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The Treatment of Primary Childhood Acute Lymphocytic Leukemia with Intermediate Dose Methotrexate*

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A. Summary

Fifty-four consecutive children with acute lymphocytic leukemia (ALL) were treated from August 1974 until December of 1976 at Rosewell Park Memorial Institute (RPMI) according to a protocol which substituted cranial irradiation with systemic intermediate dose methotrexate (IDM) 500 mg/m^2 each 3 weeks for a total of 3 courses immediately following induction. Of 54 patients, 52 went into remission (96%). There were 35 standard risk and 17 increased risk patients according to age and presenting white blood count (WBC). As of September 1979 9 of the 35 standard risk patients had relapsed: (five central nervous system (CNS), three systemic, and one testicular. The overall disease control is comparable to other published methods of therapy involving cranial irradiation but has the added advantage of not exposing these children to the long range side effects currently being observed in children who had previously been treated with prophylactic cranial irradiation.

B. Introduction

The last decade and a half has seen dramatic improvement in the survival and actual "cure" of children with ALL. This improvement has been due principally to (1) the use of CNS "prophylaxis" and (2) effective systemic chemotherapy (Aur et al. 1971, 1972, 1973; Holland 1976; Hustu et al. 1973; Pinkel et al. 1977; Simone et al. 1975).

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In the first half of the 1960s as improved systemic chemotherapy resulted in longer duration of complete remission, it became apparent that approximately 50% of these children would develop CNS leukemia (Evans et al. 1970). Once they developed CNS leukemia, very few were cured. In the mid-1960s effective methods of CNS prophylaxis were first employed to prevent overt CNS leukemia and eventual systemic relapse and death. In 1968 Cancer and Leukemia Group B (CALGB) in Protocol 6801 utilized prophylactic intrathecal methotrexate (IT MTX) and found that instead of 50% developing overt CNS leukemia, only 23% of the children developed this complication (Holland 1976), which has yet to be improved upon in subsequent CALGB studies. At approximately the same time investigators at St. Jude Cancer Research Center introduced the technique of cranial RT and IT MTX as CNS prophylaxis. This method reduced the incidence of CNS disease to approximately 10% (Aur et al. 1971, 1972, 1973; Hustu et al. 1973; Pinkel et al. 1977), which has not been confirmed in larger cooperative group studies.

However, cranial RT clearly cannot eradicate leukemic cells in sanctuaries other than the cranial cavity, e.g., the gonads, liver, and spleen. Furthermore, there has evolved a growing concern with immediate and long-term toxicity from prophylactic cranial RT. Therefore in 1974 we began a study with the following objectives: (1) to prevent the development of CNS leukemia without employing cranial RT and (2) to intensify systemic therapy and thus eradicate leukemic cells in other sanctuaries, which has been more recently emphasized by late testicular relapses in two cooperative group studies (Land et al. 1979;

Baum et al. 1979). This study was based on clinical pharmacologic data demonstrating that intravenous IDM at a dose of 500 mg/m^2 given over 24 h was capable of diffusing across the CNS barrier in amounts adequate to eradicate most, if not all, leukemia cells in the CNS (Wang et al. 1976) and, hopefully, simultaneously penetrate other sanctuaries to a like degree. This report describes the clinical results of this study.

C. Materials and Methods

Fifty-four patients with newly diagnosed ALL were treated according to the protocol depicted in Fig. 1, which was instituted in the Department of Pediatrics at RPMI in August 1974. This was conducted as a pilot study and no randomization was planned.

Following induction with steroids, vincristine, and L-asparaginase, three courses of IDM were administered at three weekly intervals. IDM was administered at 500 mg/m^2, one-third by intravenous (IV) push and two-thirds by IV infusion over 24 h. IT MTX at 12 mg/m^2 was initially given on day 15, 22, 29 and then administered from ½ to 2 h after the initiation of IV MTX. Twenty-four h following completion of IV MTX, a single dose of citrovorum factor (leucovorin) was given at 12 mg/m^2. With moderately severe mucosal ulceration, the subsequent course of IDM was delayed until there was complete healing. The next IDM course was then administered at full dosage, but an additional dose of leucovorin at 12 mg/m^2 was injected 72 h from the start of IDM (48 h after completion of IDM). Following intermediate dose MTX, the patient received maintenance therapy consisting of daily oral 6-mercaptopurine and weekly oral MTX and pulse doses of steroid and vincristine (Fig. 1). Dexamethasone was used interchangeable with prednisone and 15 patients received the former.

All children with ALL or acute undifferentiated leukemia who could not be identified as acute myelocytic leukemia or acute myelomonocytic leukemia were entered on the study. Cell surface markers were not routinely done when this study was initiated.

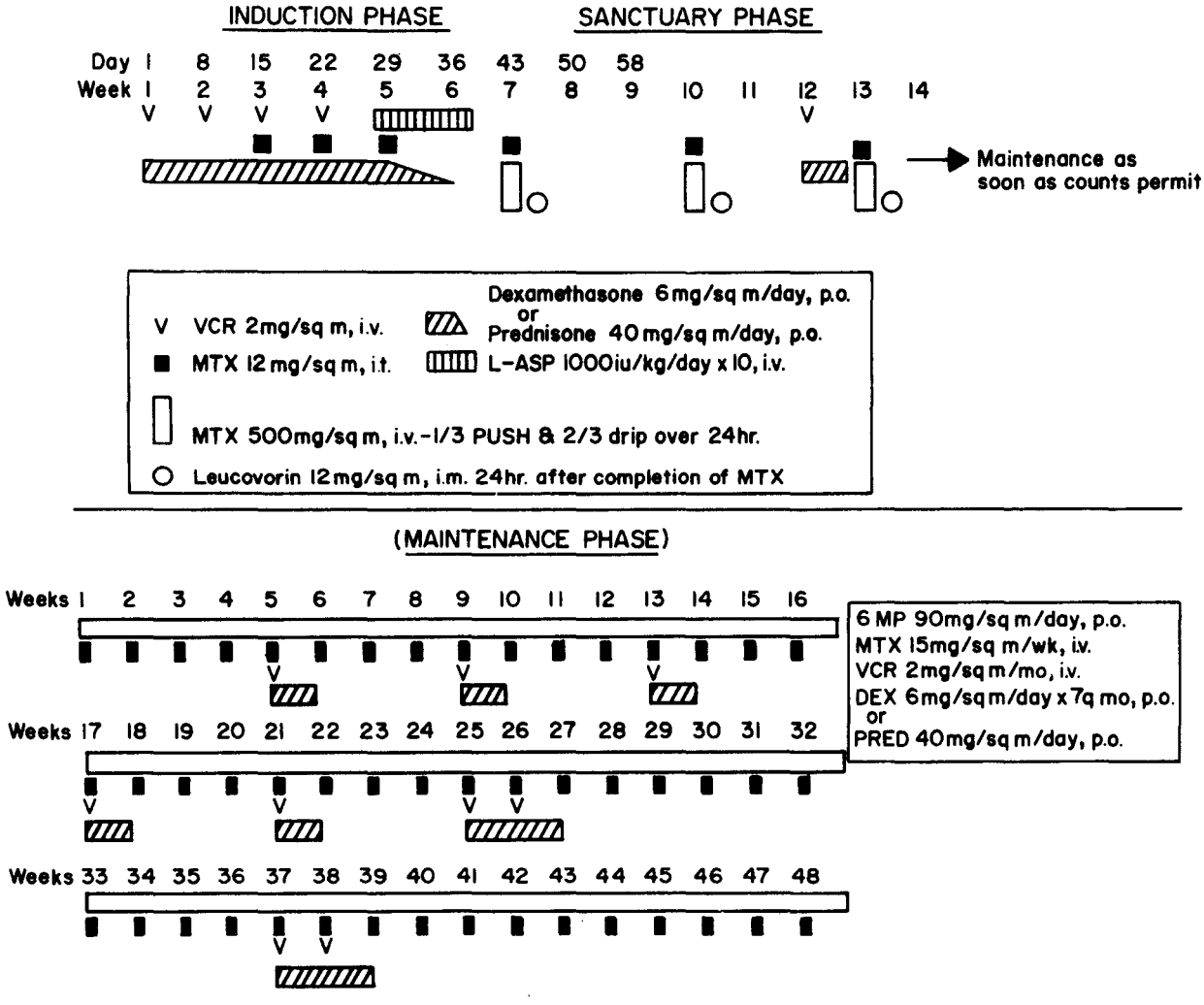

Fig. 1. Schema of treatment in ALL employing IDM

From August 1974 until December 1976, when the study was closed to patient accrual, 54 patients were entered ranging in age from 6 months to 17 years.

Patients were classified as standard risk or increased risk in terms of age or WBC at presentation, i.e., those patients less than 2 years or greater than 10 years of age and those patients who had a WBC greater than 30000/mm^3 were defined as being increased risk. There were 19 children classified as increased risk, 17 of which went into remission and 35 children who were standard risk, all of whom went into remission. Two children (increased risk) probably had CNS leukemia at diagnosis – one presented with papilledema, and one had a right facial palsy of central type, but when spinal taps were performed on these two children two weeks later, no blasts were detected in the cerebrospinal fluid (CSF).

Patients with hyperuricemia or elevated blood urea nitrogen levels received appropriate short-term therapy for these conditions prior to beginning antileukemic therapy. Red cell and platelet transfusions were used as needed. Peripheral blood counts and appropriate blood chemical determinations were performed at frequent periodic intervals.

Spinal taps were performed routinely until week 13 of therapy and then at the first symptom or signs indicative of a CNS problem. All children in remission had spinal taps performed from February 1979 through July 1979.

Bone marrow aspirates were examined prior to the onset and again at completion of induction therapy and every 2–3 months thereafter, or at any time the peripheral blood was suspicious of a relapse. The criteria for determining complete remission have been published previously (Ellison et al. 1968). A remission bone marrow has normal granulopoiesis, thrombopoiesis, and erythropoiesis with fewer than 5% lymphblasts and less than 40% lymphocytes plus lymphoblasts. The patient's activity, physical findings, and peripheral blood must have reverted to normal. Induction failure was defined as those patients not achieving a remission bone marrow (less than 5% blasts) by day 42.

Leukoencephalopathy was defined clinically by the persistant unexplained presence of confusion, somnolence, ataxia, spasticity, focal neurologic changes, and seizures (Rubinstein et al. 1975; Kay et al. 1972; Price et al. 1975).

For purposes of analysis, complete remission status was terminated by: (1) bone marrow relapse (greater than 25% blast cells), (2) development of meningeal leukemia (two blasts cells on cytologic preparations of the CNS or ten cells/μl not attributable to chemical meningitis, (3) biopsy-proven leukemic cell infiltration in extramedullary organs, and (4) death while in remission. Patients were taken off chemotherapy after 4 years of continuous sustained remission. There are now 14 standard risk patients and three increased risk off all therapy.

All plots of remission duration were determined by actuarial life table analysis. The duration of remission was calculated through August of 1979.

D. Results

Of 54 patients, 52 (96%) achieved complete remission. The two inductio ailures were both in the increased risk group.

As of 1 September 1979 all patients in continuous remission have been followed for 36 to 72 months. A total of 20 patients (38%) have relapsed. These included: ten CNS relapses, nine systemic relapses, and one testicular relapse. Eleven of 17 increased risk patients (64%) and 9/35 standard risk patients (25%) have relapsed (Table 1).

Table 1. Current analyses

Site of relapse	CNS	10
	Systemic	9
	Testes	1
Risk factor and relapse[a]	Increased risk	11/17
	Standard risk	9/35
Time on study	44–80 months	
Median time on study	52 months	

[a] Number of relapses/number of patients achieving complete remission, June 1980

Of the nine standard risk patients who relapsed, there were five CNS relapses, three systemic relapses and one testicular relapse. Three of the nine have died (Figs. 2–4).

Of the 11 increased risk patients who relapsed, five were in the CNS and six were systemic. Nine of the eleven patients have died. No CNS relapse was detected in those patients who had cerebrospinal fluid analysis performed routinely from February 1979 through July 1979.

One of the increased risk children who developed CNS leukemia was a 22-month-old male who presented with a central right facial palsy at diagnosis which subsequently disappeared with induction therapy and was thought to be due to CNS leukemia, but a spinal tap was not performed until 2 weeks later and there was no lymphoblasts in the CSF at this time. His CNS relapse occurred 23 months after diagnosis. Eight of the 52 children who entered complete remission have died.

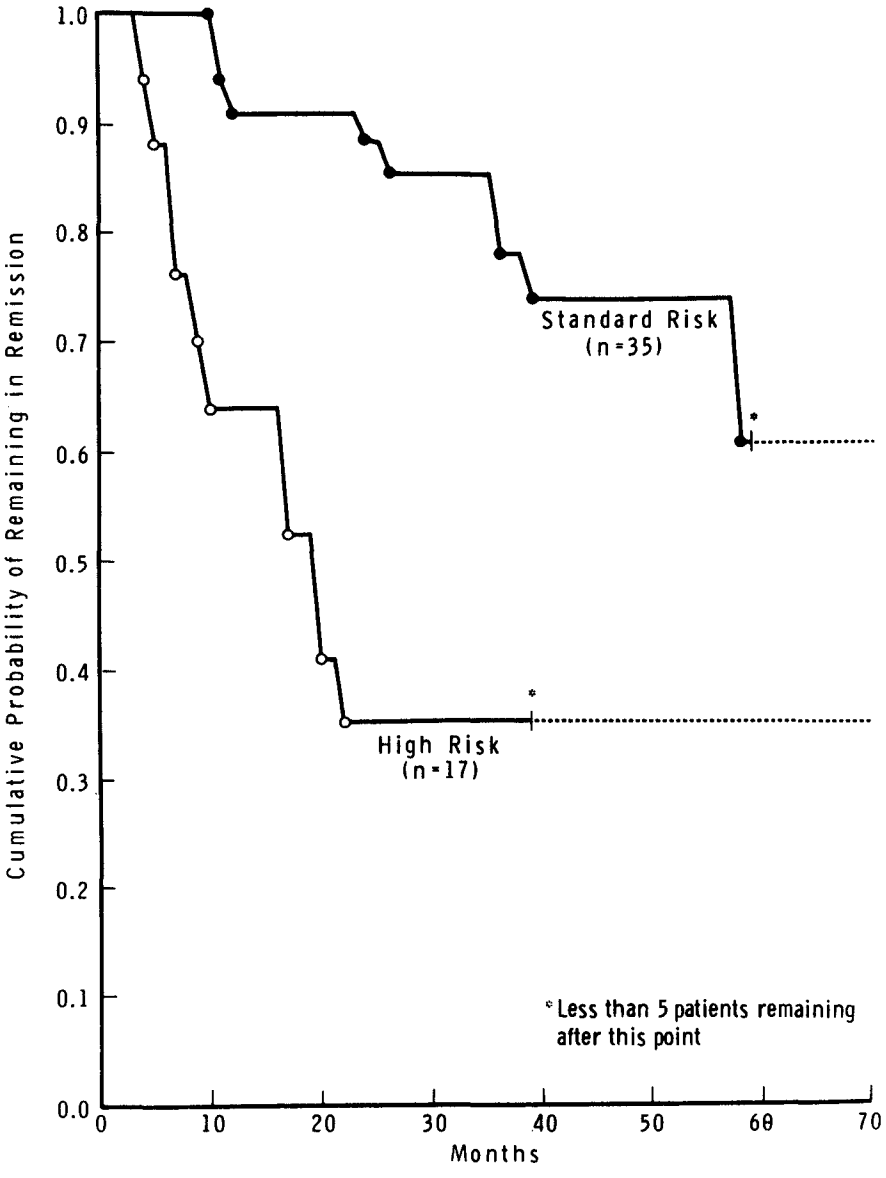

Fig. 2. Duration of *complete* remission employing IDM. Standard risk and high risk (see text)

E. Toxicity

The toxicity (Table 2) from the IDM included:

1. Vomiting occurring in 20/52 patients and was most pronounced during the first 2–4 h after the institution of IDM but occasionally persisted for 24–48 h;
2. Oral ulceration occuring in 20/52 patients with oral mucositis in 14 and pharyngitis in six patients. This was mild in 17/20, i.e., there were small ulcers which did not substantially interfere with orlke;
3. Hematologic toxicity occurring in 12 patients which, however, was minimal in its

Table 2. Toxicity results as of June 1980

Vomiting (with administration)	20/52	
Hematological		
WBC	2 (<3000/mm^3)	0 (<1500/mm^3)
Hgb	10 (<10 gm%)	0 (<8 gm%)
Platelets	0 (<100,000/mm^3)	
Mucositis	14/52 (3 moderate and 11 mild)	
Pharnygitis	6/52	
Hepatic	11/52 (mild)	
Skin	3/52	
Renal	0/52	

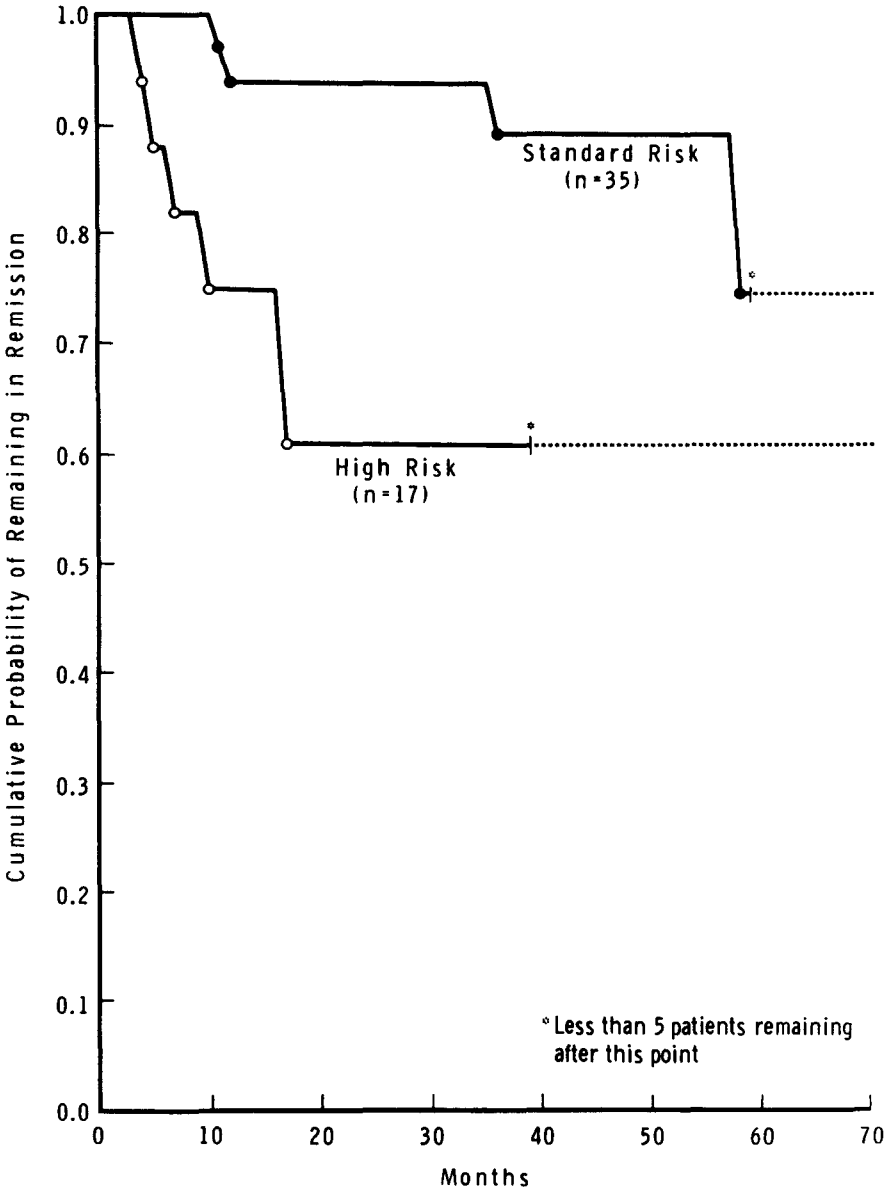

Fig. 3. Disease-free interval systemic+ remission includes bone marrow and testicular relapse only

severity; there were no related clinical manifestations;

4. Hepatic toxicity occurring in 11 patients as evidenced by increased liver enzymes, particularly the SGOT. However, the peak SGOT was less than twice the normal level and returned to normal in all cases; and
5. Transient maculopapular rashes occurring in three cases and lasting for several days.

No case of renal toxicity was noted.

The overall regimen has been very well tolerated. There has been no life-threatening toxicity and no deaths secondary to IDM. Furthermore, there have been no cases of leukoencephalopathy and no interstitial pneumonia associated with IDM. One adolescent experienced anaphylaxis with the first dose of L-asparaginase. There have been neither infectious deaths nor toxic deaths for any patient while in remission on this study.

F. Discussion

The clinical data upon which this study was based was that of the early work of Djerassi who demonstrated the effectiveness of high doses of MTX in ALL (Djerassi et al. 1967). CALGB Protocol 6601 demonstrated that the greatest proportion of children remaining in complete sustained remission were those who received the intensive cycles of IV MTX (18 mg/m^2) daily for 5 days every 2 weeks (i.e., they received 90 mg/m^2 as a total dose every 2 weeks) and reinduction pulses of vincristine and prednisone for a period of 9 months (Holland 1976). In addition, CALGB Protocol 6801 demonstrated that "prophylactic" IT MTX during induction was important in decreasing the overt CNS leukemia. Furthermore, Habhbin et al. (1975) reported data suggesting that intensive systemic chemotherapy

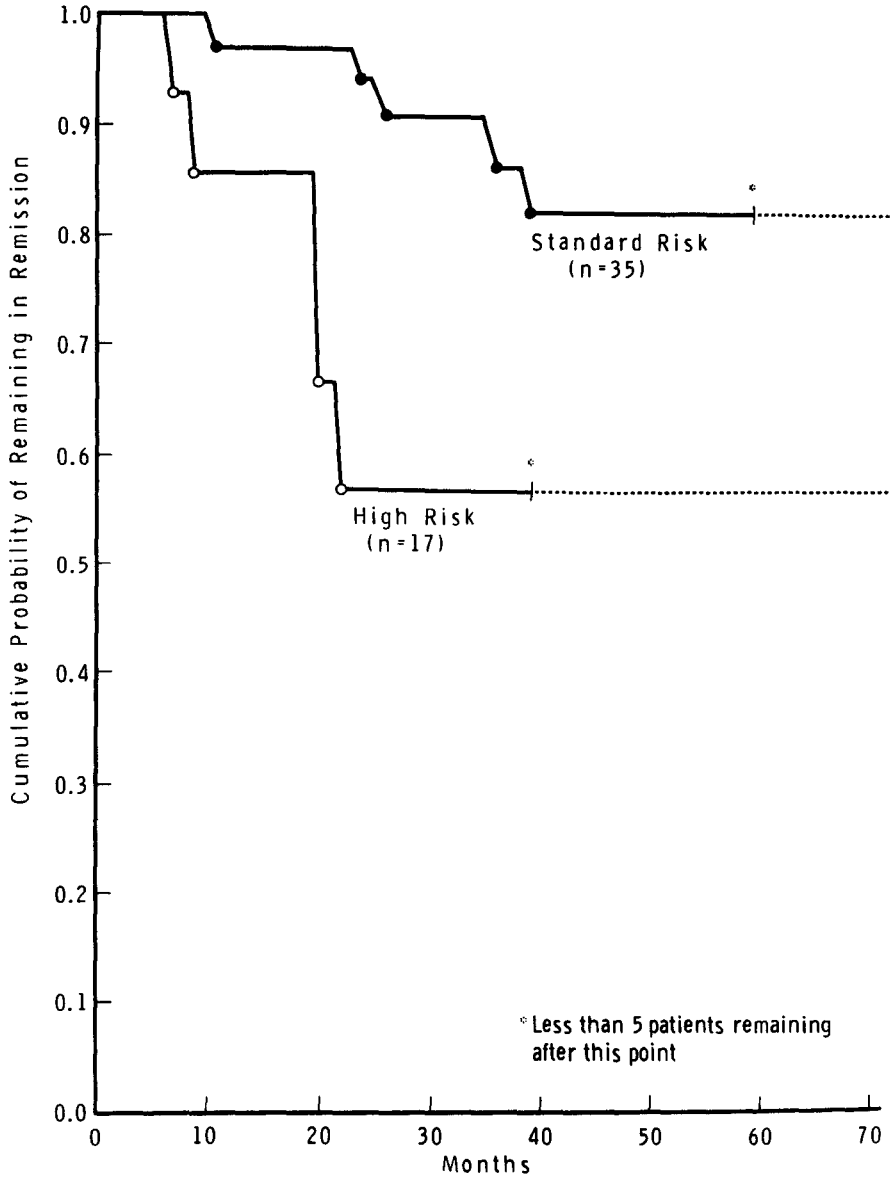

Fig. 4. Disease-free interval CNS relapse only

may decrease the incidence of CNS leukemia.

The pharmacologic basis of this study includes the following: (1) reports showing that intravenous IDM resulted in MTX levels of 10^{-7} M reaching the CNS axis and diffusing into the CSF (Wang et al. 1976), and (2) the studies of Oldendorf and Danson (1967) using C^{14} sucrose in rabbits and Bourke et al. (1973) using C^{14}-5-flurouracil in monkeys demonstrating that the concomitant use of intrathecal with intravenous injection led to higher levels of drug in the CSF and more even distribution throughout the CNS than with either method alone and the findings that when MTX is given only via lumbar puncture the distribution of MTX throughout the CSF ist very variable (Shapiro et al. 1975). Studies in man corroborate these animal observations, i.e., higher levels of CSF MTX are obtained with concomitant administration of IT and IV MTX than with either technique alone (Shapiro et al. 1975). Thus the technique employed in the present study of simultaneous IDM plus IT MTX enables one to more effectively bathe the CNS axis. The serum MTX levels following 500 mg/m^2 remain at 10^{-5} M for the 24-h infusion period (Wang et al. 1976; Freeman et al. 1977); therefore, it is anticipated that this will afford greater protection to other sanctuary sites such as gonads, liver, and spleen.

The clinical objectives of this study have been attained to a certain degree in the standard risk patient. The first objective to prevent CNS leukemia has been partially achieved as evidenced by the fact that only 5/35 standard risk patients developed CNS leukemia and 10/52 of the entire population experienced this complication (Fig. 4). This incidence is similar to that seen in a compara-

ble cooperative study (CALGB Protocol 7111) (Jones et al. 1977). Furthermore, our objective to dispense with the need for cranial RT now appears even more important that when the study was designed in 1974. A recent study of children treated with prophylactic cranial RT and IT MTX or IT cytosine arabinoside showed that 53% developed abnormal findings as detected by computerized tomography (CT) (Peylan-Ramu et al. 1978). These findings included dilated ventricles, intracerebral calcifications, demyelination, and dilation of subarachnoid space. Signs of endocrinologic long-range effects have been reported as evidenced by a reduction in growth hormone secretion in children treated with prophylactic cranial RT (Shalet et al. 1976). A comparable CT scan study has been undertaken in our 43 patients (Ochs et al. 1978). Only 19% showed abnormal changes, and furthermore, these findings were much less marked than those reported by Peylan-Ramu et al. No calcifications and no patients with decreased attenuation coefficient were seen in any of the 43 cases. In a similar study from Norway, the investigators found only 1 child out of 19 with an abnormal CT scan. These patients had been treated with IDM similar to the schedule described in this report (Kolmannskog et al. 1979). The possible effect of prophylactic cranial RT on psychological, neurologic, and intellectual development is the subject of studies now in progress.

The overall relapse rate in this study is 20/52 and the CNS relapse rate as the initial site of failure is 10/52. Thus, 10/20 relapses occurred first in the CNS.

In a recent comparison by Green et al. it was demonstrated that patients treated at RPMI (standard risk) with IDM (Fig. 2) were maintained in *complete* remission significantly longer than two other groups of patients. One group consisted of those treated with prophylactic IT MTX (Children's Cancer Study Group CCG-101) and the other of those who received IT MTX and prophylactic RT (Sidney Farber Cancer Institute SFCI-73-01). This was in spite of the fact that CNS relapse rate was higher in the IDM-treated group (Fig. 4) compared to the irradiated group (Green et al., to be published). In this same comparison the increased risk group of patients did better in terms of CNS relapse and complete remission when treated with IT MTX and cranial irradiation.

Another large study (CALGB Protocoll 7111) recently reported by Jones et al. (1977) has demonstrated a protective value of cranial RT and IT MTX alone in preventing CNS leukemia but not benefit in the overall complete remission rate. This was the result of an increased incidence of hematological relapse in the patients who received cranial RT. The British Medical Research Council also has observed a higher rate of hematologic relapse in these patients receiving prophylactic craniospinal radiation than in those without CNS prophylaxis (Medical Research Council 1973). In the British study the radiated group, either cranial or craniospinal, had a greater lymphopenia, which may reflect a pertubation of the immune surveillance system and thus lead to a greater systemic relapse (Medical Research Council 1975, 1978).

Moe and Seip (1978) patterned their study in Norway closely after the one reported here; their results are preliminary, but to date there have been only 5 of 69 patients relapsing. Seventy-eight percent of the children have been followed for 18 months or more and are in complete remission.

It appears reasonable on the basis of present information to advance the conclusion that the treatment of children with ALL who fall into the standard risk category (age and WBC) can effectively be treated by IDM plus IT MTX in terms of better overall control of disease. Furthermore, the long-term risks and complications of cranial irradiation (Peylan-Ramu et al. 1978; Medical Research Council 1975; Fishman et al. 1976; Freeman et al. 1973; McIntosh et al. 1977) can be avoided with this type of therapy.

Children who are at increased risk appear to be protected by the use of cranial irradiation, but the way is clear to improve upon the present schedule of IDM in terms of dose escalation and pulse dose administration through the 1st year of remission. Such studies are currently under way in a number of centers.

The second objective, i.e., to intensify systemic treatment (Fig. 3) and thus to prevent other sanctuary site infiltration, has also been reasonably achieved. Only one male child (26 males) developed testicular relapse. We attribute this to effective serum levels of MTX which presumably can eradicate disease in sanctuary sites such as the liver, spleen, and gonads.

In conclusion, we can state that the use of a systemic form of therapy, as opposed to a local form (RT to cranium), appears to confer greater protection to standard risk children with ALL than the use of cranial RT. In addition, we can avoid the long-range complications of cranial RT. In the high risk patients, cranial RT and IT MTX appears superior to the systemic form (IDM); however, manipulation of this form of therapy (increasing dose and pulse therapy) may overcome this disadvantage.

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