

Combination Intrathecal Therapy for Meningeal Leukemia: Two Versus Three Drugs

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The comparative effectiveness of intrathecal (IT) combination chemotherapy using two agents, methotrexate (MTX) and hydrocortisone (HDC), and three agents, MTX, HDC, and cytosine arabinoside (CA), in treating meningeal leukemia was determined in a randomized Southwest Oncology Group study. Following central nervous system (CNS) remission induction the same regimen was used for periodic maintenance until CNS relapse supervened. Complete CNS remission was achieved in 100% of 43 children given two-agent therapy and in 96% of 48 children given three-agent therapy. Length of CNS remission for two-agent therapy was 1–150+ wk, median, 47.2 wk; for three-agent therapy, remissions

were 1–190+ wk, median 64.6 wk. Differences in length of remission curves were not of statistical significance ($p = 0.71$). Toxicity of combination IT chemotherapy in the two- and three-agent regimens was reduced compared to that of IT MTX alone for CNS remission induction and maintenance. The additive effects of the IT drug combinations have been less than expected. The cytotoxic activity of these agents when administered simultaneously or sequentially is not fully understood. Further studies are clearly indicated to determine optimum doses, schedules, and sequences for the chemotherapeutic agents which can be given intrathecally in combination.

THE USE OF INTRATHECAL (IT) COMBINATION CHEMOTHERAPY is a logical consequence of the demonstration of increased effectiveness of systemically administered drug combinations when compared with single agents. Although exceptions exist to the principle of increased effectiveness of drug combinations, they are rare in pediatric oncology, the most notable examples being Burkitt lymphoma, stages I and II, and promyelocytic leukemia. The scope of combination IT chemotherapy is limited by the number of agents which can be given IT with freedom from severe toxicity. Late effects of combination IT chemotherapy are not yet fully appreciated. Improved survival in acute lymphocytic leukemia (ALL) of childhood will soon allow comparative observations as to delayed toxicity and late effects of IT chemotherapy,

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cranial radiotherapy, and combination chemotherapy–radiotherapy, permitting rational selection of the most appropriate CNS regimen for prophylaxis or active therapy.

Pilot IT studies of various combinations of methotrexate (MTX), hydrocortisone (HDC), and cytosine arabinoside (CA) at a single institution showed no greater toxicity for any combination than might be expected from IT MTX alone.⁹ The deletion of MTX was associated with decreased effectiveness. After the relative safety of combination IT chemotherapy had been established, a group study was undertaken to determine the comparative effectiveness of two drugs (MTX and HDC) versus three drugs (MTX, HDC, and CA) given IT in the treatment of active meningeal leukemia. As the superiority of IT MTX maintenance had been established,^{10,11} provision was made for continuing IT maintenance therapy. Early maintenance was incorporated on a sliding time scale in an attempt to salvage the sizable number of patients, approximately 25%, relapsing within 8 wk of completion of CNS remission-induction therapy.

The comparative effectiveness of the two- and three-drug CNS remission induction and maintenance regimens is the subject of this report.

MATERIALS AND METHODS

From April 22, 1971, through October 8, 1973, 114 Southwest Oncology Group (SWOG) pediatric patients with active meningeal leukemia were entered on a randomized study of two versus three drugs given IT, after informed, written consent had been obtained from parents or guardians. The diagnosis of meningeal leukemia required (1) a cerebrospinal fluid (CSF) mononuclear cell count of 10/cu mm or more with no cultural, serologic, or clinical evidence of infection, or (2) the demonstration of blast cells in any number in the CSF. Prior steroid therapy, prior CNS prophylaxis, and the number of previous episodes of meningeal leukemia were not considered in the randomization procedure. Patients in marrow remission and marrow relapse were randomized separately as previous studies had shown an increased length of CNS remission for those children in marrow remission.^{10,11}

The rate of response and population distribution of children entering the two- and the three-drug treatment groups, in marrow remission or in marrow relapse, showed no significant statistical differences with respect to the following parameters: sex, race, histologic type of leukemia, age at diagnosis, white blood cell count (WBC) at diagnosis, prior CNS prophylaxis, prior meningeal leukemia, number of prior episodes of meningeal leukemia, CSF WBC on entry onto study, and other manifestations of extramedullary disease.

The dosage schedule employed in three-drug (“triple”) IT therapy was as follows: MTX 15 mg/sq m (top dose 15 mg), HDC 15 mg/sq m (top dose 15 mg), and CA 30 mg/sq m (top dose 30 mg), IT, every 4–5 days, with one additional treatment beyond that required to induce complete CNS remission (CSF mononuclear cell count less than 10/cu mm and blast cells no longer present in the CSF). A minimum of four treatments was prescribed. Two-drug therapy employed the doses given above for IT MTX and HDC, deleting IT CA. Elliott’s B solution was used as the dilutant for the IT medications. The agents were injected into the intrathecal space in the order described. The same doses were used for two- and three-drug maintenance therapies. Maintenance was started early, i.e., 2 wk after the completion of CNS remission induction, and a sliding time scale was used to increase treatment intervals to 4, 6, and 8 wk, as shown in Fig. 1. Maintenance was then continued at intervals of 8 wk until CNS relapse was documented. Partial remission status was not recognized as a valid concept or a desirable treatment goal. Patients who did not achieve complete CNS remission were judged to be treatment failures. No arbitrary number of treatments was required before declaring a treatment failure, as the continuation of therapy was usually limited by increasing toxicity. Relapse was diagnosed when (1) the CSF mononuclear cell count rose to more than 10/cu mm or (2) blast cells appeared in the CSF in any number.

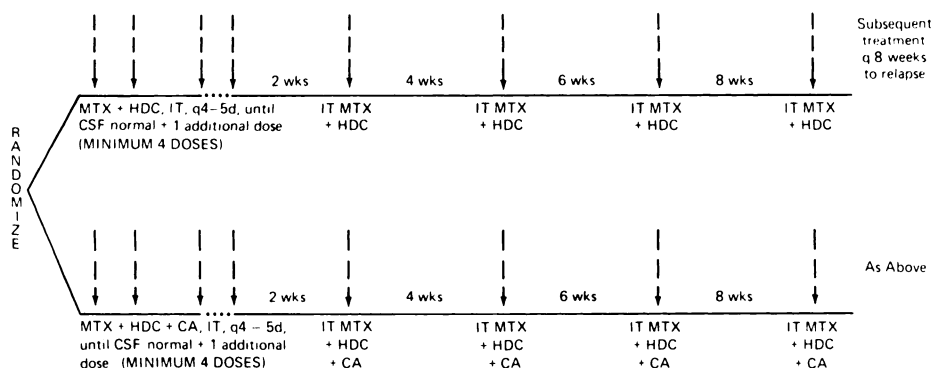


Fig. 1. Randomization schema for assignment to intrathecal remission-induction and maintenance therapy, two versus three drugs. A sliding time scale was used early in maintenance to increase the treatment interval in a stepwise manner.

Previously initiated systemic chemotherapy was continued during the CNS study. Steroid therapy was administered only upon specific indication, i.e., as a part of in-progress maintenance therapy or as a part of systemic reinduction or maintenance therapy. Leucovorin, 15 mg/sq m (top dose 15 mg), was given intramuscularly or intravenously at the time of each IT treatment to prevent systemic effects of intrathecally administered MTX. The physical and hematologic status of each patient was documented at intervals of 8 wk or less. Full supportive care was given for any complication of the leukemic disease or its therapy.

Duration of remission curves used in the comparisons between the regimens were computed by the Kaplan-Meier life table method. On each curve, patients not experiencing a CNS relapse are indicated by a short vertical line.

RESULTS

There were 114 patients entered on the study, and 91 were evaluable for therapeutic effect: 5 did not meet the criteria for study entry and were judged ineligible, and 18 were nonevaluable. Reasons given for nonevaluability were as follows: early death (2), intolerable toxicity (3), lost to follow-up (2), refused further therapy (1), major protocol violation (9), and other (1).

CNS Remission-Induction Rate

Of the 91 evaluable children, 43 received the two-drug IT combination and 48 received the three-drug combination. The complete response rate for two-drug IT therapy was 100%; 2 of 48 receiving three drugs IT failed to respond, giving a complete response rate of 96%. This difference was not of statistical significance.

Length of CNS Remission

Among the 33 children in bone marrow remission who received IT MTX + HDC, CNS remission induction therapy, and one or more maintenance treatments, CNS remission range was 1-150+ wk, median 52.3 wk. Remissions among the 32 children given IT MTX + HDC + CA who achieved CNS remission and received one or more maintenance treatments lasted 1-159+ wk, median 64.1 wk. The length of CNS remission curves for children in marrow

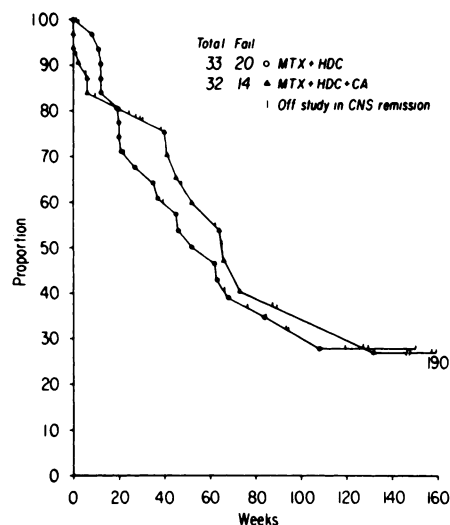


Fig. 2. Duration of CNS remissions for children entering two- versus three-drug study in bone marrow remission.

remission are shown in Fig. 2. Children with no documented CNS relapse, including those who died or were lost to follow-up while in CNS remission, are indicated by vertical marks on the curves. A comparison of the length of remission curves for the two treatments (Fig. 2) showed no statistical difference ($p = 0.60$).

Among 10 children given two-agent IT therapy who entered the study in bone marrow relapse, length of CNS remission was 3–98 wk, median 24 wk; among the 16 children given three-agent IT, length of remission was 7–190+ wk, median 33.9 wk. Comparison of length of remission curves for these two groups of children (Fig. 3) showed no statistical difference ($p = 0.77$).

When patients in marrow remission and marrow relapse on each treatment regimen were pooled, two-agent IT therapy produced remissions of 1–150+ wk, median 47.2 wk, and three-agent IT therapy produced remissions of 1–190+ wk, median 64.6 wk. Again, length of remission curves for the two treatment groups (Fig. 4) showed no statistical difference ($p = 0.71$).

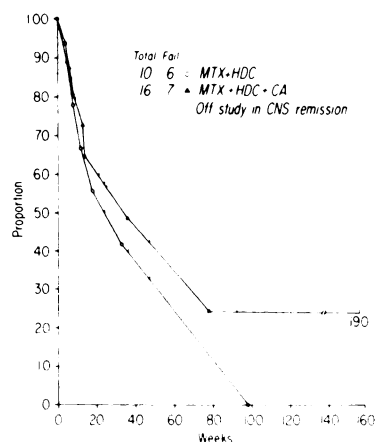


Fig. 3. Duration of CNS remissions for children entering two- versus three-drug study in bone marrow relapse.

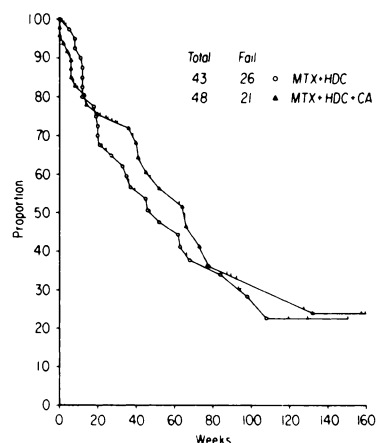


Fig. 4. Duration of CNS remissions for children entering two- versus three-drug study in bone marrow remission or relapse.

Time to Bone Marrow Relapse

The time to bone marrow relapse could be determined for 38 of the 65 children entering the study in bone marrow remission. The length of the existing marrow remissions in these children ranged from 3 to 707 days, median 119 days.

Toxicity

Three “nonevaluable” children experienced very early toxicity as described during remission induction, which made continuation on the study either difficult or inadvisable: two-drug therapy—severe arachnoiditis (1 patient) and convulsions (1 patient); three-drug therapy—transient aphasia and quadriplegia (1 patient). The severe and life-threatening toxicities encountered throughout the course of therapy in the 91 evaluable children are detailed in Table 1.

Of 43 evaluable patients receiving two-drug IT therapy, 8 experienced the toxicities tabulated. In 4 of these 8 children toxicity consisted of some variant of the symptom complex of headache, fever, nausea, and vomiting which frequently follows IT therapy. The absence of serious manifestations of the symptom complex in patients given three-drug IT therapy, while of interest, was not

Table 1. Severe and Life-threatening Toxicities of IT Therapy in 91 Children

Treatment Regimen (No. of Patients Treated)	Specific Toxicity	No. of Patients With Specific Toxicity (Degree*)
IT MTX + HDC (N = 43)	Fever	1 (S)
	Nausea and vomiting	3 (S)
	Headache	3 (S)
	Back pain	1 (S)
	Convulsions	2 (S), 1 (LT)
	Mouth ulcers	1 (S)
IT MTX + HDC + CA (N = 48)	Mouth ulcers	1 (S)

*S, severe; LT, life threatening.

of statistical significance. The occurrence of seizures in patients given two drugs IT but not in children given three drugs IT was likewise not of statistical significance. The concentration of pooled toxicities in the two-drug regimen was of note but has no apparent explanation and has not been of clinical significance.

Evidence of degenerative CNS changes, i.e., leukoencephalopathy, was sought with particular diligence by special request of supplementary information from all investigators in addition to their routine follow-up toxicity reports. In two instances a diagnosis of leukoencephalopathy was suggested clinically; in neither case was there biopsy confirmation of this diagnosis. One child developed severe headache and lethargy 2 wk after his second maintenance treatment with two agents and died suddenly. "Stiff spells" without loss of consciousness occurred on the day of death. CSF opening pressure was 240 mm H₂O; the CSF WBC was normal. In 1964 the boy had received 3800 rad to each orbit for retinoblastoma. The second boy developed headache, vomiting, and separated sutures in the sixth month of nonstudy retreatment with the three-drug IT regimen. Cranial radiotherapy was given with two agents IT; two-agent maintenance followed. Generalized seizures now occur.

DISCUSSION

No direct comparisons have yet been made in randomized studies between IT MTX alone and combination IT therapy using identical maintenance schedules. In Table 2 current data are compared with previously published data on lengths of maintained CNS remissions using IT MTX as a single agent. The extremely high percentage of patients in marrow remission in SWOG CNS

Table 2. Lengths of CNS Remissions With Various Maintained CNS Treatment Regimens

Study	Treatment Regimen	No. of Evaluable Patients	Percent in Marrow Remission	Length of Median CNS Remission (wk)
SWOG CNS 2 ¹⁰	IT MTX induction; maintenance beginning at 6–8 wk and continuing at same interval	19	94	67.4
SWOG CNS 3 ¹¹	IT MTX induction; bimonthly maintenance beginning at 8 wk	26	73	34.3
NCI ³	IT MTX induction; weekly consolidation × 6; monthly maintenance	13	Unknown	33.4
Current study	IT MTX + HDC induction; "early" maintenance beginning at 2 wk and progressing to 8-wk intervals	43	77	47.2
Current study	IT MTX + HDC + CA induction; "early" maintenance beginning at 2 wk and progressing to 8-wk intervals	48	67	64.6

study 2 is of note. IT MTX patients in SWOG CNS studies 2 and 3 who developed CNS relapse within 8 wk of CNS induction were deleted from the maintenance series; all patients achieving CNS remission were included in the current study. The early maintenance regimen beginning 2 wk after CNS remission induction, as used in the current study, was designed specifically to salvage that group of patients, approximately 25% of CNS responders, who relapse within 8 wk of achieving CNS remission. A significant difference in clinical material thus existed between maintenance groups of the prior SWOG CNS studies and the current study with 25% of the patients, the early relapsers, being deleted from prior studies and all CNS responders being included in the current study. Two- and three-drug IT therapy, in *all* remitters, produced CNS remissions similar in length to those achieved by the better 75% given IT MTX alone in SWOG CNS study 2 and superior to those in SWOG CNS study 3. With the use of consolidation and monthly maintenance, the National Cancer Institute (NCI) study material³ also contained all CNS remitters, the potential early relapsers having been temporarily salvaged. Interpretation of the NCI data was further hampered by lack of information as to the bone marrow status of the patients.

The institution of early maintenance at 2 wk with stepwise lengthening of the maintenance interval to 8 wk resulted in a cumulative relapse rate of 5.5% (exclusive of treatment failures) at 10 wk for all children in the two- versus three-drug study. Prompt institution of maintenance therapy appeared to be an effective means of reducing the number of early CNS relapses, i.e., those occurring within 8 wk of CNS remission induction. As judged by present criteria, CNS remission must be a relative state with a high probability of residual occult disease. A need for a better understanding of the kinetics of CNS leukemia is apparent.

A comparison of early CNS relapses between children entering the study in marrow remission and marrow relapse showed early CNS relapse to be more frequent in the latter group.

The lack of significant additive effect with the use of IT MTX and CA in combination has been disappointing. In 1972 CA and MTX were reported to show antagonism when used simultaneously in inhibition studies of L 1210 cells in tissue culture.⁶ With murine lymphoma cells, simultaneous or prior (6 hr) administration of MTX has been observed to increase the cellular deoxycytidine triphosphate pool which "partially overcomes the inhibition of growth which cytosine arabinoside produces."¹³ Results of studies using spleen colony-forming unit counting techniques have suggested, however, that MTX and CA should be given within a short period of time of each other to maximize killing of proliferating L1210 cells.² These studies emphasized the complexity of the cytotoxic drug interactions in cancer chemotherapy. The species specificity of such interactions has not been determined and it should be remembered that expectations from CA therapy in L 1210 leukemia have not been realized in childhood leukemia.

The pilot studies of combination IT chemotherapy indicated that the anti-leukemic effect of IT HDC in individual cases resulted in significant reduction of side effects of other intrathecally administered agents.¹² This effect has been

confirmed in a randomized national study conducted in Japan.^{4,5} In this study "side effects" were noted in 12½% of patients receiving IT MTX + HDC, 60% of those receiving IT MTX alone, and 66% receiving IT MTX + CA. The present study was remarkable in its lack of serious side effects. Components (one or more) of the symptom complex commonly seen after IT therapy (fever, headache, nausea, and vomiting) occurred to a severe degree in only 4 of the 91 children receiving combination IT therapy. In a previous study a 38% incidence of these particular side effects was found in children given IT MTX alone for CNS remission induction and maintenance.¹⁰

Serious neurologic sequelae and systemic effects were not noted among 13 children treated with IT CA by Wang and Pratt¹⁴ or the 10 patients reported by Band et al.¹ Two instances of paraplegia following IT CA therapy are now known.⁸ As with paraplegia associated with IT MTX therapy, this event would also appear to be sporadic when associated with IT CA therapy. In the current series, the patients who had seizures were all receiving two drugs IT. One patient receiving three-drug therapy experienced transient aphasia and quadriplegia during remission induction and was removed from the study; no serious neurologic toxicity occurred during the study in patients continuing on the three-drug regimen. Clinical findings suggestive of leukoencephalopathy were observed during a subsequent, nonstudy course of three-drug IT therapy in 1 patient. None of the other children given IT CA had clinical or autopsy findings of leukoencephalopathy. The report of Rubinstein et al.⁷ must therefore be interpreted as showing an association between very intensive systemic and CNS therapy, as required for progressive disease, and the development of leukoencephalopathy.

The ability of systemically administered steroids to influence CNS leukemia has been well recognized. In a previous study of IT therapy in which patients were receiving comparable systemic maintenance therapy, often with periodic steroid reinforcement, no effect of systemic steroid therapy could be demonstrated on the outcome of CNS therapy.¹⁰ Among children entering the present study in bone marrow remission, 21 of 33 given two agents IT received one or more courses of systemic steroid therapy; 20 of 32 given three agents IT received steroids systemically. It would therefore be very difficult to discern any differences ascribable to systemic steroid therapy when comparing the therapeutic results of the IT regimens under study.

The 48 children receiving CA as a part of three-drug IT therapy constituted the largest group of patients in whom the use of IT CA has been reported. Although suggested by comparison with published data, additive effects of IT CA, when used in combination with MTX and HDC, have not yet been clearly demonstrated.

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