Remission Maintenance Therapy for Meningeal Leukemia: Intrathecal Methotrexate vs. Intravenous bis-Nitrosourea

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Central nervous system infiltrates have become a major cause of morbidity among leukemic children and may constitute a site from which a remission marrow is again infiltrated. Conventional intrathecal methotrexate (IT MTX) therapy produces excellent palliation and complete reversal of abnormal cerebrospinal fluid findings for periods ranging from 6 to 414 days (median 87 days). The CNS remission maintenance potential of (1) IT MTX, 12 mg/sq m, every 6–8 wk, and (2) bis-nitrosourea (BCNU), 100 mg/sq m intravenously, every 6–8 wk were compared with “no therapy” maintenance. Only those children in CNS remission 6–8 wk following induction therapy were eligible for randomization to the maintenance study. The duration of CNS remission for BCNU-maintained and “no therapy” patients was similar, with a median length of remission of 96 days and 112 days, respectively. The median duration of remission for the MTX maintenance group was 472 days. The differences in length of CNS remission between the MTX group and the other two groups were statistically highly significant (p < 0.01 for both comparisons). Headache, fever, and/or vomiting occurred in 38% of the children after one or more of the intrathecal maintenance treatments and, in general, symptoms tended to worsen as maintenance continued.

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The treatment of meningeal leukemia has been studied systematically by the Pediatric Division, The Southwest Cancer Chemotherapy Study Group (SWCCSG) since 1962. Central nervous system (CNS) infiltrates are now a major cause of morbidity among leukemic children in marrow remission and may constitute a very serious clinical complication when marrow relapse supervenes. The incidence of meningeal leukemia has increased from less than 10%, prior to 1954, to 50% in recently published data. Current intensive treatment regimens are markedly prolonging survival in acute lymphocytic leukemia of childhood with the major component of the prolonged survival being the long initial marrow remission. As the CNS has been considered a "sanctuary" from which a remission bone marrow may be infiltrated, the eradication of meningeal leukemia is of paramount importance. Intrathecal methotrexate (IT MTX) has been highly successful in treating meningeal leukemia, but the durations of the resulting CNS remissions have been short and range from 6–414 days (median 87 days). Methods of prolonging IT MTX-induced remission have been sought and the effectiveness of interval maintenance doses of IT MTX and of intravenous 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU) in prolonging IT MTX-induced remissions are herein reported.

**Materials and Methods**

Beginning July 20, 1967, children less than 15 yr of age with CNS leukemia who were under the care of SWCCSG members were entered in the study after informed parental consent had been obtained. IT MTX 12 mg/sq m, was given twice weekly until the cerebrospinal fluid white blood cell (CSF WBC) count fell to less than 10/cu mm. Following induction of CNS remission, random assignments were made among the three maintenance programs shown in Fig. 1 which employed (1) IT MTX, 12 mg/sq m, every 8 wk; (2) BCNU, 100 mg/sq m IV, every 8 wk; and (3) "no therapy.”

The CSF was monitored at intervals of 8 wk and whenever symptoms suggested CNS recurrence; relapse diagnosed when the CSF WBC count rose above 10/cu mm. Beginning September 29, 1967, provision was made for BCNU dosage increases to 125 mg/sq m for the second treatment and 150 mg/sq m for subsequent treatments if no toxicity occurred. Because of the high relapse rate at the time of the first follow-up lumbar puncture, the treatment interval was shortened to 6 wk, the figure given in the schema, as of January 24, 1968. The study was closed to entries on March 26, 1969, and the cutoff date for analysis of duration of remission data was February 1, 1970. The 47 children evaluable for maintenance were distributed among the regimens as follows: (1) MTX, 19; (2) BCNU, 15; and (3) "no therapy”, 13.

![Diagram](https://www.bloodjournal.org)
The duration of the CNS remissions was measured as the number of days from the last induction treatment to CNS relapse (CSF WBC $\leq$ 10/cu mm or leukemic infiltrates in the central nervous system on postmortem examination). The absolute duration of CNS remission could not be determined for those children (1) lost to follow-up while alive and in CNS remission, (2) expiring in CNS remission but having no postmortem examination, or (3) expiring in CNS remission with no evidence of CNS leukemia on postmortem examination. Children in the last category were considered to be lost to CNS follow-up through death.

The occurrence of bone marrow relapse during CNS remission was considered to be an independent event and patients in this clinical situation were continued on study.

The population and disease characteristics of the children assigned to the three maintenance regimens were examined statistically to determine whether any regimen had been weighted with unfavorable cases. Monocytic and granulocytic leukemia were not reported for any of the maintenance regimens. Differences in nomenclature among the various investigators precludes any further comment on histologic type as a factor influencing response to therapy. No significant differences were found among the groups in age, sex, or race distribution. The treatment groups were also shown to be similar in number of previous episodes of CNS leukemia for each child, duration of leukemia at the onset of CNS involvement, duration of leukemia at the onset of the current CNS episode, the number of children in bone marrow relapse and bone marrow remission when the study was initiated and in survival from onset of leukemia.

Pretreatment CSF mononuclear cell counts were compared among the treatment groups. Counts exceeding 1000/cu mm were found in nine of the MTX group, two of the BCNU group and two of the “no therapy” group. The excess of patients with high initial CSF mononuclear cell counts in the MTX group as compared with the other two groups was of statistical significance ($p < 0.05$ for both comparisons). Of all the parameters examined, only this showed a statistically significant difference among the maintenance groups, suggesting that the MTX group might have been less favorable because of the increased number of children with pretreatment CSF mononuclear cell counts in excess of 1000/cu mm.

**Results**

**Duration of Remission**

The duration of remission, range and median, for each maintenance regimen is shown as follows in Table 1: MTX, 84-607 days (median 472 days); BCNU, 56+–203 days (median 96 days); and “no therapy,” 77–183 days (median 112 days). There was a highly significant difference between the curve for MTX-treated patients and the curves for no therapy and BCNU-treated patients ($p < 0.01$ for both comparisons). There was no difference between the curves for BCNU and “no therapy” patients presented in Fig. 2. These curves are constructed from data on patients who have relapsed on study with (1) CSF WBC exceeding 10/cu mm or (2) CNS infiltrates on postmortem examination. In the MTX group, data have been censored for four patients continuing in remission for 112, 372, 474, and 547 days and for six patients lost to follow-up by death without postmortem evidence of relapse after 130, 222, 247, 376, 376,
Fig. 2.—Length of remission curves for the three CNS remission maintenance regimens. Remissions were measured from the last day of remission induction therapy to relapse. The curves include only those patients in CNS remission at the time of randomization to maintenance therapy (about 50 days after remission induction). Approximately 25% of patients relapsed prior to randomization.

and 525 days. Data from only one of the BCNU group was subject to censor for the above reasons; no data required censoring in the “no therapy” group.

Because of the marked differences in duration of remission, data were examined further to determine the incidence of concomitant steroid administration during remission induction and remission maintenance. No differences were found in the incidence of steroid administration during remission induction among the different maintenance programs. The frequency of prednisone administration was greatly increased in the MTX maintenance group, with 17 of the 19 children having received the agent. One child was receiving VAMP (includes prednisone 120 mg/sq m/day for 14 days every 28 days) and four children were on a systemic therapy protocol study employing purinethol maintenance with “reinforcement” prednisone (60 mg/sq m/day for 28 days followed by 7 days of decremental therapy) or prednisone plus VCR every 120 days; 12 children received prednisone (60 mg/sq m/day for 28 or 35 days followed by 7 days of decremental therapy) in combination with VCR and/or daunorubicin for reinduction of remission of systemic disease. Only 6 of 15 patients received prednisone during BCNU maintenance. One child was receiving VAMP therapy, a second child was receiving systemic reinforcement with prednisone as described above, and four children were receiving prednisone plus VCR and/or daunorubicin for remission induction. In the “no therapy” group, 7 of 13 patients received prednisone during the maintenance
phase of the study. One patient received prednisone reinforcement; the other six children received prednisone plus VCR and/or daunorubicin for reinduction of marrow remission. All patients who received prednisone during the remission maintenance phase of the CNS study had received prednisone two or more times according to one of the schedules described above prior to entrance on the CNS study.

**Toxicity**

The incidence of various toxic manifestation of IT MTX remission induction therapy was similar to that previously reported by our Group. Eight of the 19 children (38%) receiving MTX maintenance had complaints of headache, fever, and/or vomiting after one or more of their maintenance treatments. These complaints arose after the first treatment in two children, second treatment in one child, third treatment in two children, fifth treatment in one child, and tenth treatment in two children. In general, symptoms became more severe with continued therapy, though some subsequent treatments were well tolerated. In only one child were symptoms of such severity as to require hospitalization after two of the treatments.

A single child receiving MTX maintenance developed severe and persistent symptoms of peripheral neuritis following his seventh maintenance treatment. Intrathecal therapy was discontinued, but the neuritic symptoms persisted to death.

The toxic side effects of BCNU therapy were as follows: venous pain, two patients; vomiting, two patients; leukopenia, one patient; and thrombocytopenia, four patients. Venous pain was of sufficient degree to warrant modification of therapy in one patient, and thrombocytopenia resulted in reduced doses or treatment delays in all four patients.

**DISCUSSION**

Standard or conventional chemotherapy for meningeal leukemia consists of IT MTX, 0.5 mg/kg (12 mg/sq m), every 4 or 5 days until the CSF WBC falls to normal range. Following such therapy, CSF relapse can be anticipated in approximately 3 mo. Intrathecal maintenance appeared a logical solution to the problem; but pilot studies proceeded slowly because of toxic reactions to the drug. Further caution seemed indicated following the report of neurotoxicity (seizures) in 4 of 35 children given IT aminopterin, 2.5 mg/sq m or IT MTX 12 mg/sq m at monthly intervals. With the demonstration of fewer side effects when the treatment interval was increased to 8 wk, further investigation of the potential of maintenance therapy seemed indicated.

Intensive efforts have been directed toward the development of compounds that will pass the blood-brain barrier and permit treatment of meningeal leukemia with systemically administered compounds. One of these compounds, BCNU, was found to be effective in controlling L1210 leukemia, and showed some degree of effectiveness in treating human meningeal leukemia. Doses of 150 mg/sq m × 3 produced CNS remissions in three of the six children treated. Thrombocytopenia occurred in all, despite discontinuation of systemic antileukemic therapy; two children expired with uncontrollable gastro-
intestinal hemorrhage. The other four children recovered from thrombocytopenia in 2–7 wk. When used as an adjuvant to systemic therapy, BCNU, 100 mg/sq m, intravenously at intervals of 8 wks was well tolerated and did not interfere with the overall treatment plan.12 This schedule appeared suitable for prophylactic use in the prevention of recurrent meningeal leukemia, and such a maintenance regimen was selected for comparison with IT MTX maintenance at intervals of 6–8 wk.

Meningeal leukemia with an initial CSF WBC of 1000/cu mm or more has been reported by Hardisty as having a poorer prognosis than meningeal leukemia with lower initial CSF WBC counts.13 Thirty-eight per cent of the reported high CSF WBC count patients expired within 13 wk and 33% had CNS relapse. The durations of the CNS remissions, range and median, among our patients with CSF WBC of 1000/cu mm or more were as follows: MTX (nine patients) 84–607 days (median 181 days); BCNU (two patients), 85 and 158 days; and “no therapy” (two patients), 135 and 156 days. The CNS remission data was slightly better than would be predicted from the Hardisty figures with improvement in both survival and CNS remission duration being more marked in the MTX maintenance group.

Improvement in the symptomatic and objective findings of CNS leukemia following systemic administration of adrenal corticosteroid analogues has been recognized for some time.14,15 The analogue, dexamethasone, has been reported to be particularly effective in alleviating symptoms of meningeal leukemia and has been recommended as an emergency “substitute” therapy when definitive treatment must be delayed for 1–2 days.16 The influence of dexamethasone used in this manner upon CSF findings has not yet been reported; papilledema and cranial nerve palsies were not changed significantly. Data from our study have been examined to determine whether or not steroid administration might have contributed to the marked difference in duration of remission between the MTX and the other two maintenance regimens. No difference in the incidence of prednisone (the steroid analogue which was used almost exclusively) administration was found among the regimens during the remission induction phase of the study. The incidence of steroid administration during the remission maintenance was greatly increased in the MTX group. All of the children, however, had received at least two previous (14 day or 4–5 wk) courses of prednisone. Prednisone when used alone as initial systemic therapy has produced complete marrow remission in 69% of 35 children, with a median duration of remission of only 29 days.17 The second course of prednisone, used alone, produced complete marrow remissions in 32% of 38 children, with a median duration of remission of 28 days. In view of these data, third or subsequent systemic courses of prednisone should not be expected to have a significant effect on the duration of CNS remission.

Even though the primary purpose of this investigation was the study of CNS remission duration, the accumulated data permits some observations on the relationship of CNS relapse and bone marrow relapse. The CNS remissions were clearly longer in patients who were in bone marrow remission, with a median duration of 123 days, compared to 44 days for patients who were in
bone marrow relapse. The overall difference between the curves was highly statistically significant \( p < 0.01 \).

Among patients entering on study in marrow remission, the median time to any “failure” (death, CNS or marrow relapse) was 89 days, compared with a median of 123 days for CNS relapses only. This suggests that, on the average, marrow relapse precedes CNS relapse by approximately 1 mo. The difference between time to any failure and time to CNS relapse is statistically significant \( p < 0.05 \). Figure 2 gives length of remission curves for the three maintenance groups where relapse is defined as CNS relapse only. If relapse is defined as any failure, there is still a substantial advantage in “time to failure” length for the MTX maintained group. The median times to any failure were: MTX, 191 days; BCNU, 87 days; and “no therapy”, 105 days.

In children with prolonged CNS remissions the occurrence of several marrow relapses during the CNS remission was not unusual. Among the 19 children in the MTX maintenance group, four remained in marrow remission throughout their CNS remission. Six children had a single marrow relapse; four children had two marrow relapses and four children had three marrow relapses. These data suggest that marrow and CNS involvement are independent or that maintenance therapy is only suppressive, resulting in occult CNS disease capable of invading the marrow.

Study design permitted a second CNS induction and randomization for maintenance therapy following CNS relapse on the first study maintenance regimen. Four of the MTX maintenance patients had been enrolled previously in BCNU or “no therapy” treatment groups. Comparisons of lengths of CNS remission for the MTX regimen and the previous regimen were as follows: 343 vs. 117 days; 607 vs. 146 days; 474+ vs. 127 days; and 318 vs. 141 days. Second entries on the BCNU and “no therapy” regimens produced remission lengths as follows when compared with previous entry on either of these regimens: 105 vs. 154 days; 93 vs. 85 days; 105 vs. 54 days; and 102 vs. 93 days. The superiority of MTX regimen is evident in this small number of patients who provide their own control data.

The patients in whom the remission maintenance regimens were tested are considered to be a select group, as a total of 21 patients relapsing in less than 8 wk during the first 7 mo of the study and in less than 6 wk during the last 10 mo of the study were excluded from the remission maintenance study on the basis of their having relapsed before maintenance could be initiated. The three maintenance groups were similar in population, disease and treatment characteristics except for (1) increased numbers of patients with initial high CSF WBC counts in the MTX group, presumably a poor prognostic factor and (2) increased number of patients receiving systemically administered steroids during remission maintenance in the MTX group. The influence of the latter factor cannot be determined, though a low level of steroid sensitivity was possible in many children due to multiple previous exposures. The superiority of the MTX maintenance regimen was of such a degree that maintenance IT MTX must be considered in planning therapy for all children with meningeal leukemia. More effective maintenance may be possible in the
future through schedule adjustments as indicated by the characteristics of CNS relapse curves.

In no case was there life-threatening toxicity during the MTX maintenance phase of the study. Headaches, fever, and/or vomiting were experienced by approximately one third of the children after one or more of their maintenance treatments. In general, symptoms tended to become more severe as therapy continued and could possibly make continuation of treatment intolerable.

**SUMMARY**

After induction of CNS remission with conventional IT MTX therapy, patients were randomly assigned among the following maintenance regimens: (1) IT MTX, 12 mg/sq m every 6 wk; (2) BCNU, 100 mg/M2 IV every 6 wk, and (3) "no therapy." The durations of the CNS remissions, range and median in days for the evaluable patients, by regimen, were as follows: MTX (19 patients) 84–607 days (median 472 days); BCNU (15 patients) 56+ to 203 (96) and "no therapy" (13 patients) 77–183 (112). Differences between medians for MTX and each of the other two regimens were statistically highly significant. In addition, differences between relapse curves for MTX and each of the other two regimens were statistically highly significant (p < 0.01 for both comparisons). Results of MTX maintenance showed such superiority that the regimen should be considered for all children with meningeal leukemia. Headache, fever and/or vomiting occurred in 38% of children receiving IT MTX maintenance. As these symptoms tended to worsen with continuing therapy, the severity of the symptoms might well dictate discontinuation of such a regimen.

**REFERENCES**

10. Rall, D. P., Ben, M., and McCarthy,


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