Prevention and Treatment of Meningeal Leukemia in Children

By Donald Pinkel and Shiao Woo

The story of meningeal leukemia illustrates three lessons in medical therapeutics: how a biologic safety net can obstruct success, how the safety net can be evaded, and how its evasion can result in unexpected benefits. Early studies of the pharmacokinetics of methotrexate (Mtx) and 6-mercaptopurine (6MP) demonstrated their poor diffusion from plasma into cerebrospinal fluid (CSF) through the protective biologic blood-CSF barrier.1-2 The barrier was soon evaded by direct intrathecal injection of Mtx and later by intravenous administration of high doses of Mtx that yielded therapeutic levels in the CSF.3-5 Meanwhile, it was shown that prevention of meningeal leukemia by an additional method of evasion, cranial radiation, when combined with multiple drug systemic chemotherapy, resulted in a 50% cure rate of acute lymphoid leukemia (ALL).4 Unexpected benefits of high-dosage Mtx were a 10-fold reduction of isolated testicular relapse and a probability that it also decreased the risk of hematologic cure.5,6 Thus, much of the progress in curing ALL resulted from a biologic safety net that required evasion.

The purpose of this communication is to briefly review the nature of meningeal leukemia, to summarize recent studies of its prevention and treatment, and to suggest guidelines for its management.

PATHOLOGY

Meningeal leukemia arises from neoplastic lymphocytes or myelocytes in cranial arachnoid tissue.7,8 The proliferating cells originate in walls of superficial veins and extend through the superficial arachnoid into the arachnoid surrounding arteries, veins, arterioles, and venules as they course into and through the brain. With increasing mass, the leukemia cells reduce the caliber of these vessels, producing cerebral hypoperfusion. Eventually, they can burst out of the arachnoid trabeculae into the CSF, resulting in leukemic meningitis that leads to symptoms of morning headache, vomiting, meningeal hemorrhages, and papilledema.9 With further increase in mass, the leukemia cells can pass through the pia-arachnoid barrier into brain parenchyma, producing further cerebral dysfunction.10 In some cases, such as B-cell ALL and acute myelomonocytic leukemia with eosinophilia and chromosomal inversion 16, adult tumor masses are formed with symptoms of discrete brain tumors. Because cranial nerves pass through the leptomeninges, they and their vasculature can be compressed and damaged by leukemic infiltrates, resulting in clinical neuropathy, including leukemic optic neuritis and consequent optic atrophy.11,12 Hypothalamic and pituitary invasion can result in endocrine disturbances, including accelerated growth, Cushing's syndrome, and diabetes insipidus. Spinal leptomeningeal leukemia can extend to dorsal nerve roots, producing tabetic symptoms, or to the cauda equina, causing paraparesis.

CLINICAL DIAGNOSIS OF MENINGEAL LEUKEMIA

Although most children and many adults probably have some degree of asymptomatic meningeal leukemia at diagnosis, the clinical diagnosis of meningeal leukemia in the patient without neurologic symptoms or signs is not always clear. One definition commonly used requires a cell count of 5 or more per microliter of CSF and the presence of unequivocal leukemic blast cells on a cytospin preparation.13 However, this definition is challenged by reports that the presence of blasts in the CSF at diagnosis or during therapy increases the risk of meningeal relapse regardless of cell count.13-14 Another problem is differentiation of leukemic from normal lymphocytes in the CSF. Patients with leukemia frequently develop CSF lymphocytosis for various reasons, often with transformed normal lymphocytes. Staining for terminal deoxynucleotidyl transferase (TdT) is helpful in the distinction between leukemic and normal lymphocytes.15-18 Unequivocal identification of leukemia cells in the CSF, regardless of cell count, signifies clinical meningeal leukemia. When uncertain, CSF examination is repeated in 1 to 2 weeks.

FACTORS IN MENINGEAL LEUKEMIA

In addition to the blood-CSF barrier, several other factors figure in the development of meningeal leukemia. Age is
important. Infants and preschool children are more susceptible
than adolescents and adults, possibly because a higher propor-
tion of their vasculature is in the leptomeninges. Biologic features of the leukemia are also important. High
initial peripheral blood leukemia cell counts, male sex, leu-
kemia cells in the CSF, T-cell or B-cell immunophenotype,
the presence of the Philadelphia chromosome, French-Amer-
ican-British (FAB) M5 morphology, and FAB M4 morphol-
ogy with eosinophilia and chromosomal inversion 16 are
associated with higher risk of meningeal leukemia.
Systemic chemotherapy is another factor. Full-dosage
continuation chemotherapy carries a lower risk of meningeal
leukemia than half-dosage. Asparaginase depletes CSF as-
paragine and dexamethasone diffuses into CSF more readily
than prednisone, so that use of these agents may contribute
to reduction of meningeal leukemia. The roles of high-
dosage antimitabolites and intrathecal therapy are discussed
later.
When meningeal leukemia develops, both the frequency
of survival and quality of survival are considerably reduced.
Table 1 summarizes the historical outcome of children who
had initial clinically isolated meningeal relapse of ALL be-
tween 1967 and 1979 and were treated with systemic chem-
otherapy and central nervous system (CNS) radiotherapy with
or without intrathecal chemotherapy. Only 17% of the
children survived and their survival was marked by a high
frequency of significant neurologic disorders. Prevention of
meningeal leukemia is essential to cure of children with
ALL.

METHODS OF PREVENTION AND TREATMENT OF MENINGEAL LEUKEMIA

Three methods are useful for prevention of meningeal
leukemia: intrathecal injection of antileukemia antimitabo-
lites with or without corticosteroids, high-dosage intravenous
administration of the antimitabolites sufficient to achieve
therapeutic levels in the CSF, and meningeal radiation ther-
apy. After three decades of clinical trials, their relative val-
ues, indications, and risk/benefit ratios are still subjects of
controversy.

With intrathecal chemotherapy there is the question of
using Mtx alone; Mtx and cytarabine (Ara-C); or Mtx, Ara-
C, and a soluble corticosteroid, notably hydrocortisone or
methylprednisolone. Another question is how soon, how of-
ten, and how long should they be administered and whether
an Ommaya reservoir should be used. Perhaps most im-
portant is whether cranial meningeal irradiation needs to be
added to intrathecal therapy, especially in those deemed to
be at higher risk of meningeal leukemia. Although parapare-
sis and encephalopathy have been reported after intrathecal
medication, with proper preparation and administration mor-
bidity is low.

The diffusion of drugs into perivascular leptomeninges is
dependent on the ebb and flow of cerebrospinal fluid from
the subarachnoid space, which is distant from arterioles and
venules deep in the brain. For this reason, radiation therapy
early in remission was introduced for prevention of menin-
geal leukemia. Although effective, cranial irradiation can
result in several adverse sequelae, including fever and som-
nolence 6 to 8 weeks later; neuropsychologic impairment;
growth disturbances, both local and pituitary-mediated; leu-
koencephalopathy; cerebral microangiopathy; and brain tu-
mors. Preschool children experience more growth inhibi-
tion and neuropsychologic sequelae than older children and
girls more than boys. When radiation is extended to the
spine, it impairs spinal growth, increases risk of cardiac
dysfunction, and impedes future administration of systemic
hematosuppressive chemotherapy.

The choice of radiation modality, volume, and dose varies
from one study to another but, when used, cranial radiation
is generally preferred for prevention and craniospinal for
treatment. To be remembered is that portals need to be
sufficient to encompass all leptomeningeal tissue, including
that within the optic nerve and cauda equina.

The third and most recent method of preventing and treat-
ing meningeal leukemia is high-dosage antimitabole therapy.
By administering high-dosage Mtx by continuous intra-
venous infusion over 24 hours, CSF levels in the therapeutic
range may be achieved. The ratio of CSF to plasma con-
centration of Mtx is increased in the presence of overt menin-
geal leukemia. Delayed leucovorin rescue prolongs expo-
sure, increasing the opportunity for Mtx uptake and storage
by leukemia cells in the exposed arachnoid. In a similar
way, intravenous 6MP (1,200 mg/m2 over 24 hours) achieves
continuous plasma concentrations in the 6 pmol/L range and
maintains cytotoxic CSF concentrations of approximately 1
µmol/L, about 20% of plasma concentration. Finally, CSF
levels of Ara-C approximate 20% to 40% of plasma levels
and the drug is more slowly converted to its degradation
product, Ara-U, in CSF than in plasma. High-dosage intra-
venous Ara-C is demonstrated to be effective in meningeal
leukemia.

The toxicity of high-dosage intravenous antimitabolite ad-
ministration is well described and affects the central nervous
system as well as hematopoiesis, epithelium, liver, kidneys,
and lungs. Although most of these effects are reversible,
children who have received prior cranial radiation are espe-
cially susceptible to permanent leukoencephalopathy and ce-
rebral microangiopathy after parenteral Mtx.
PREVENTION OF MENINGEAL ALL

Table 2 summarizes the results of more recent published studies that use the three methods described for prevention of meningeal leukemia in patients with ALL.57-66 Earlier results are tabulated in a previous review.69 Interpretation of these results is confounded by differences in patient selection, in systemic chemotherapy, in technical factors, in length of follow-up, and in data analysis.

However, the predominance of tabulated data support the conclusion that extended intrathecal therapy is highly effective for preventing meningeal leukemia in patients with “low-risk” and B-precursor ALL.58,63-67 When combined with intensive systemic chemotherapy, it is also effective in “intermediate-risk” ALL.68 The combination of intrathecal therapy with intermediate-dose Mtx (1 g/m²/24 h) and intermediate-dose Ara-C (1 g/m²/24 h) or high-dose 6MP (1 g/m²/72 h) (intrathecal and intravenous drugs administered separately to reduce neurotoxicity) appears to be effective in prevention of meningeal relapse in “high-risk” B-precursor ALL as well.64,65 This conclusion is further supported by the results of a 1986-1991 Pediatric Oncology Group (POG) study based on the Krance et al study64 (Vita Land, personal communication, August 1993). Of 415 children with high-risk and standard-risk B-precursor ALL receiving similar treatment with intravenous Mtx, Ara-C, and three-drug intrathecal therapy, only 18 (4%) have developed isolated meningeal relapse. A weakness of these studies is lack of information about the CSF concentrations of antimetabolites achieved by intermediate- and high-dosage intravenous infusions.

The question remains whether three-drug intrathecal therapy is superior to Mtx therapy alone. Historically, combination antimitabolite therapy has been more effective than single agents in ALL. One might expect Mtx and Ara-C to affect different leukemia cells as well as to act synergistically in others, although, with regard to hydrocortisone, one report suggests that it protects myeloid leukemia cells from Ara-C.54,70 Recently, the POG felt compelled to revert to three-drug intrathecal therapy in a study when the use of Mtx alone appeared to be resulting in more meningeal relapses than expected.

As noted in Table 2, very high doses of intravenous Mtx combined with extended intrathecal chemotherapy were reported to be effective in preventing meningeal relapse in patients at exceptionally high risk of relapse and in infants less than 1 year of age.50,61

Patients with B-cell ALL and T-cell ALL have a high risk of early meningeal leukemia.23,71 With regard to B-cell ALL, recent reports indicate that intensive intrathecal and high-dosage intravenous chemotherapy are effective in its prevention and possibly for treatment.13,72-75 Currently, cranial irradiation is excluded entirely in some treatment protocols and is administered only for overt meningeal leukemia in others.

With regard to T-cell ALL, a recent Childrens Cancer Group (CCG) report describes the outcome of children with lymphomatous presentation or T-cell immunophenotype ALL who were randomized to receive or not receive preventive cranial radiotherapy early during remission.76 All received multiple systemic drugs in standard dosage and extended intrathecal Mtx therapy. For patients with initial white blood cell (WBC) counts of 50,000/µL or higher, the 5-year actuarial CNS relapse rates were significantly different: 9% for those who received cranial radiotherapy and 27% for those who did not. There was no significant difference in rate for those with initial WBC counts less than 50,000/µL. This suggests that cranial irradiation is needed in patients with lymphomatous presentation or T-cell ALL with initial WBC counts of 50,000/µL or greater. However, it is possible that the use of high-dosage intravenous and three-drug intrathecal therapy might obviate this need.

Both intravenous Mtx or Ara-C therapy and cranial irradiation can produce neurologic and neuropsychologic disorders.34-36,77 However, cranial irradiation results in growth disturbances and, more ominously, cranial tumors later in life, especially in preschool children.37,38,42-44 The majority of children with ALL are cured and appear destined to normal life spans and the risk of radiation induced cranial solid tumors appears to be continuous throughout life. This appears to be the prime reason why cranial radiotherapy should be avoided in the face of equivalent efficacy of intensive intrathecal and intravenous antimitabolite therapy.

To summarize, the data available lead to the conclusion that extended intrathecal chemotherapy and systemic chemotherapy appropriate to the biologic species and/or risk group is as effective as radiation-containing regimens for prevention of meningeal ALL, and preferable, in children with B-precursor ALL, low- and intermediate-risk ALL, B-cell ALL, and T-cell or lymphomatous ALL with initial WBC counts less than 50,000/µL. Whether the administration of high-dosage intravenous chemotherapy and three-drug intrathecal therapy will also eliminate the need for preventive cranial irradiation in patients with T-cell ALL or lymphomatous presentation with WBC counts above 50,000/µL remains to be seen.

PREVENTION OF MENINGEAL AML

Less study has been made of the prevention of meningeal leukemia in AML. One reason is that systemic treatment regimens are less effective than in ALL so that hematologic relapse most often pre-empts initial meningeal relapse. An early report of preventive cranial radiation and intrathecal methotrexate in children with AML indicated that it served its purpose but did not alter survival.79 Table 3 summarizes experience with various methods used to prevent meningeal relapse in AML.20,22,79-81 Again, interpretation is confounded by the heterogeneity of the patients, their leukemia phenotypes, and the selection, dosage, schedule, and duration of their chemotherapy. However, the general consensus is that repeated administration of intermediate to high dosage of Ara-C and intrathecal Ara-C with or without intrathecal Mtx are probably adequate measures.

Recently, it was suggested on the basis of a nonrandom comparison that preventive cranial radiotherapy reduced the frequency of hematologic relapse in children with AML and led to higher cure rates.84 This concept fits an hypothesis of early studies of preventive meningeal therapy.4 The hypotho-
# Table 2. Prevention of Meningeal Relapse of ALL

<table>
<thead>
<tr>
<th>Reference</th>
<th>Method</th>
<th>Patients</th>
<th>Isolated Meningeal Relapse</th>
<th>Overall Outcome %</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="1986">Steinherz et al</a></td>
<td>IT Mtx + Ara-C, extended</td>
<td>89 high risk</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Cranial RT 18 Gy Intensive chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><a href="1987">Littman et al</a></td>
<td>Cranial RT 18 Gy Early IT Mtx</td>
<td>250 low risk</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>IT Mtx, extended</td>
<td>254 low risk</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td><a href="1988">Abromowitch et al</a></td>
<td>IV Mtx 1 g/m²/24 h</td>
<td>154 B-precursor</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>IT Mtx, extended</td>
<td>Cranial RT 18 Gy</td>
<td>155 B-precursor</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>IT Mtx, extended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV Mtx 33 g/m²/24 h</td>
<td>53 high risk</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>IV cytarabine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IT Mtx + Ara-C, extended</td>
<td>50 &lt;1 yr age</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>IV Mtx 1 g/m²/24 h</td>
<td>59 low risk</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td><a href="1988">Abromowitch et al</a></td>
<td>IV 6MP 1 g/m²/8 h</td>
<td>IT Mtx, extended</td>
<td>108 low risk</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>IT Mtx, Ara-C, HC, extended</td>
<td>Cranial RT 18 Gy</td>
<td>233 high risk</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>IT Mtx, Ara-C, HC, extended</td>
<td>IV Mtx 1 g/m²/24 h</td>
<td>45 high risk B-precursor</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>IT Mtx, Ara-C, HC, extended</td>
<td>IV Ara-C 1 g/m²/24 h</td>
<td>54 low risk B-precursor</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>IT Mtx, Ara-C, HC, extended</td>
<td>IT Mtx, Ara-C, HC, extended</td>
<td>83 high risk</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>IT Mtx 1 g/m²/24 h</td>
<td>IV 6MP 1 g/m²/8 h</td>
<td>518</td>
<td>20</td>
</tr>
<tr>
<td><a href="1993">Gelber et al</a></td>
<td>Cranial RT 18-28 Gy</td>
<td>IT Mtx, extended</td>
<td>577 B-precursor</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>IT Mtx, Ara-C, HC, extended</td>
<td>IV Mtx 1 g/m²/24 h</td>
<td>575 B-precursor</td>
<td>48</td>
</tr>
<tr>
<td><a href="1993">Tubergen et al</a></td>
<td>Cranial RT 18 Gy IT Mtx, early</td>
<td>697 intermediate risk</td>
<td>42</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>IT Mtx, extended</td>
<td>691 intermediate risk</td>
<td>51</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Cranial RT 18 Gy IT Mtx, early</td>
<td>131 intermediate risk</td>
<td>19</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td>IT Mtx, extended</td>
<td>Standard chemotherapy</td>
<td>128 intermediate risk</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>IT Mtx, extended</td>
<td>Standard chemotherapy</td>
<td>384 intermediate risk</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>IT Mtx, extended</td>
<td>IT Mtx, early Standard chemotherapy</td>
<td>374 intermediate risk</td>
<td>16</td>
</tr>
</tbody>
</table>

Abbreviations: IT, intrathecal; IV, intravenous; HC, hydrocortisone; RT, radiation therapy; EFS, event-free survival; DFS, disease-free survival.

* Additional data provided by Harland Sather (August 1993).
† Data derived from same study.
MENINGEAL LEUKEMIA

Table 3. Prevention of Meningeal Relapse in Acute Myeloid Leukemia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Method</th>
<th>Patients</th>
<th>Isolated Meningeal Relapse</th>
<th>Overall Outcome %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pui et al*43 (1985)</td>
<td>IT Mtx, extended, Cranial RT 24 Gy at completion of therapy</td>
<td>138</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Creutzig et al*9 (1986)</td>
<td>Cranial RT 18 Gy, IT Mtx, early</td>
<td>119</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chessells et al* (1986)</td>
<td>IT Mtx and/or Ara-C, extended</td>
<td>66</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Grier et al*23 (1987)</td>
<td>None</td>
<td>45</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Amadori et al*6 (1987)</td>
<td>IT Ara-C, extended</td>
<td>45</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Steuber et al*8 (1991)</td>
<td>IT Ara-C, early, SC or IV Ara-C, 150 mg/m² q 8 h x 3 d, 300 mg/m²/d x 3 d</td>
<td>107</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ravindranath et al*91 (1991)</td>
<td>Cranial RT (24 Gy), IT Mtx, early</td>
<td>170</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ravindranath et al*91 (1991)</td>
<td>IT Ara-C, early, IV Ara-C, 3 g/m² q 12 hr x 4</td>
<td>238</td>
<td>9</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations: SC, subcutaneous; CCR, continuous complete remission.
* Thirty-five of 184 patients had CSF leukemia cells at diagnosis; no adverse effect on outcome.

sis was that exposure to suboptimal concentrations of anti-leukemic drugs in the CSF promoted development of drug resistance by leukemic cells in the arachnoid. These drug-resistant cells then were the nidus of systemic relapse with resistant leukemia. However, historical comparison of two POG studies of childhood AML, one using cranial radiation and the other not, fail to show a significant difference in event-free survival (Table 3).82,83

TREATMENT OF MENINGEAL LEUKEMIA

The significance of a few leukemia cells in the CSF at diagnosis without symptoms and of their appearance in the CSF, with or without symptoms, during or after completion of systemic chemotherapy, may differ. Meningeal leukemia at diagnosis is usually sensitive to chemotherapy, whereas meningeal leukemia that occurs during adequate systemic and intrathecal chemotherapy is more likely resistant or relatively resistant to chemotherapy. Meningeal leukemia developing after cessation of chemotherapy might be the result of inadequacy of intrathecal and systemic chemotherapy or drug resistance. The distinction is not clear but there is currently a trend to use cranial or craniospinal radiotherapy and intensive intrathecal therapy for isolated meningeal relapse but to rely on intensive intrathecal therapy and intermediate to high-dosage systemic therapy for the patient who at diagnosis has less than 5 leukemia cells/μL and no clinical evidence of meningeal leukemia.12 One reason is the problem of administering intermediate- to high-dosage antimetabolites, specifically Mtx, once therapeutic radiation has been delivered to the cranium or craniospinal axis. This consideration led POG to delete cranial irradiation in children with B-cell ALL who presented with meningeal leukemia.13 Although the cure rate is lower for such children than for those without meningeal leukemia at diagnosis, it is not caused by meningeal relapse.

Table 4 summarizes the results of treatment of clinically isolated meningeal relapse with various methods.68,85,89 Although hematologic relapse and death caused by refractory leukemia often follows isolated meningeal relapse, outcome has improved in recent years with extended intrathecal chemotherapy and meningeal irradiation accompanied by adequate systemic chemotherapy. An important question is whether the irradiation needs to be cranial and spinal or whether cranial irradiation alone is sufficient. Its importance derives from the additional serious sequelae observed when spinal irradiation is administered. Considerable hematopoietic tissue is reached by irradiation when spinal ports are used, resulting in lengthy hematopoietic suppression and poor hematologic tolerance of subsequent hematopoietic chemotherapy.33 Secondly, spinal growth is inhibited, leading to reduced stature and possibly lordosis as the abdominal viscera enlarge with age.50 Thirdly, the spinal radiation fields increase considerably the number of organs and volume of tissue at increased risk of radiation injury and carcinogenesis.

The practice of administering craniospinal irradiation for meningeal relapse was originally based on experience with medulloblastoma, where the presence of neoplastic cells in the cerebrospinal fluid necessitated spinal irradiation to avoid spinal recurrence.90 This practice was supported by a British study that randomly compared cranial versus craniospinal irradiation for treatment of overt meningeal relapse of ALL.91 All eight patients in first meningeal relapse who received cranial radiotherapy developed a second meningeal relapse in a median period of 15 weeks. In contrast, 4 of 9 receiving craniospinal radiotherapy were alive and without meningeal leukemia 2.5 to 4 years later. However, the patients received only six intrathecal doses of a single drug at body surface area rather than age-related dosage before irradiation, and no intrathecal therapy after irradiation. Perhaps more importantly, they received low-dosage systemic chemotherapy.
that would not be expected to influence the course of meningeal leukemia.

A POG comparative study\textsuperscript{55} suggested that cranial and craniospinal irradiation were equally effective in preventing second meningeal relapse (Table 4). The poor overall outcome in the cranial radiotherapy group was attributable to relapse at other sites. However, the equivalent results in the two groups for prevention of second meningeal relapse might have been caused by the extended use of intrathecal drug therapy in the children who received cranial irradiation but not in those who received craniospinal irradiation, rather than therapeutic equivalence of the two methods of irradiation.

Three other studies support the use of cranial irradiation without spinal irradiation for treatment of isolated meningeal relapse: a POG study\textsuperscript{86} that also used extended three-drug intrathecal therapy, a German study\textsuperscript{87} that included high-dose intravenous Mtx as well as extended three-drug intrathecal therapy, and an unpublished retrospective comparison of St Jude data (Judith Ochs, personal communication, January 1994). In the St Jude comparison, 15 children received 18 to 24 Gy of cranial radiotherapy after a median 17 months of intrathecal chemotherapy and 14 children, comparable with regard to initial WBC and duration of first remission, received 24 Gy of cranial radiotherapy and 12 to 24 Gy of spinal irradiation after a median 15 months of intrathecal chemotherapy. Ten of each group are alive and well 10 years or more since radiation therapy. This suggests that craniospinal irradiation has no therapeutic advantage over cranial irradiation when preceded by extended intrathecal drug therapy.

The high risk of hematologic relapse after isolated meningeal relapse, and the problem of delivering intensive systemic chemotherapy to prevent it once cranial or craniospinal radiotherapy has been administered, have led to further studies in which radiotherapy is delayed. This allows intensive treatment with intrathecal drugs and with intravenous chemotherapy in sufficient dosage to establish therapeutic levels in the CSF. The outcome of two such pilot studies, one by Mandell et al\textsuperscript{58} and the other by POG,\textsuperscript{89} are summarized in Table 4. The POG protocol consisted of remission induction with dexamethasone, vincristine, daunorubicin, and three-drug intrathecal therapy; 6 weeks of consolidation with high-dosage Ara-C and L-asparaginase; and 12 weeks of intensification with etoposide, cyclophosphamide, intermediate high-dose intravenous Mtx, and high-dose intravenous 6MP, followed by craniospinal irradiation (24 Gy/15 Gy). Subsequently, the patients received conventional dosage of Mtx and 6MP and vincristine and cyclophosphamide for 18 months. With 62 patients registered in the study and 45 having completed the first 6 months of chemotherapy and the radiation therapy, the 2-year event-free survival estimate is 83\% (±10\%). Only 1 patient had a second isolated meningeal relapse and only 1 patient experienced relapse before irradiation. These early results are superior to past POG experience with treatment of isolated meningeal relapse, but further follow-up is required.

Several experimental approaches are being made to treat-ment of meningeal leukemia. Among them are intrathecal 6MP, intrathecal diaziquone, high-dosage intravenous 6MP, and high-dosage intravenous thio-TEPA.\textsuperscript{54,92,94} The antileukemic drug, cladribine, was reported to clear leukemia cells from CSF in 2 of 3 patients when administered by continuous intravenous infusion for 5 days.\textsuperscript{95} Total body irradiation with a craniospinal "boost," combined with myeloablative che-

### Table 4. Treatment of Isolated Meningeal Relapse in ALL

<table>
<thead>
<tr>
<th>Reference</th>
<th>Method</th>
<th>Patients</th>
<th>Second Isolated Meningeal Relapse</th>
<th>Hematologic Relapse</th>
<th>Other Failure</th>
<th>Overall Outcome (%)</th>
</tr>
</thead>
</table>
| Land et al\textsuperscript{55} (1985) | Cranial RT 24 Gy  
IT Mtx, Ara-C, HC, extended  
Craniospinal RT 24/14 Gy  
IT Mtx, Ara-C, HC, early | 29 2 1 9 | 0 1 0 | 2 0 2 | 2 0 2 | 4 yr DFS 14\% 70\% |
| Mandell et al\textsuperscript{58} (1990) | IT or ITV Mtx, Ara-C  
Intensive chemotherapy  
Delayed 14-21 mo cranial and spinal RT 18/12 Gy | 8 1 1 0 | 8 1 1 | 8 1 0 | 8 1 0 | 4 yr DFS 72\% 5 yr EFS 72\% |
| Henze et al\textsuperscript{92} (1991) | Cranial RT 24 Gy  
IT Mtx, Ara-C, HC, extended  
IV Mtx 1 g/m\textsuperscript{2}/36 h | 120 35 12 | 120 35 12 | 120 35 12 | 120 35 12 | 4 yr DFS 46\% 5 yr EFS 46\% |
| Winick et al\textsuperscript{93} (1993) | Cranial RT 24 Gy  
IT Mtx, Ara-C, HC, extended | 20 8 9 1 | 20 8 9 1 | 20 8 9 1 | 20 8 9 1 | 5 yr EFS 10\% 2 yr EFS 10\% |
| Gelber et al\textsuperscript{93} (1993) | IT Mtx, Ara-C, 17 patients  
BMT, 3 patients | 45 1 5 1 | 45 1 5 1 | 45 1 5 1 | 45 1 5 1 | 2 yr EFS 83\% 2 yr EFS 83\% |

Abbreviation: ITV, intraventricular.

* Data not reported. Remissions terminated in a total of 16 patients treated with cranial radiotherapy and 5 treated with craniospinal radiotherapy.
motherapy and autologous marrow transplantation, has been suggested for treatment of isolated meningeal relapse. Adding the severe immediate and late toxicity of such measures appears unacceptable when approximately one-half of children are surviving isolated meningeal relapse with current treatment and there is no convincing evidence of a therapeutic advantage of marrow transplant procedures in ALL.

It seems advisable that patients with meningeal relapse of ALL, either isolated or combined with other sites, be registered on institutional or collaborative studies designed to answer questions about the optimal method of management with regard to both cure rate and quality of survival. The present trials of intensive intrathecal and high-dose intravenous antineoplastic chemotherapy followed by meningeal irradiation appear to be a reasonable approach. Randomized comparative study is needed to determine whether craniospinal irradiation is more effective than cranial irradiation in the context of modern chemotherapy. If it is not advantageous, the next question might be whether any irradiation is necessary for optimal cure rate.

Scant data is available about treatment of isolated meningeal relapse in AML because it is usually followed quickly by hematologic relapse and death. However, the methods used for meningeal relapse of ALL, intensive intrathecal and systemic chemotherapy and possibly radiation therapy, would appear reasonable.

DOSE AND TECHNIQUE OF INTRATHecal THERAPY

Because the brain develops and matures before other organs, the volume of CSF is more closely related to brain size than weight or body surface area. Although brain size is best reflected by head circumference, it is also related to age of the patient. It is now customary to use age to determine intrathecal drug doses, as indicated in Table 5. In using age-related dosage of intrathecal Mtx, caution must be exercised in infants. Intrathecal Mtx slowly infuses from the CSF into plasma so that it behaves like a prolonged intravenous infusion. When dosage is age-related, the plasma Mtx levels can be expected to be considerably higher in infants than in older children and adults, resulting in systemic Mtx toxicity. The same can occur in patients with renal dysfunction. Some ALL protocols specify administration of one dose of leucovorin 24 hours after intrathecal Mtx to "rescue" the patient from excessive systemic Mtx toxicity.

Careful formulation, preparation, and administration of the drugs are essential. They need to be free of preservative and freshly dissolved in preservative-free buffered saline or balanced salt solution. The solution is brought to room temperature, millipore-filtered, and injected slowly without aspiration after allowing approximately one-half the injection volume to flow freely from an atraumatic lumbar puncture. The injection is performed with the patient in the lateral recumbent position to reduce caudal drug concentration. Immediately after injection the patient is placed in the ventral Trendelenburg position to reduce lumbar hydrostatic pressure and promote cephalad diffusion of the drugs, as demonstrated in primates.

The use of Ommaya reservoirs is questionable because the ventricles lack leptomeningeal tissue, ventriculitis is more serious than meningitis, foreign bodies in the brain are hazardous, and rarely are reservoirs needed for technical reasons.

DOSE AND TECHNIQUE OF RADIATION THERAPY

For ALL, early attempts at CNS prophylaxis using 5 and 12 Gy (1 Gy = 100 rad) of craniospinal irradiation were unsuccessful. When the radiation dose was increased to 24 Gy, the isolated CNS relapse rate decreased to less than 10%. Twenty-four gray became the standard prophylactic dose for cranial irradiation in combination with intrathecal methotrexate. In recent years, it was found that a dose of 18 Gy was equally efficacious. It is still uncertain whether the incidence and/or severity of any neuropsychologic effect attributed to cranial irradiation are less after 18 Gy of cranial irradiation than after 24 Gy. Nonetheless, in children with ALL, 18 Gy is now the standard dose when cranial irradiation is administered for preventive meningeal therapy.

For the treatment of established meningeal leukemia, some evidence in the literature suggests that craniospinal irradiation is the preferred treatment. When craniospinal irradiation is used for established meningeal leukemia, the radiation doses range from 24 to 30 Gy for the cranium and from 15 to 24 Gy for the spine. The spinal axis is usually treated to a lower dose mainly because of the belief that chemotherapeutic agents administered intrathecally are distributed better over the spinal meninges than over the cranial meninges.

For cranial irradiation, the patient is simulated for opposed lateral treatment fields and the entire cranial meningeal surface is covered. Special attention is given to the posterior retina (which may harbor leukemic cells), the posterior globe (as the meningeal reflection along the optic nerve comes very close to the posterior aspect of the globe), the cribriform plate, and the middle cranial fossa. The treatment fields are shaped using cerrobend. An attempt is made to shield the roots of the maxillary teeth in children. Cobalt-60, 4 MV, or 6 MV photons are suitable. A dose of 1.5 to 2 Gy per treatment fraction is usually prescribed to the midplane. Hypofractionated cranial irradiation has been performed in a limited fashion and theoretically has a potential advantage of decreasing late morbidity. However, it has not been rigorously studied in large numbers of patients. It is interest-

<p>| Table 5. Age-Related Dosage of Triple Intrathecal Drugs |</p>
<table>
<thead>
<tr>
<th>Age</th>
<th>1 yr</th>
<th>2 yr</th>
<th>3 to 8 yr</th>
<th>9 yr and Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mtx</td>
<td>8</td>
<td>10</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>8</td>
<td>10</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Ara-C</td>
<td>16</td>
<td>20</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>Volume</td>
<td>5.3 mL</td>
<td>6.7 mL</td>
<td>8 mL</td>
<td>10 mL</td>
</tr>
</tbody>
</table>

Drugs are preservative-free and dissolved in preservative-free Elliott's B, Ringer's lactate, or buffered saline solution.
ing to note that, in a recent CCG study, patients whose prophylactic cranial fields did or did not encompass the entire meningeal surface had equivalent CNS relapse rates. Nevertheless, it should be emphasized that meticulous radiotherapy technique in cranial irradiation remains a sound policy.

For craniocerebral irradiation, the patient is simulated in the prone position, usually with positioning devices such as the alpha cradle and a special head positioning device (either one commercially available or custom-made from plaster of Paris). For young children who cannot cooperate by holding still, sedation or general anesthesia is needed. The spinal axis is usually treated down to the bottom of the thecal sac. Although the thecal sac usually ends at about the second or third sacral vertebral body, a magnetic resonance image scan of the lumbosacral spine provides an accurate position. In a few institutions, electrons have been used to substitute for photons for the spinal irradiation of young children.

It is important to emphasize that craniocerebral irradiation is a technically difficult and tedious procedure that requires careful attention to many details. For this reason, it needs to be performed in institutions where there has been sufficient experience by the radiation oncologist, physicist, dosimetrist, and technologist.

**Dosage and Technique of Intravenous Chemotherapy**

The optimal methods for using intravenous chemotherapy to prevent or treat meningeal leukemia are undetermined.\(^{19,52}\) Drug dosages and schedules vary considerably in published studies and often lack correlative evaluation of plasma and CSF concentrations. Drugs tend to clear more slowly from CSF than plasma, increasing exposure time and raising concentration \(\times\) time values. CSF concentrations tend to reach maximum levels at the end of continuous infusions. Perhaps most importantly, the low number of cells in the CSF prevents measurement of incorporation of the drugs into cell metabolism. This is particularly important with the antileukemic antimetabolites since their effectiveness depends on enzymatic conversion within cells: Mtx to Mtx polyglutamate, Ara-C to Ara-C triphosphate, and 6MP to thioguanine nucleotides.

For methotrexate, CSF concentrations reach levels approximately 3% of steady-state plasma levels.\(^{3,19,55}\) Prolonged 24- to 36-hour infusions and delayed leucovorin rescue at 48 hours increase exposure time. If an Mtx concentration of 1 \(\mu\)mol/L is considered therapeutically adequate, an Mtx steady-state plasma concentration of 35 to 50 \(\mu\)mol/L is probably sufficient. This can be expected with a continuous infusion of approximately 3,000 mg/m\(^2\) over 24 hours after an initial bolus of 10% of the dose. Higher CSF:plasma ratios are reported in the presence of overt meningeal leukemia.\(^{39}\) Considerable precaution must be taken with regard to renal and hepatic function, hydration, alkalinization, and avoiding drugs that can reduce clearance of Mtx. Leucovorin dosage and duration are based on plasma Mtx concentrations.

For Ara-C, either bolus administration or continuous infusion results in CSF concentrations approximately 20% to 40% of plasma concentrations, partly because of longer persistence of Ara-C in CSF than in plasma.\(^{55,101-104}\) The CSF to plasma ratio of Ara-C concentrations tends to be lower with increasing dosages of intravenous Ara-C. If a 1 \(\mu\)mol/L CSF concentration is considered adequate, a continuous intravenous infusion of 2,000 mg/m\(^2\) over 24 hours should suffice to achieve it. Repeated injections of 3,000 mg/m\(^2\) over 2 hours every 12 hours or 3,500 mg/m\(^2\) by continuous 24-hour infusion maintain CSF concentrations in the 3 \(\mu\)mol/L range.

For 6MP, continuous infusion of 1,000 to 1,200 mg/m\(^2\) over 24 hours achieves CSF concentrations of approximately 1 \(\mu\)mol/L, which is considered therapeutic.\(^{54}\) However, unlike Mtx and Ara-C, high-dosage intravenous 6MP has not been demonstrated to produce remissions of overt meningeal leukemia. As with Mtx, precautions are required with regard to renal and hepatic function and hydration.

In summary, high-dosage intravenous antimetabolite chemotherapy achieves therapeutic levels in the CSF that can serve to prevent meningeal relapse, and, with Mtx and Ara-C, to treat meningeal relapse. Optimal dosages and schedules need to be determined.

**Summary**

The prevention of meningeal leukemia has long been a keystone in its cure. The need was recognized when it became apparent in the 1950s and 1960s that meningeal relapse heralded hematologic relapse and a fatal course and that its incidence increased as systemic chemotherapy became more effective in controlling hematologic and visceral leukemia.\(^4\)

Evasion of a biologic safety net, the blood-CSF barrier, is required to prevent meningeal leukemia. Three methods are used: meningeal radiotherapy, intrathecal administration of antileukemia drugs, and high-dosage intravenous antileukemia drugs. Recent and current clinical studies reflect a continuing dialogue about which methods are preferable and under what circumstances. For prevention of meningeal leukemia, extended intrathecal therapy and intensive systemic chemotherapy appear to be as effective as radiotherapy for most patients. For treatment of overt meningeal leukemia, meningeal radiotherapy may be necessary. However, its administration compromises subsequent systemic chemotherapy so that delay may be advisable to allow intensive systemic chemotherapy for control of concurrent hematologic and visceral leukemia, whether clinically evident or not. For patients with meningeal leukemia at diagnosis, cranial irradiation may be delayed or possibly omitted if evidence of disease is minimal and craniospinal irradiation is probably required as well as intensive intrathecal and systemic chemotherapy. Hopefully, current and future studies will dispel the uncertainties and better quantitate risks and benefits of alternative methods.

Whatever method is used, careful attention to technical details is required to assure optimal efficacy at the least possible expense in immediate toxicity and late sequelae.
REFERENCES


32. Sullivan MP, Chen T, Dyment PG, Hvizdala E, Steuber CP: Equivalence of intrathecal chemotherapy and radiotherapy as central
MENINGEAL LEUKEMIA


70. Yang GS, McCulloch EA: Hydrocortisone protects the blast cells of acute myeloblastic leukemia from cytotoxic arabinoside. Blood 76:338a, 1990 (abstr, suppl 1)


Prevention and treatment of meningeal leukemia in children

D Pinkel and S Woo