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Acute Lymphoblastic Leukemia in Adults: Results of Intraventricular Maintenance Chemotherapy for Central Nervous System Prophylaxis and Treatment

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Abstract—*The results of intraventricular (i.vt.) chemotherapy in 36 cases of adult acute lymphoblastic leukemia (ALL) were analyzed to define a useful and reliable form of central nervous system (CNS) prophylaxis. Patients received methotrexate (MTX) via an Ommaya reservoir six times every 4 weeks. This was repeated when bone marrow relapse occurred. Intraventricular maintenance CNS prophylaxis during half a year appeared adequate, since primary CNS relapses were seen in ony two patients (5.6%). These patients had failed to follow the prophylaxis schedule. The procedure was implemented and repeated relatively easily and did not lead to neurotoxic problems.*

The i.vt. route was also satisfactory for the treatment of initial and recurrent episodes of meningeal leukemia (ML). The therapy reduced morbidity caused by ML to a minimum.

INTRODUCTION

IMPROVEMENTS in systemic chemotherapy have gradually prolonged survival time in adults with acute lymphoblastic leukemia (ALL). Meningeal leukemia (ML) has then become a problem in adults just as in children. Without central nervous system (CNS) prophylaxis to protect the meninges around the entire neuraxis, this complication occurs in up to 60% [1–5]. The basis of the presymptomatic treatment has been cranial radiation of 24 Gy in combination with five to six intrathecal (i.t.) injections of methotrexate (MTX). Following treatment the incidence of primary CNS relapse in children varied between 5 and 15% [6–10]. The results in adults were very similar [11–13]. However, this combination can cause a leuko-encephalopathy, especially in the developing brain, which results in neurological symptoms and a lower performance in neuropsychological testing [14, 15]. This has led to the search for less toxic alternatives. It has been shown that 18 Gy cranial radiation is as effective as 24 Gy [7, 16]. Another possibility is to use i.t. drugs alone, administered directly in the lumbar subarachnoid space or in the cerebral ventricles through an Ommaya reservoir [6, 10, 17–20]. The latter has several advantages: it avoids disturbance of the blood–brain barrier by radiotherapy; it offers a predictable distribution of drugs along physiological pathways; and it easily allows examination of the cerebrospinal fluid (CSF). In this study we report on the use of intraventricular (i.vt.) chemotherapy for CNS prophylaxis and treatment of ML. The efficacy and toxicity of this approach were studied in 45 successive adult ALL patients.

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PATIENTS AND METHODS

Prophylaxis

Thirty-six adult ALL patients received i.vt. chemotherapy for CNS prophylaxis from July 1976 until July 1986. An Ommaya reservoir was inserted in most cases immediately after achieving complete remission (CR). In T-cell and B-cell ALL patients this was done as soon as circulating blasts had disappeared by systemic therapy. Patients with a mediastinal mass and circulating lymphoblasts of T-cell phenotype were excluded from this evaluation.

The implantation was preceded by a spinal tap to exclude asymptomatic ML. CNS prophylaxis consisted of six injections of 15 mg MTX, every 4 weeks. When a bone marrow (BM) relapse occurred a new CNS prophylaxis course was initiated. In the

case of a CNS relapse i.vt. treatment was repeated together with systemic reinduction.

Treatment

Fourteen patients with ML were treated via the i.vt. route. ML was diagnosed when any number of blast cells was seen in the CSF or in case of pleiocytosis of 5 or more cells/mm^3, which could not be explained by infection or other complications. Five patients had received CNS prophylaxis. The other nine patients belonged to three categories: asymptomatic ML was present in five patients at initial diagnosis; overt ML appeared at the end of induction in two cases; in the other two ML occurred simultaneously with the first systemic relapse. One of the latter was referred, the other had refused standard prophylaxis. Two patients in the first category never achieved BM remission.

For ML, i.vt. MTX was given every 4 days until clearance of the CSF. The MTX dose was adjusted according to the MTX levels in the CSF. When the response was inadequate, MTX was alternated with 100 mg cytosine arabinoside (AraC), or it was substituted by AraC. After obtaining CNS remission, CNS consolidation was established with four weekly and two biweekly injections. Thereafter CNS maintenance was given six times every 4 weeks.

Systemic induction chemotherapy consisted of daily prednisolone (P) for 6 weeks and weekly vincristine (V) which was combined with doxorubicin (A) during the last 3–4 weeks. CR was followed by consolidation with asparaginase. Patients failing to achieve CR were given an AML-like course with AraC, 6-thioguanine and A. Maintenance therapy with V, P, 6-mercaptopurine and MTX was continued for 3 years, or until relapse of ALL. Four patients received a bone marrow transplantation in first remission.

The log-rank test was used for statistical analysis of survival data.

RESULTS

Patient data and risk factors for the development of ML are summarized in Table 1. Based on the literature a white blood cell (WBC) count over 25 × 10^9/l, platelets lower than 20 × 10^9/l and an elevated serum lactic dehydrogenase (LDH) were considered to be risk factors of ML [5].

Table 1. Patient characteristics

	Prophylaxis	ML
Number	36	9
Sex m/f	22/14	5/4
Age (years)	14–62	16–73
median	22	52
Type:		
common-ALL	24 (4)	6
T-ALL	6	1
B-ALL	—	2
nonB, nonT-ALL	6 (1)	—
Initial WBC × 10^9/l		
<25	27 (3)	3
>25	9 (2)	6
Initial platelets × 10^9/l		
<20	6	2
>20	30 (5)	7
Serum LDH U/l		
<600	18 (2)	4
>600	18 (3)	5

Number of patients developing ML in parentheses.

Efficacy of CNS prophylaxis

The overall results are summarized in Table 2. CR was achieved in all 36 patients, 13 of whom remained free of disease with a median follow-up of 33+ months. In this category two patients died of unrelated causes (chondrosarcoma, suicide). Patients who relapsed did so within 1–79 months (median 9 months). Five patients developed ML: three simultaneously with BM relapse at 3, 11 and 71 months. In two patients who had not received optimal prophylaxis ML terminated CR (5.6%). Insertion of the reservoir was delayed in one case due to infection, while in the other the prophylaxis was disrupted because the draintip needed replacement.

Efficacy of ML treatment

Results of CNS treatment in nine cases without prophylaxis and in five cases with prior prophylaxis are given in Table 2. Of the 14 patients three were not evaluable: one died of systemic disease shortly after placement of the reservoir; another preferred radiation treatment. In the third patient, who relapsed in BM and CNS after 6 years, the drain was not functioning well and craniospinal radiation was given before malfunctioning of the device could be corrected. The patient, however, died of systemic disease. CNS remission could be obtained in all evaluable patients. The median duration of the first CNS remission was 4 months, it was shorter in patients with overt ML (2 months) than in asymptomatic patients (6 months). Patients with CNS relapses had a median survival of 17 months (range 4–72). In four patients CNS remission continued till death, and one was still in remission (6+ months), when the study was closed. The median survival from diagnosis of ML was 7 months (range 0–26). The CNS prophylaxis group had better results (see Table 2).

Final outcome and comparison between subgroups are given in Table 3.

Table 2. Results of CNS prophylaxis and treatment

	Prophylaxis +	Prophylaxis + ML +	Prophylaxis − ML +
Number	36	5	9
1st remission duration	15 (1–104+)	10 (1–56)	7 (1–8)
Survival	40 (3–118+)	18 (13+–72)	10 (4–23)
Survival from Dx ML	—	11 (1–26)	5 (0–22)
CNS remission duration	—	4 (4–7)	4 (1–16)

Values in months, range in parentheses.
Dx: diagnosis.

Table 3. Comparison of remission duration and survival between different subgroups

		Median value (months)	*P* value
Survival	P+/P−	40/10	<0.005
	ML−/ML+	58/17	<0.025
	P+ML+/P−ML+	18/10	<0.10
	P+ML+/P+ML−	18/58	<0.50
Remission duration	P+/P−	15/7	<0.05
	P+ML+/P−ML+	10/7	<0.30
	P+ML+/P+ML−	10/24	<0.40
Survival from Dx ML	P+/P−	11/5	<0.60

P = prophylaxis, ML = meningeal leukemia, +/− = present/absent.

Complications

Two types of technical problems were encountered. Drain occlusion necessitated renewal in two patients after 1 and 6 years. In another patient the draintip wandered from the ventricle to a subependymal position; this required repositioning.

Patients received cotrimoxazol for 3 days as pre- and postoperative therapy when the reservoir was inserted. Bacterial meningitis was diagnosed when bacteria could be identified in the CSF. Meningitis followed reservoir handling in three cases, once postoperatively and in two instances after puncturing the reservoir. The infections were caused by bacteria from the permanent skin flora. Symptoms and signs were always mild without cranial nerve involvement. A week long course of intravenous (i.v.) and i.vt. antibiotics (cefradine or cefuroxim) cured the meningitis without the necessity of removing the reservoir.

One ML patient experienced a mild reversible MTX encephalopathy.

DISCUSSION

Although prophylactic therapy has greatly diminished the occurrence of ML, which method is the most effective and the least neurotoxic is still under discussion [21]. Even studies using the same method (cranial radiation with ± 5 i.t. MTX injections) have considerable variations in effectiveness. The rate of primary CNS relapses in children varied btween 1.3 and 15% [6–10, 17, 22]. The incidence in adults was 0–10.7% [11–13]. The inconsistency in outcome was more pronounced when lumbar i.t. MTX alone was used. The incidence of primary CNS relapses in children was as low as 5.5–6.9% or as high as 18.5–44% [6, 7, 10, 17, 19]. The better outcome was perhaps due to a longer period of prophylaxis (1–3 years). At The Memorial Hospital in New York the primary CNS relapse rate of adults was 11.1% on the L2 protocol and 2.8% on the L10–L10M protocol [19–20]. In another study the rate was 4.3% [13]. The lower incidences corresponded with i.t. treatment maintained during 2–3

years, and with the use of the i.vt. route in patients with an initial WBC count over 20 × 10^9/l in the L10–L10M study. Systemic chemotherapy was also more intensive in the latter. It is of interest to note that adults on the L2 protocol, in contrast to children, did not receive maintenance i.t. MTX [23].

In our study only two cases of ML in the prophylaxis group were primary CNS relapses (5.6%). This is comparable with the results in other studies, since the prophylaxis in these two patients was not optimal.

The choice between the different CNS prophylaxis methods is determined not only by the effectiveness. Long-term side-effects, interference with other treatment modalities and ease of application must also be considered. In adults the impact of an isolated CNS relapse is probably different from the same event in children who experience less BM relapses and have longer remission durations [24]. Since the meninges are at risk with every new episode of leukemia, the CNS prophylaxis in adults must be designed in such a way that it can be repeated easily. Leukemic cells can remain dormant in the CNS [25]. This requires long periods of treatment, but the exact length has not been determined. A reservoir facilitates extended treatment and reliable distribution of drugs in the subarachnoid space [26]. Also it enables frequent CSF examinations essential for diagnosing still asymptomatic ML, and drug level monitoring. Lumbar i.t. injections of toxic drugs can cause local inflammation and fibrotic reactions, which make spinal taps gradually more difficult to perform and drug distribution unreliable. These drawbacks of i.t. injections are avoided by the i.vt. approach. Following i.vt. injections, chemical arachnoiditis was rare. In one elderly patient with symptomatic ML a mild but reversible MTX encephalopathy was seen. The metabolic rate in older patients is often lower [27]. Therefore in older patients and in patients with blockage of the CSF pathways, we now start with a lower dose of MTX and the CSF drug levels are determined more frequently.

The question remains why the Ommaya reservoir has not been used more often for prophylactic purposes since the i.vt. administration of drugs has been the accepted therapeutic modality for ML, meningitis carcinomatosa and fungal meningitis [28–31]. One important factor could be that CNS prophylaxis originates from childhood series. Adults are certainly more verbal, complaining about the unpleasant repeated spinal taps, which necessitates a more acceptable solution. The technical problems, the risk of introducing infection through the reservoir and the possibility of drug toxicity may have discouraged some. Our experience is more positive. With careful antiseptic handling of the reservoir (458 punctures in 45 patients), we were able to limit the instances of meningitis to three, all caused by commensal bacteria. This never required removal of the reservoir. An early diagnosis and combined i.v. and i.vt. antibiotics are essential. Cefradine 50 mg and cefuroxim 30 m instilled daily in the cerebral ventricles were both well tolerated, resulting in complete recovery with normal functioning of the reservoir.

Technical problems at the time of insertion of the device depend mostly on the experience of the neurosurgical staff. Other failures can originate from choroid plexus tissue enveloping the draintip and eventually obstructing the perforations. Spontaneous displacement of the catheter tip from a position in the lateral ventricle into the brain parenchyma can occur. These rare complications can be corrected. It is conceivable that growth of the brain and skull in infants could contribute to displacement of the cannula.

Some factors are related to a greater risk of developing ML, such as high initial WBC (>25–50 × 10^9/l) LDH >600, T-cell ALL, L3 morphology and an age under 20 [5, 32–34]. In our small study the importance of the risk factors was not so clear (see Table 1). ML was an initial finding in two patients with B-ALL and in one with T-ALL. An early start of prophylaxis in the other T-cell leukemias could have counteracted the increased risk. The age distribution of the ML cases was remarkable. The median age of patients without previous CNS treatment was 52 years, while in the propyhylaxis group it was 18. However, this does not mean that one age group is more prone to develop ML since the whole prophylaxis group had a median age of 22.

This study suggests some influence of CNS prophylaxis on the duration of the first remission and the survival (Table 3). It is impossible to separate the contributions of additional factors such as the presence of initial ML. The first remission duration is in the range of the results in some other studies in adults with CNS prophylaxis, although the median survival is longer [11–13]. In this respect the results in the L2 and L10–L10M protocols are certainly better [19–20] but the rate of all CNS relapses is comparable. Furthermore we did not lose patients because of ML. It is unlikely that the difference in length of CNS prophylaxis played a greater role in their more favorable results than did the more intensive systemic therapy.

The response of ML to i.vt. treatment was independent of prior CNS prophylaxis, simultaneous BM relapse or not. When the ML was symptomatic CNS remission duration was shorter (2 months) than when it was asymptomatic (6 months). This is similar to Stewart *et al.*'s results [5].

In conclusion it can be emphasized that a CNS

prophylaxis regimen must have the flexibility to be repeated, if required. Maintenance presymptomatic treatment via a reservoir is a convenient method. Furthermore i.vt. chemotherapy can treat CNS relapses well. It does not interfere with systemic chemotherapy, because the remaining BM capacity is not compromised, and cranial or craniospinal radiation is seldom necessary. Also neurotoxicity is prevented by leaving the blood brain–barrier intact as long as possible. Intensification of CNS prophylaxis in certain types of ALL or in patients with high WBC counts must be studied. The optimal duration of the prophylaxis has yet to be determined in a randomized trial. Our impression is that half a year will be adequate. A better overall outcome in adults with ALL will depend on the success of prolonging BM remissions.

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