Effect of Prophylactic Cranial Irradiation in Acute Lymphoblastic Leukemia in Children

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CNS prophylaxis with 18 or 24 Gy cranial irradiation plus intrathecal methotrexate was given to 134 childhood acute lymphoblastic leukemia patients who had got bone marrow remission (M1) after remission induction chemotherapy from August 1979 to December 1986.

The rate of initial total CNS relapse was 14.2% (19/134), the rate of isolated CNS relapse was 5.2% (7/134), and the rate of CNS relapse concomittantly combined with bone marrow relapse or testicular relapse was 9% (12/134). Male sex or older age was accociated with higher CNS relapes and the initial peripheral leukocyte count over 50,000/ul had higher relapse rate. Relapse with radiation dose of 18 Gy was somewhat lower than that with 24 Gy. Within 4 years after CNS prophylaxis occurred 89% of the total CNS relapses, 100% of the isolated CNS relapses, and 83% of the combined CNS relapses. Adjusted to exposed cases to risk of CNS relapse, the total CNS relapse rate was 11.9% during maintenance chemotherapy and 4.9% after maintenance chemotherapy.

Key Words: Acute lymphoblastic leukemia, CNS prophylaxis, Cranial irradiation, CNS relapse

INTRODUCTION

Meningeal relapse, primarily an arachnoidal disease[1,2], remains a major clinical obstacle for the cure of childhood leukemia after bone marrow remission. The incidence of meningeal relapse was reported to be 50%~85%[3~5] and the meningeal leukemia has two points; overt meningeal leukemia is less amenable to cure[6~10], and largely will be followed by systemic relapse[7,11~13].

The concept of Pinkel in the St Jude Children's Research Hospital about pathogenesis was that at the time of diagnosis leukemic cells already exist in the meninges and, even after bone marrow remission is achieved, and proliferation of remaining cells resulted in the meningeal leukemia, because systematically administered chemotherapeutic agents cannot reach sufficient concentration in the meninges and cells proliferate to be meningeal relapse[14]. His postulation was soon supported by the dramatic reduction of meningeal relapse after treatment of meningeal subclinical disease at early remission. It was a breakthrough. Since prophylactic or presymptomatic treatment toward the meningeal sanctuary site became an important component of antileukemic therapy from early seventies, meningeal realpse rate was rapidly reduced to 5% ~10% and survival was also increased[11,15~17].

We analyzed incidence and patterns of CNS relapse in childhood ALL patients treated with prophylactic cranial irradiation and intrathecal chemotherapy during last 8 years, to know efficacy of our prophylactic regimen, a form of standard method, and to find which subset of patients had higher CNS relapse despite of the prophylaxis.

MATERIALS AND METHODS

From August 1979 to December 1986, 155 children younger than 15 were diagnosed as acute lymphoblastic leukemia and got prophylactic cranial irradiation (PCI) and intrathecal methotrexate (IT MTX). The number of eligible patients in this analysis was 134, because 21 patients who had meningeal leukemia at diagnosis, did not achived M1 marrow status (blasts<5%), or did not complete the whole course of maintenance chemotherapy were excluded. All but 2 cases were followed up and median follow-up period of relapse-free patients was 49 months.

Boys were more common (64%), and the age of

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Table 1. Patient Characteristics

Charateristics	No. of Pts (%)
Sex	
Male	86 (64)
Female	48 (36)
Age (year)	
< 1	4 (3)
1 – 4	58 (43)
5 – 9	39 (29)
10 – 14	33 (25)
WBC count (/ul)*	
– 9,999	67 (50)
10,000 – 49,999	34 (25)
50,000 –	33 (25)

* : initial peripheral count

Table 2. Groups of Patients

PG*	No. of Pts (%)
Good	6 (4)
Intermediate	80 (60)
Poor	35 (26)
Infant	4 (3)
Lymphoma-Leukemia	9 (7)

* : Prognostic group by the Children's Cancer Study Group[40]

72% of patients were in range from 1 to 9, and 50% of patients had initial peripheral WBC count equal to or greater than 10,000/ul (Table 1). Infants were treated till April 1985 and 4 infants were included in this study. One boy with Down's syndrome and ALL was observed. When the patients were categorized into prognostic group (PG) by criteria of the CCSG (Children's Cancer Study Group), Intemediate PG was the most common (60%) and was followed by Poor PG (26%) (Table 2). Six patient with Good PG were treated till 1984 but we didn't treat this group of patients from 1985.

CNS treatment consisted of PCI and IT MTX. The dose of MTX was 6 mg, 8 mg, 10 mg and 12 mg for patients under 12 months, 12~23 months, 24~35 months, and over 36 months of age, respectively and IT MTX was delivered 5~6 times from induction phase with PCI. Radiation was delivered with Rt & Lt parallel opposed whole brain ports including retroorbital spaces, cribriform plate, and C2 vertebra segment using Co-60 gamma rays. The total dose was 1,800 cGy/10 fx or 2,400 cGy/12 fx. Eight patients with extreme leukocytosis over 100,000/ul at diagnosis had emergency cranial irradiation of 4 ~6 Gy/2~3 fx immediately for prevention of intracranial hemorrhage[18,19].

Table 3. Patterns of Initial Relapse

Pattern	No. of Pts. (%)
CNS	19/134 (14.2)
Bone Marrow	29/134 (21.6)
Testis	6/134 (4.5)
Bone Marrow & Testis	1/134 (0.7)
Total	55/134 (41.0)

Table 4. Patterns & Rate of CNS Relapse

Pattern		No. of Pts. (%)
Isolated	CNS	7/134 (5.2)
Combined	CNS & BM	10/134 (7.5)
Combined	CNS & Testis	2/134 (1.5)
Total		19/134 (14.2)

After CNS prophylaxis, clinical or CSF examination was periodically done during or after maintenance chemotherapy period. Diagnosis of meningeal relapse was made when CSF contained mononuclear cells over 5/cubic mm and any lymphoblast, or when there were cranial nerve palsy or signs of hypothalamic involvement[19,20]. Initial relapse site or pattern was analyzed and isolated CNS relapse was separated from CNS relapse combined with marrow or testicular relapse (combined CNS relapse) and chi-square test was used for statistic comparison.

RESULT

There were 55 relapses and 34.5% (19/55) of them was initial CNS relapse (Table 3). So the total CNS relapse rate was 14.2% (19/134); isolated CNS relapse rate was 5.2% and combined CNS relapse rate was 9% (Table 4). Of total CNS relapse 36.8% (7/19) was the isolated and among 12 combined CNS relapses 83% (10/12) was combined with systemic bone marrow relapse.

Male showed higher relapse than female and older age was associated with higher CNS relapses. The relapse was high, 18.2%, in cases with

Table 5. CNS Relapse by Age, Sex, and Initial WBC Count

Characteristics	Patterns of Relapse			Total (%)
	CNS	BM & CNS	Testis & CNS	
Age (year)				
< 1	–	–	–	0/ 4 (0)
1 – 4	1	4	–	5/58 (8.6)
5 – 9	3	3	–	6/39 (15.4)
10 – 14	3	3	2	8/33 (24.2)
Sex				
Male	3	9	2	14/86 (16.3)
Female	4	1	–	5/48 (10.4)
WBC (/ul)*				
– 9,999	6	3	1	10/67 (14.9)
10,000 – 49,999	–	2	1	3/34 (8.8)
50,000 –	1	5	–	6/33 (18.2)

* : Initial peripheral count

Table 6. CNS Relapse by Prognostic Group and Treatment Period

PG*	Number relapsed Patients		Rate Total (%)
	On-therapy	Off-therapy	
Good	0/ 6	0/ 2	0
Intermediate	8/80	3/41	13.8
Poor	6/35	0/15	17.1
L-Leukemia#	2/ 9	0/ 3	22.2
Infant	0/ 4	–/–	–
Total	16/134 (11.9%)	3/61 (4.9%)	14.2

* : Prognostic group by the Children's Cancer Study Group

\# : Lymphoma-leukemia

WBC count over 50,000/ul, and was especially high, 37.5%, in cases with WBC count over 100,000/ul (Table 5).

The poorer the prognostic group, the higher the CNS relapse rate was (from nil to 22.2%) (Table 6). But no relapse in the Infant group didn't actually mean their low risk of of relapse, but too short survival time for the meningeal relapse to occur because all infants had marrow relapse and failed to survive 2 years. Low risk groups (Good+Intermediate) showed a lower relapse rate than High risk group (Poor+Lymphoma-Leukemia), that was, 12.7% vs 18.2% of total relapse or 7.0% vs 13.6% of combined relapse.

CNS relapse rate was somewhat higher with 24 Gy than with 18 Gy, and was most high (37.5%) in patients who had previous irradiation of 4~6 Gy at diagnosis because of extreme leukocytosis (Table 7).

Total CNS relapse rate decreased as the time elapsed after CNS prophylaxis and so 68% and 89% of total relapses occurred within 2 and 4 years after CNS prophylaxis, respectively, and 57% and 100% of isolated relapses, 75% and 83% of combined relapses, respectively (Table 8).

When the relapse which occurred during maintenance chemotherapy period (on-therapy relapse) could be separated from the relapse which occurred after maintenance chemotherapy period (off-therapy relapse), on-therpay total CNS relapse rate was 84.2% (16/19) among the total CNS relapse, and was 11.9% (16/134) among all eligible patients. Whereas all the isolated CNS relapse was on-therapy relapses, all the off-therapy relapse was the combined relapse (Table 9).

Thus, all patients had meningeal relapse rate of 14.2% after CNS prophylaxis, and on-therapy relapse rate of 11.9% (16/134), but off-therapy relapse rate of 2.2% (3/134). Meanwhile, off-therapy relapse rate was 4.9% (3/61) for 61 patients who survived on-therapy period.

Table 7. CNS Relapse by Radiation dose and Prognostic Group

Dose (Gy)	Relapse Pattern	Number relapsed / Patients				Total (%)
		Good	Intermediate	Poor	Lymphoma-Leukemia	
18	Isolated	0/6	5/79	0/21	1/5	6/115 (5.2%)
	Combined	0/6	6/79	2/21	0/5	8/115 (7.0%)
24	Isolated	–	0/ 1	0/ 8	0/2	0/ 11 (0.0%)
	Combined	–	0/ 1	2/ 8	0/2	2/ 11 (18.2%)
18*	Isolated	–	–	1/ 6	0/2	1/ 8 (12.5%)
	Combined	–	–	1/ 6	1/2	2/ 8 (25.0%)

* : Previously had emergency irradiation due to extreme leukocytosis

Table 8. Time Interval of the CNS Relapse from the First Day of the CNS Prophylaxis

Time (Months)	CNS	BM & CNS	Testis & CNS	%
1 – 24	4	8	1	68 (13/19)
25 – 48	3	1	–	21 (4/19)
49 –	–	1	1	11 (2/19)

Table 9. On-therapy or Off-therapy Pattern of CNS Relapses

Pattern	CNS	BM & CNS	Testis & CNS	Total (%)
On-therapy	7	8	1	16/134 (11.9)
Off-therapy	–	2	1	3/134 (2.2)

DISCUSSION

The diagnosis of meningeal leukemia largely depends upon microscopic criteria, because recently most of patients are asymptomatically diagnosed as meningeal leukemia by periodic CSF examination. Thus the incidence at diagnosos, and during or after antileukemic therapy could vary. Our criteria of the diagnosis, over 5 mononuclear cells or any lymphoblasts in CSF, has been used by some studies [21,22], but differed from criteria of others[7,23~26]. And change of criteria could be found even in the prospective studies such as CCSG (Children's Cancer Study Group) or Total Therapy protocol of SJCRH (St Jude Children's Research Hospital). To overcome the inconsistency or contoversy in the definition of CNS leukemia, the recommendation of the 1985 Rome Workshop on Poor Prognosis ALL[27], whcih defined the CNS leukemia as >5 mononuclear leukocytes/ul of CSF with morphologically unequivocal lymphobast in cytocentrifuge sample, will be a good guideline.

The prototype regimen of CNS prophylaxis was introduced by pioneering studies of the SJCRH based on experimental result that intracerebrally inoculated L1210 leukemic cells had been successfully cured by CNS irradiation and cyclophosphamide[28]. Their 'Gold Standard' regimen consisted of 24 Gy cranial irradiation in 18 days, plus concomittant five doses of intrathecal methotrexate (IT MTX), 12 mg/sq m, every 3 to 4 days[11,15~17], and their study from 1962 to 1975 showed that the rate of initial CNS relapse had dramatically reduced from 62% ot 4.4%~10% by craniospinal irradiation or cranial irradiation plus IT MTX. Thereafter this regimen was largely accepted as useful standard[29,30].

Based on the conventional prophylactic regimen, a CNS relapse rate exceeding 10% is unacceptable and the goal should be to decrease it to less than 5%[31]. So our result of isolated CNS relapse rate of 5.2% is in quite acceptable range. Many reported that initial CNS relapse did influence bone marrow remission and both forms of relapse influenced survival except some studies[7,32,33] asserted that CNS relapse was not necessarily followed by bone marrow relapse and death, and that improvements in survival was probably the result of more effective systemic chemotherapy and better general management.

Certain factors at diagnosis have been reported to be associated with CNS relapse after bone marrow remission. The initial number of peripheral WBC reported to be prognostic[3,4,7,12,24,29,34,35].

Higher WBC count has two possibilities, access of relatively large number of cells ot the CNS and higher rate of replications of the cells within the CNS[3]. Counts over 10,000/ul, 20,000/ul, 25,000/ul, or 50,000/ul were reported to be associated with higher relapse, thus it was agreed upon that the higher the count, the greater the incidence of CNS relapse was and the earlier the relapse time might be. Our result of higher relapse with higher WBC count also well matched to the general tendency, but cases with WBC count over 50,000/ul seemed to require intensification of our present regimen.

High incidence of relapse was reported in adult, children younger than 2 years or older than 9 years[29,36,37]. This report showed that children older than or equal to 10 years had two times as high relapse rate as children younger than 10 years, was well consistent with other reports. Sex was not related with the CNS relapse or initial association reappeared after 3 years[3,38]. There was somewhat but not significantly higher relapses in boy in this analysis, too.

T-cell type ALL by the cell surface marker had the higher rate of CNS relapse, and commonly associated with mediastinal mass, higher WBC count, or pre-treatment CNS disease[29,36,39]. Mediastinal mass, hepatomegaly, splenomegaly, and especially massive lymph node enlargement which represented the lymphomatous presentation had higher rate of CNS relapse, too[3,4,29,35]. Thrombocytopenia was also correlated with higher CNS relapse[3,4].

Aforementioned factors were largely included in categorization of many prognositic groupings[7,22,25,26,40]. Our result of isolated CNS relapse rate of intermediate PG, to which rather large number (80 cases) belonged, was 6.3% (5/79) with 18 Gy PCI and was similar to result from the CCSG, 5%[40].

CNS relapse by time interval is peculiar. The monthly rate of relapse was 3.8% till the first 24 months and then decreased to 2%, or relapse rate was fairly constant in the first 2.5 years and then decreased without CNS prophylaxis[3,9]. The result that 81% of relapses were observed within 36 months after prophylaxis[31] showed a similar pattern, that was, of gradual decrease of the CNS relapse when the rate was calculated in all patients. But it will reveal a different pattern when the number of patients at risk for each time interval were taken into consideration, and the data from the CCSG that proportion of patients experiencing CNS relapse by life table analysis showed increasing pattern of relapse till 5 years from randomization[25]. And still our patients have off-therapy total CNS relapse of 4.9%, when exposure to risk was adjusted.

Prototypic dose of 2,400 cGy was determined by the SJCRH after it was evident that early trials of SJCRH in sixties using 5~12 Gy was ineffective. But after the CCSG showed that dose could be decreased to 1,800 cGy without sacrificing control of CNS leukemia in patients with initial WBC count less than 50,000/ul, and after studies indicated that SJCRH's standard regimen were not as benign as originally reported[41] after short-term follow-up in limited number of patients, 18 Gy have been administered to all children by the CCSG. Our data by the radiation dose showed that higher radiation dose ironically tended to result in higher relapses, but was probably due that 24 Gy was delivered to the rather high risk groups, and that number of patients treated with 24 Gy was small, and that cases with extreme leukocytosis at diagnosis were, as previosly mentioned, associated with high rate of relapses. But by the results of the CCSG 101 and 143 trial, rate of CNS relapse was not adversely affected when the total dose was reduced from 24 Gy to 18 Gy or when daily doses of 120 to 150 cGy were used rather than 180 to 200 cGy in all prognostic groups[24,25,42].

Increasing attention has been paid to the adverse late effects of therapy, because large number of patients have survived prolonged time. CNS irradiation with 24 Gy was implicated in a number of late sequelae, including decline in I.Q. scores[43~45], decreased psychoneurologic function and intellectual development[43,46~50], growth impairment[51], and secondary oncogenesis[52]. It is not known if reducing the radiation dose from 24 Gy to 18 Gy will result in a detectable decrease in the late sequelae. Although percentile in height and weight after 18 Gy was slightly better than those with 24 Gy, significant impairment was observed after both doses compared to those with IT MTX alone[51].

There have been many trials to avoid cranial irradiation or to reserve it for the overt CNS relapses. Intrathecal chemotherapy alone had controversy in its results. IT MTX with or without reinduction IT therapy during systemic chemotherapy resulted in CNS relapses of 4 to 10 times as high as irradiation[4,7,21,36]. But triple drug IT chemoprophylaxis had the same efficacy as 24 Gy cranial irradiation and IT MTX by the Pediatric Oncology Group[22] which, in the meanwhile, evoked many

arguements that regimen of systemic chemotherapy was more intensive and periodic reinduction IT therapy with steroid ws done only in the IT groups, that follow-up period was too short, that patients with lymphomatous presentation were excluded, and finally that detailed neurotoxicity was not reported[27]. But following report from POG did not find any difference between IT triple with and without 24 Gy irradiation[26]. So it might be said that IT chemotherapy with periodic reinduction IT therapy could be administered to a group of patients without compromising previous efficacy.

Intensive systemic chemotherapy such as inermediate-dose MTX, high-dose MTX, or others with leucovorin rescue and IT chemotherapy was tried by some institutes. The rate of intial isolated CNS relapse was reported upto 33% in early studies[53,54], and to be 5% to 9% and those of total relapse rate was about 12% in recent studies[23,55]. But more vigorous systemic regimen failed to improved the result. Furthermore one study showed a significantly higher CNS relapse rate with high dose MTX than with 24 Gy plus IT MTX[33].

There were some studies concerning comparison among standard regimen with 24 Gy, high-dose MTX with IT MTX, and IT MTX alone. A cross study comparison showed that cranial irradiation was the most effective regimen in prevention of CNS relapse in patients of standard-or high-risk and also in achievement of disease-free survival in high-risk patients, and that high-dose MTX resulted in the highest disease-free survival of standard-risk patients only[56]. Standard regimen of that study had a eligibility bias of excluding T-cell ALL that had high risk of CNS relapses. Full scale I.Q. was significantly low with 24 Gy irradiation[44,45]. But there was no difference in memory impairment between HD MTX group and 18 Gy irradiation group, though visuo-spatial memory and verbal memory were impaired in both groups[57]. As for the time interval of relapses one study showed a persistent tendency of relapse after maintenance chemotherapy using intensive regimen without irradiation[55].

But we must see the fact that chemotherapy is not exempt from inducing neurotoxicity, and that MTX given during or after CNS irradiation of 20 Gy or more is much more likely to produce severe neurologic sequelae [43,47~49,56,58]. This will be used in determination of treatment sequence of combined treatment in the future trial.

Standard prophylactic regimen including cranial irradiation resulted in an incidence of about 5% of CNS relapse evidently as our result. Whether cranial irradiation will be replaced by systemic chemotherapy in cetain subsets of risk group or whether it will be eliminated from the antileukemic regimen is uncertain. But it is mandatory to tailor the method of CNS prophylaxis according to risk of the meningeal relapse that individual childhood ALL patients has.

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═국문초록═

소아 급성 임파구성 백혈병에서 예방적 전뇌 방사선조사의 효과

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1979년 8월부터 1986년 12월까지 관해유도 치료후 골수 관해(M1)가 온 134예의 소아 급성 임파구성 백혈병 환아가 18 Gy 또는 24 Gy의 전뇌 방사선 조사와 척수강내 methotrexate 주입의 예방적 중추신경계 치료를 받았다.

중추신경계에서 처음 재발한 환자는 14.2%(19/134)였고 이중 중추신경계에서만 재발한 예는 5.2%(7/134), 골수 또는 고환에서의 재발과 동시에 재발한 예는 9%(12/134)였다. 남아와 연령이 많을수록 중추신경계 재발이 높았으며 진단당시 말초혈액내의 백혈구수가 50,000/ul 이상인 예의 재발율이 높았다. 방사선 조사량 24 Gy에서의 중추 신경계 재발율이 18 Gy인 경우보다 높았으나 유의하지는 않았다.

전체 중추신경계 재발예 중 89%가 예방적 중추신경계 치료개시후 4년이내에 발생하였으며, 중추신경계에서만 재발예는 100%가, 중추신경계와 골수 또는 고환의 재발과 동시에 재발한 예의 83%가 각각 관찰되었다. 재발의 위험이 있는 환자를 감안한 전체 중추신경계 재발율은 유지 화학 요법 기간 중에는 11.9%였고 유지화학 요법 종료 이후의 기간에서는 4.9%였다.