2	1975	42/M	2	L.T	CB	EIP		R	40						147	NED
3	1975	57/M	4	L.O	CB	ND		R	40						12	DNK
4	1979	55/F	6	R.P	UC	S		M	40				X		38	DNK
5	1980	58/M	5	R.P	CB	IM		M	40				X		18	DWD
6	1982	61/F	3	R.C	CB	EIP		M	40		40	X	X		86	NED
7	1983	69/M	2	R.F	UC	ND	IM	R	40			X*			36	DNK
8	1983	45/M	6	R.T	CB	IM		R	40						32	DWD
9	1983	69/M	6	L.F	CB	IM	ND	R	40			X	X		11	DNK
10	1984	65/F	6	L.O	CB	S	ND	R	40						48	NED
11	1985	47/M	3	L.T	CB	IM	ND	R	40						60	NED
12	1984	54/M	4	R.F	UC	IM		R	40						28	DNK
13	1985	63/F	6	R.F	CB	IM	ND	R	8						1	DWD
14	1985	74/F	3	R.T	CB	S	IM	B	30						3	DWD
15	1985	64/F	3	L.O	CB	ND		R	—						1	DWD
16	1985	31/M	6	R.T	CB	EIP	ND	R	40			X		X*	60	NED
17	1985	71/M	2	R.P	IM	S	ND	R	40						24	DNK
18	1986	68/M	4	L.F	CB	IM	ND	R	40			X*			5	DWD
19	1986	57/M	2	R.C	CB	ND	IM	R	40			X	X		12	DWD
20	1986	61/F	3	L.T	CB	ND		R	40	36*		X*	X*		14	DWD
21	1986	55/M	1	L.P	CB	S		B	40			X*	X*		6	DWD
22	1986	16/F	3	AH	LB	ND		R	36	18		X	X		42	NED
23	1987	67/F	4	L.C	CB	ND		R	42	14		X			36	DNK
24	1987	66/F	3	L.P	CB	S		M	42	10		X			36	NED

Abbreviations

Dur = duration of symptoms (months). Loc: Tumour localisation L = left, R = right, F = frontal, T = temporal, O = occipital, P = parietal, C = cerebellium, AH = anterior hypophysis. Signs: ND = neurological deficit, EIP = elevated intracranial pressure, S = seizures, Surg: R = tumour resection, M = macroscopically radical resection, B = biopsy. Irradiation: WB = whole brain, B = boost to tumour, S = spinal irradiation. Chemotherapy: i.v. = intraveneous, i.t. = intrathecale, i.a. = intra-arterial. Cause of death: DNK = death cause not know, NED = no evidence of disease, DWD = dead of disease. * = chemotherapy at recurrence. Hist: Histology, CB = centroblastic, IM = immunoblastic, LB = lymphoblastic, UC = unclassifiable. All patients except Nos. 13, 14 and 15 improved after the initial treatment.

complete normalization of the CT after one week of corticosteroid medication, but the tumour recurred after a few months and the patient died 6 months later. Two other patients had normal CT scan on arrival at the hospital and had received steroid medication for a few days. In both patients CT scan showed tumour regrowth 4–6 weeks later.

One of the most prominent neurological symptoms was personality changes including apathy or slowness of thought and confusion (8 patients) and psychotic disorder (one patient). These neuropsychological changes appear to be associated with diffuse tumour involvement of the periventricular white matter or the corpus callosum (6, 8). Although 8 patients with neuropsychological changes markedly improved after dexamethasone and irradiation, all patients died of the disease 1–32 months after treatment start. Another important sign was neurological deficit which was seen in 14 patients. In only three patients was elevated intracranial pressure registered at presentation. These figures corrrelate well with results from other studies (10, 27, 29).

Radiotherapy has been considered to be the main treatment for PCNSL but there is still some controversy concerning optimal radiation fields and dose levels. There seems to be little doubt that the whole brain should be treated, as multiple leasions or extensive involvement by a single lesion are common and failure frequently occurs at sites other than those originally involved. In the present study the 17 patients who received a total brain irradiation with 40 Gy or more had a longer survival than the 4 patients who received a lower dose. Three of the patients (cases 22, 23, 24) who received a boost dose to the tumour region after whole brain irradiation are alive without evidence of disease. In 22 of the patients marked improvement was noted in neurological status and on CT scan after irradiation. This reflects the marked radiosensitivity of these tumours (10, 26, 27).

Unlike the reports from other studies, we did not see development of meningeal lymphoma (reported to occur in 25% of the patients). One of our patients had recurrence of the tumour at another site than the initial (patient 19 who had spinal recurrence). In other studies intra-cranial recur-

rences have been reported to occur in 60% of the patients. One reason for this can be that a great proportion of our patients with localized disease were treated with a combination of pre- and post-irradiation chemotherapy and received a high irradiation dose with a boost to the tumour region.

There has been no systematic study of the potential additive benefit of systemic chemotherapy when combined with irradiation of primary CNS lymphoma. Loeffler et al. (35) reported a median survival of 44 months for patients receiving chemotherapy in addition to irradiation compared to 14 months for those only irradiated. Methotrexate (Mtx) has been shown to produce long-term remissions in patients with recurrence following whole brain radiotherapy (10, 35, 37). Hochberg & Douglas, in their study (10) reported 8 complete responders among 13 patients treated with 3.5 g Mtx/m^2 every 3 weeks for 3 courses. Many authors, however, have reported adverse CNS effects after administration of Mtx. To achieve therapeutic concentration of Mtx in the brain (10^{-6} mol/l lasting 24 h) doses of 6–8 g have to be given i.v. If the patient has received earlier brain irradiation a reduction of the dose must be considered due to the partial breakdown of the blood—brain barrier (37). In many cases with leukoencephalopathia after high-dose methotrexate administration, leucovorin rescue with only 10 mg has been given. As the cerebrospinal fluid concentration of leucovorin after systemic administration is 10–100 times lower than the serum concentration, it could be postulated that for adequate CNS rescue, a systemic dose 10–100 times higher than needed for systemic rescue would be required. Nine patients in our study received chemotherapy as part of the initial treatment and 4 patients at recurrence. Due to the small number of patients and the variety of chemotherapy regimens, no conclusion could be drawn concerning the different regimens. Our retrospective study, however, suggested that the addition of chemotherapy might have prolonged the survival (Fig. 4).

Only one of our patients (No. 6) had an infra-tentorial manifestation. She received chemotherapy as supplement to irradiation and is alive without sign of disease after 70 months.

In summary, priamry cerebral lymphomas may present two distinct patterns of which the solitary intra-cranial mass is the most common. Combination of surgery, chemotherapy and whole brain irradiation with a boost dose to the tumour will in many of the localized cases produce long-term survival. The multifocal diffuse infiltrating type has an extremely poor prognosis regardless of treatment and an expected survival of less than a year. Patients with pronounced neuropsychological changes have a poor outcome, due to the underlying diffuse infiltration of the white matter. As is also seen in other more common brain tumours, the initial performance status is markedly associated with survival. Steroid dependency after operation may be a poor prognostic sign.

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