Original Articles

LOW INCIDENCE OF CNS RELAPSE WITH CRANIAL RADIOTHERAPY AND INTRATHECAL METHOTREXATE IN ACUTE LYMPHOBLASTIC LEUKEMIA

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Objectives: *To assess the incidence of isolated central nervous system (CNS) relapses in patients of acute lymphoblastic leukemia (ALL) treated with a protocol containing cranial irradiation and intrathecal methotrexate as CNS directed therapy.* ***Design:*** *Prospective non randomized study* ***Setting:*** *Department of Medical Oncology, Tata Memorial Hospital.* ***Subjects:*** *623 children of ALL on MCP 841.* ***Methods:*** *CNS relapse was diagnosed, if upon examination of the CSF, more than 50 cells/µl were observed, or a count of 5 cells which were unequivocally lymphoblasts.* ***Results:*** *The incidence of isolated CNS relapse was 1.75% with the use of this treatment. Age, sex, white blood cell count, platelet count, lactic dehydrogenase and immunophenotyping were not significantly related to isolated CNS relapse.* ***Conclusion:*** *A low incidence of isolated CNS relapse demonstrates the adequacy of the presymptomatic CNS therapy.*

Key words: *Leukemia, Cranial radiotherapy, Relapse.*

THE last two decades have witnessed a dramatic improvement in the prognosis of children with acute lymphoblastic leukemia (ALL). One important contributing factor has been the use of improved treatment of sanctuary sites, especially the central nervous system (CNS). The objective of CNS therapy is to eradicate microscopic foci of leukemic cells in the CNS, usually present at the time of diagnosis. In the absence of presymptomatic CNS therapy, 50-70% of patients are likely to experience CNS leukemia(l,2). Current protocols for ALL report an isolated CNS relapse incidence between 2-8%(3). We report here a low incidence of CNS relapse in our patients of ALL treated with cranial radiotherapy and intrathecal methotrexate.

Subjects and Methods

Patients with a confirmed diagnosis of ALL were accrued on MCP-841 protocol *(Fig. 1)* between the study period of June 1986 and December 1993. The data was analyzed in June 1994. Patients with: *(i)* WBC counts of 10,000/cu mm or less; *(ii)* age 3 to 6 years, both inclusive; *(iii)* no prominent lymphadenopathy (<3 cm diameter in each nodal region); *(iv)* no mediastinal mass; *(v)* no organomegaly (liver and spleen); *(vi)* a normal CSF and absence of cranial nerve palsies were defined as low risk, whereas all others were labeled high risk cases. Treatment comprised four drug induction using vincristine, L-asparaginase, daunomycin and prednisolone and

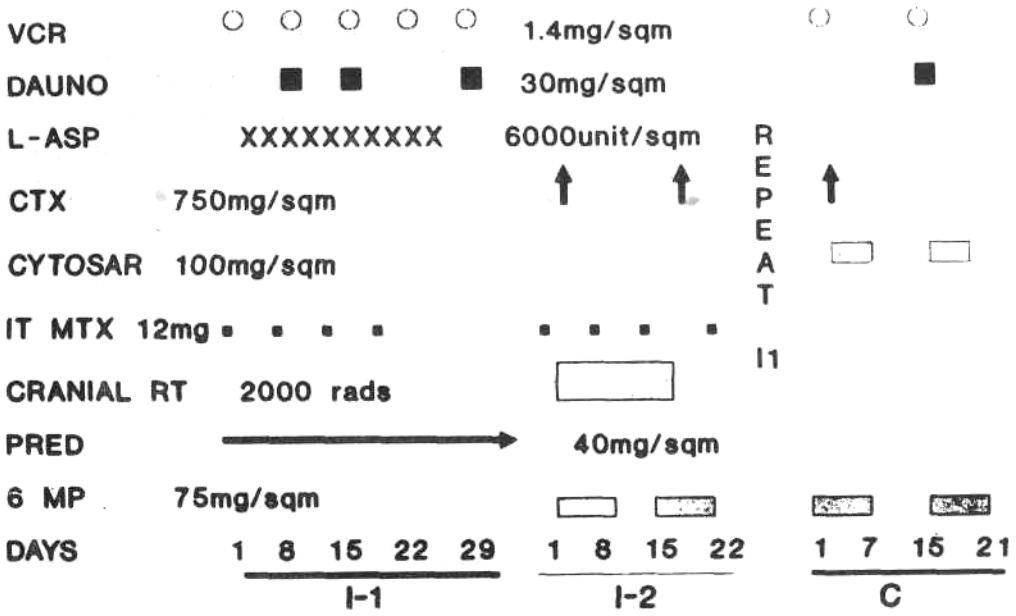

Fig. 1. The MCP-841 protocol. VCR: Vincristine; DAUNO: Daunorubicine; L-ASP: L-asparaginase; CTX: Cyclophosphamide; CYTOSAR: Cytarabine; IT MTX: Intrathecal methotrexate; RT: Radiotherapy; Pred: Prednisolone, 6MP: 6 Mercaptopurine; sqm: square meter.

consolidation with cyclophosphamide and cytosine arabinoside. CNS prophylaxis comprised 12 doses of intrathecal methotrexate (10 mg/m^2) at weekly intervals during induction phases of treatment and cranial radiotherapy in the dose of 20 Grey given in 10 fractions of 200 rads/day. Cerebrospinal fluid examinations were done monthly during induction/consolidation phases of treatment and 3 monthly for the next 2 years during maintenance therapy. In case of a bone marrow relapse, CSF examination was mandatory to rule out concurrent CNS disease.

CNS relapse was diagnosed, if upon examination of the CSF, more than 50 cells/ µl were observed, or a count of 5 cells which were unequivocally lymphoblasts.

Results

A total of 623 patients were entered onto protocol MCP-841 between June 1986 and December 1993. The majority of our patients (97%) were high risk cases. Clinical and laboratory characters of the subjects is given in Table I. Out of 623 patients, 568 patients received cranial radiotherapy, as 55 patients were induction deaths or failures. Out of the subjects who received cranial radiotherapy and 12 doses of intrathecal methotrexate, 10 patients had an isolated CNS relapse indicating a relapse rate of 1.76%. The patient characteristics of the relapsed cases are summarized in Table II. All except two patients were less than 14 years at the time of diagnosis. In addition 8 patients had CNS and bone marrow relapses. Table III indicates the number of patients relapsing at other sites. We applied the Chi-square test to assess the significance of various prognostic factors such as age, sex, white blood cell count, platelet count, lactic dehydrogenase and immunophenotyping for patients with CNS relapses and also for patients with

TABLE I-*Patient Characteristics*

Features	No. (%)
Age (yr)	
2-3	48 (8)
3-6	237 (38)
6-14	220 (35)
14-24	118 (19)
Sex	
Male	420 (67)
Female	203 (33)
Hemoglobin (g/dl)	
≤8	323 (52)
>8	300 (48)
WBC Count (Per cu mm)	
< 10,000	259 (42)
10,000-99,999	275 (44)
>100,000	89 (14)
Platelet Count (per cu mm)	
< = 10,000	225 (36)
≤ 10, 000	398 (64)
LDH (Units / L)	
≤1000	265 (43)
>1000	263 (42)
ND	95 (15)
Phenotype	
C-ALL	361 (58)
T-ALL	116 (19)
NULL	61 (10)
Not done	85 (13)

relapses elsewhere. None of the factors bore any significance to isolated CNS relapse, whereas patients with high WBC count and LDH had a higher chance of bone marrow relapses. Our disease free survival in this cohort of patients was 56.5% by the Kaplan Meir estimate and the event free survival was 46.8%. At present, 355 patients are alive and disease free. Of these, 298 patients are those who have completed therapy and 57 patients are still receiving maintenance chemotherapy. The median follow up for patients accrued in 1993 is 21 months.

Discussion

Since the first report from St. Jude Children's Research Center on the efficacy of pre-symptomatic radiation therapy in preventing CNS relapse(4), cranial radiotherapy in combination with intrathecal chemotherapy has become a standard part of treatment of children with ALL. With the use of pre-symptomatic CNS therapy, the MRC UKALL VIII(5) trial was associated with an isolated CNS relapse rate of 7% which is comparable to the 9% rate in the population based Nordic series(6). The St. Jude study XI for childhood ALL has reported an isolated CNS relapse rate of 5%(7) and Gelber *et al*.(8) in their analysis have reported a rate of 6%. We report here a low CNS relapse rate of 1.75%. This is probably because of 2000 rads of cranial radiotherapy and 12 doses of intrathecal methotrexate.

With the improvement in survival of children with ALL, attention has now been focused on the late sequelae of cranial radiotherapy and what exactly is optimal CNS directed therapy. CNS irradiation has been implicated in a number of adverse effects, including declining IQ scores and psychoneurological function(9,10), decreased growth(ll) and susceptibility to second malignancy. Our experience has shown a decrease in the IQ of patients receiving cranial radiation.

Freeman *et al*.(12) have compared the use of intermediate dose methotrexate with cranial radiotherapy and concluded that cranial radiotherapy offered better protection to the CNS in standard risk patients. The BFM group(13) showed that intermediate dose methotrexate could produce protection against CNS relapse,

TABLE II–*Characteristics of Patients with Isolated CNS Relapse.*

Case No.	Age	Sex	Hb (g/dl)	WBC Count (per cu mm)	Platelet Count (per cumm)	Phenotype
1. AU 12745	8	F	9.7	1,66,000	15,000	C-ALL
2. AW 02765	4	M	7	18,000	10,000	C-ALL
3. AX 00436	5	M	8.2	10,400	1,25,000	C-ALL
4. AZ 15332	2	M	3.5	7,200	20,000	T-ALL
5. BC 04762	7	M	8.2	6,300	10,000	C-ALL
6. BC O7900	13	M	10.2	3,30,000	10,000	C-ALL
7. BD 02001	14	M	3	3,400	10,000	NULL
8. BD 17751	7	M	9	61,300	9,000	C-ALL
9. BD 20383	6	F	5.5	6,400	10,000	ND
10. BF 12739	16	M	6	32,000	30,000	T-ALL

Site	No.
Bone marrow	110
Testes	12
Mediastinum	2
Bone marrow and CNS	8
Bone marrow and testes	11

similar to cranial radiotherapy but only if intensification chemotherapy was given to the group of standard risk patients. It is, however, very difficult to standardize treatment based on these data because no two studies follow the same criteria for risk stratification. With the recognition of adverse effects of radiotherapy, a number of patient characteristics like high WBC count, T-ALL, very young age, male sex, *etc.* have been identified which are at an increased risk of CNS relapse(14). Most centers advocate CNS therapy tailored according to risk stratification and cranial radiotherapy plus intrathecal methotrexate continues to be used in high risk groups. In our patient population, 97% of the children belonged to the high risk group and therefore, we used the said CNS therapy to make a uniform protocol rather than using a new treatment schedule for a small minority of patients. With this mode of therapy, we were able to offer good CNS protection. At the same time we found this protocol cost effective mainly because alternate treatment would involve intensification of chemotherapy and with this not only the cost of treatment would increase but also the finances would be steered towards supportive care. It is, however, mandatory to study the late consequences of cranial radiotherapy and assess the feasibility of alternative intensive chemotherapy schedules. In one study(14), patients were randomized to one arm receiving cranial RT and triple intrathecal and the other receiving only triple intrathecal. Patients with high counts were also included in randomization. No significant difference was noted in the duration of CNS remission or CNS relapse rate between either of the group, thereby validating the efficacy of triple intrathecal as an adequate form of CNS protection. This alternative form seems promising and needs evaluation in our set up.

REFERENCES

1. Evans AE, Gilbert E, Zandstra R. The increasing incidence of central nervous system leukemia in children. Cancer 1970, 26: 404-409.
2. Aur R, Simone J, Hustu HO, Verzosa H. A comparative study of central nervous system irradiation and intensive chemotherapy early in remission of childhood acute lymphoblastic leukemia. Cancer 1972, 29: 381-391.
3. Bleyer WA, Poplack DG. Prophylaxis and treatment of leukemia in the central nervous system and other sanctuaries. Semin Oncol 1985,12: 131-146.
4. Aur R, Simone J, Hustu HO, *et al.* Central nervous system therapy and combination chemotherapy of childhood lymphoblastic leukemia. Blood 1971, 37: 272-280.
5. Eden OB, Lilleyman JB, Richards S, Shaw MP, Peto J. Results of Medical Research Council Childhood leukemia trial UKALL VIII. Br J Hematol 1991, 78: 187- 196.
6. Kreuger A, Garwicz S, Hertz H, Janmundsson G, Lanning M, Lie SO, *et al.*Central nervous system disease in child hood acute lymphoblastic leukemia. Prognostic factors and results of treatment. Pediatr Hematol Oncol 1991, 128: 291-299.
7. Rivera GK, Pui CH, Hancock ML, Mahmoud H, Santana V, Sandland JT, *et al.* Update of St. Jude Study XI for childhood acute lymphoblastic leukemia. Leukemia 1992,, 6: 143-156.
8. Gelber RD, Sallan SE, Cohen HJ, Donnelly M, Dalton V, Tobia F, *et al.* CNS relapse in leukemias. Cancer 1993, 72: 261-270.
9. Pizzo PA, Poplack DG, Bleyer WA. Neurotoxicities of current leukemia therapy. Amer J Pediatr Hematol Oncol 1979, 1: 127-140.
10. Pavlovsky S, Castano J, Leiguard R. Neurophysiological study in patients with ALL. Amer J Pediatr Hematol Oncol 1983, 5: 79-86.
11. Kruena H, Stanhape R, Chessells JM, Leiper AD. Impaired pubertal growth in acute lymphoblastic leukemia. Arch Dis Child 1991, 66: 1403-1407.
12. Freeman Al, Weinberg V, Brecher ML, *et al.* Comparison of intermediate dose methotrexate with cranial irradiation for the post-induction treatment of acute lymphocytic leukemia in children. N Engl J Med 1983, 308: 477-484.
13. Buhrer C, Menze G, Hofman J. Central nervous system relapse prevention in 1165 standard risk children with acute lymphoblastic leukemia in five BFM trials. *In:* Acute Leukemia II. Ed. Buchner K. Berlin, Springer Verlag, 1990, pp 500-505.
14. Komp DM, Fernandez CH, Falletta JM, *et al.* CNS prophylaxis in ALL. Cancer 1982, 50: 1031-1036.

NOTES AND NEWS

ACUTE FLACCID PARALYSIS SURVEILLANCE

IAP members are requested to immediately report to the District Immunization Officer whenever they see a patient with acute flaccid paralysis. Further action will be undertaken through the existing governmental system.