A Randomized Controlled Trial Comparing Intrathecal Sustained-release Cytarabine (DepoCyt) to Intrathecal Methotrexate in Patients with Neoplastic Meningitis from Solid Tumors

Michael J. Glantz, Kurt A. Jaeckle, Marc C. Chamberlain, Surasak Phuphanich, Lawrence Recht, Lode J. Swinnen, Bernard Maria, Susan LaFollette, G. Berry Schumann, Bernard F. Cole, and Stephen B. Howell

ABSTRACT

Standard treatment for neoplastic meningitis requires frequent intrathecal (IT) injections of chemotherapy and is only modestly effective. DepoCyt is a sustained-release formulation of cytarabine that maintains cytotoxic concentrations of the drug in the cerebrospinal fluid (CSF) for more than 14 days after a single 50-mg injection. We conducted a randomized, controlled trial of DepoCyt versus methotrexate in patients with solid tumor neoplastic meningitis. Sixty-one patients with histologically proven cancer and positive CSF cytologies were randomized to receive IT DepoCyt (31 patients) or IT methotrexate (30 patients). Patients received up to six 50-mg doses of DepoCyt or up to sixteen 10-mg doses of methotrexate over 3 months. Treatment arms were well balanced with respect to demographic and disease-related characteristics. Responses occurred in 26% of DepoCyt-treated and 20% of methotrexate-treated patients (P = 0.76). Median survival was 105 days in the DepoCyt arm and 78 days in the methotrexate arm (log-rank P = 0.15). The DepoCyt group experienced a greater median time to neurological progression (58 versus 30 days; log-rank P = 0.007) and longer neoplastic meningitis-specific survival (log-rank P = 0.074; median meningitis-specific survival, 343 versus 98 days). Factors predictive of longer progression-free survival included absence of visible central nervous system disease on neuroimaging studies (P < 0.001), longer pretreatment duration of CSF disease (P < 0.001), history of intraparenchymal tumor (P < 0.001), and treatment with DepoCyt (P = 0.002). The frequency and grade of adverse events were comparable between treatment arms. In patients with solid tumor neoplastic meningitis, DepoCyt produced a response rate comparable to that of methotrexate and significantly increased the time to neurological progression while offering the benefit of a less demanding dose schedule.

INTRODUCTION

Neoplastic meningitis is a devastating complication of cancer. At least 5–8% of patients with solid tumors (predominately melanoma, breast, and lung cancer) develop symptomatic neoplastic meningitis (1–3). Ironically, therapeutic advances against extraneural cancer have translated into increasing numbers of patients who develop leptomeningeal metastases (4–9). The presence of malignant cells in the CSF reliably predicts widespread neuraxis disease (10). Standard treatment therefore requires intra-CSF chemotherapy, preferably administered through a ventricular reservoir (5, 9, 11, 12), accompanied by focal irradiation to sites of bulk disease, CSF flow obstruction, or debilitating clinical symptoms (11, 13–15). Despite these interventions, treatment remains inadequate, at least in part because the two drugs most commonly used for IT therapy, methotrexate and cytarabine, are cell cycle phase-specific agents with short half-lives within the CSF (16–21). As a result, the exposure of tumor cells in the CSF to cytotoxic drug levels may be insufficient. A third agent, triethylenethiophosphoramide (thioTEPA), is not cell cycle phase specific, but it disappears from the CSF within minutes of IT administration, potentially compromising efficacy (22, 23). Whereas more frequent IT drug administration can increase drug levels (17, 24, 25), cost and inconvenience also increase significantly with this “concentration × time” approach, and overall survival is not convincingly
improved. New agents with more favorable pharmacological profiles and improved efficacy are clearly needed.

DepoCyt is a sustained-release formulation of cytarabine capable of maintaining therapeutic drug concentrations in the CSF for prolonged periods after IT injection (16, 26). A previous Phase I/II study established an appropriate dose and administration schedule for DepoCyt (27, 28) and demonstrated that the potential to more effectively kill tumor cells in the meninges and CSF than standard cytarabine formulations. For this reason, we conducted a prospective, randomized study comparing DepoCyt to methotrexate in patients with neoplastic meningitis originating from a variety of solid tumors.

PATIENTS AND METHODS

Primary study end points were response rate, duration of response, and time to neurological progression. Secondary end points were changes in neurological symptoms and signs and overall survival.

Study Design and Patient Eligibility. This was a multicenter, prospective, randomized, open label study designed to obtain estimates of the response rate to either IT DepoCyt or conventional IT methotrexate in patients with solid tumor neoplastic meningitis. A minimum of 20 evaluable patients were to be randomized to each arm. The primary end points were response rate and time to relapse as measured by time to neurological progression; secondary end points included quality of life and overall survival. Due to the small number of patients eligible for participation, this study was not powered to detect prespecified differences in the end points unless they were very large. Anticipating possible differences in drug sensitivity, patients were stratified based on primary tumor histology into two groups: (a) breast cancer and small cell lung cancer; and (b) all other histologies. Randomization within each stratum was then accomplished using a computer-generated table of random numbers. The study was terminated after accrual of 61 patients, a number estimated to assure that 20 patients on each arm would be evaluable. This protocol was approved by the institutional review boards of all 19 medical centers participating in this trial.

All patients with histologically proven, nonlymphomatous solid tumors and cytologically demonstrated malignant cells in the CSF were eligible for participation if they were ≥18 years of age and had a KPS > 50%; no prior IT methotrexate (prior use of other IT drugs was allowed); an expected survival of at least 2 months; no other serious medical or psychiatric illness; and acceptable baseline hematological, hepatic, and renal function (platelets ≥ 80,000/mm³, WBC count ≥ 3,000/mm³, serum glucose ≤ 150 mg/dl, serum creatinine ≤ 2 times the upper limit of normal, and aspartate aminotransferase, lactate dehydrogenase, and alkaline phosphatase ≤ 3 times the upper limit of normal) and were able to give informed consent. Obstruction to normal CSF flow despite focal radiotherapy, the presence of a functioning ventriculoperitoneal shunt, or treatment with investigational chemotherapy within 14 days of study entry were prohibited. Concurrent systemic chemotherapy or radiotherapy for malignant disease outside of the nervous system, supportive therapy (including oral and i.v. corticosteroids), and limited field (but not whole brain or craniospinal) irradiation were permitted. Concurrent IT chemotherapy other than with the assigned study drug, other investigational therapy, or high-dose systemic chemotherapy was not allowed.

Before study enrollment, a complete history and physical examination and standardized neurological examination were performed, and KPS, Mini-Mental Status Exam, and FACT-CNS (29) scores were recorded. A radioisotope CSF flow study and a contrast-enhancing computerized tomographic or MRI scan of the head were performed in all patients. Spinal MRI or computerized tomographic myelography were also obtained if clinically indicated. Patients were recorded as having visible disease if subarachnoid nodules, subependymal tumor spread, enhancement and clumping of nerve roots, intraparenchymal brain or spinal cord lesions, or an epidural mass were identified on neuroimaging studies. The qualifying CSF cytology was evaluated by the participating cytopathologist at each of the study centers and was subsequently reviewed by the blinded central neurocytopathologist (G. B. S.).

Treatment Plan. Fig. 1 presents a schematic of the study design and indicates that treatment was organized into two phases that included 1 month of induction and 3 months of consolidation. Patients who attained a response (conversion of their CSF cytology from positive to negative in the absence of neurological progression) at the end of the induction phase were eligible to enter the consolidation phase. During the induction phase, patients received either DepoCyt (50 mg once every 2 weeks) or methotrexate (10 mg twice a week) by either lumbar puncture or Ommaya reservoir. During the consolidation phase, DepoCyt was administered every 2 weeks for 1 month and then every 4 weeks for 2 months, whereas methotrexate was given every week for 1 month, and then every 2 weeks for 2 months.

A treatment “cycle” was defined by the dosing interval for DepoCyt. Thus, during the induction phase and the first month of the consolidation phase, a cycle consisted of a 2-week period during which patients received either one dose of DepoCyt or four doses of methotrexate. During the last 2 months of the consolidation phase, a cycle consisted of a 4-week period during which patients received either one dose of DepoCyt or two doses of methotrexate. Overall, DepoCyt-treated patients were to receive a total of 6 doses of DepoCyt, whereas methotrexate-treated patients were to receive a total of 16 doses of methotrexate. The dose and schedule of methotrexate administration were modeled after those used in the largest and most recent previous randomized clinical trial in this disease (30). Patients on both treatment arms received dexamethasone (4 mg twice a day on days 1 through 5 of each treatment cycle) unless, in the opinion of the local investigator, dexamethasone was contraindicated. Patients treated with methotrexate also received leucovorin (10 mg, p.o.) every 6 h for eight doses, beginning 24 h after each methotrexate dose. DepoCyt was provided in sterile, preservative-free, single-use vials containing 50 mg of cytarabine. Methotrexate (10 mg in 3–5 ml of sterile, preservative-free saline) was freshly mixed at the time of administration.

Drug treatment was delayed in patients whose WBC count fell below 1,500/mm³ or whose platelet count fell below 30,000/mm³.
mm$^3$. In patients who developed bacterial meningitis, treatment was suspended until the meningitis was cured. At that point, patients with a negative CSF cytology resumed treatment.

Evaluation of Response, Safety, and Quality of Life. Follow-up physical and standardized neurological examinations and CSF cytological examinations were performed every 14 days during the induction period and first month of consolidation in both treatment arms, every 28 days during the last 2 months of consolidation, and monthly thereafter until CSF relapse or death. The primary study end point was “response” at the end of the induction period. Response was defined as a negative CSF cytology from all sites (lumbar and ventricular) that were known to be positive at study entry, plus a stable or improved neurological examination. Patients who met the criteria for cytological conversion, irrespective of whether they had progressed neurologically, were termed “cytological responders.” Patients were declared nonresponders if they had a single positive CSF cytology at the end of induction, had two consecutive suspicious CSF cytologies, or had evidence of leptomeningeal disease progression on neurological examination. Patients responding to treatment at the end of the induction period proceeded to consolidation therapy; nonresponders were withdrawn from the study and were free to receive alternative treatment. Treatment decisions were based on the interpretation of the cytopathologist at each study site. However, the final determination of response for purposes of analysis was based on an independent central review of all CSF cytologies by the study neurocytopathologist (G. B. S.), who was blinded to drug assignment and the chronology of CSF samples. All patients were followed until death.

At the end of each treatment cycle, each principal investigator determined whether his or her patients had suffered neurological progression based on a global assessment of neurological signs and symptoms and CSF cytology. Time to neurological progression was defined as time from the start of treatment until neurological progression or death, whichever occurred first. Neoplastic meningitis-specific survival was defined as time from the start of treatment until death due to the meningeal component of the patient’s disease. Patients dying from other causes (including progression of their systemic disease) were censored in this analysis.

Treatment-related toxicity was recorded using CALGB expanded Common Toxicity Criteria. Complete physical and neurological examinations, complete blood counts, serum chemistries, liver enzymes, creatinine, urinalysis, and CSF examinations for WBCs and RBCs, glucose, protein, and malignant cells were performed before each cycle of therapy, monthly after the conclusion of treatment, and at additional points when clinically indicated. Drug-related meningitis, a non-CALGB toxicity category, was evaluated as a distinct entity. Drug-related meningitis was defined as the abrupt appearance, within 4 days of IT drug administration, of neck or back pain, neck stiffness, or any two of the following signs or symptoms: (a) headache; (b) nausea; (c) vomiting; (d) fever; (e) lethargy; or (f) culture-negative CSF pleocytosis. Drug-related meningitis was graded as mild (grade 1), moderate (grade 2), severe (grade 3), or life-threatening (grade 4), based on the severity of the worst component symptom or sign.

Quality of life was evaluated by administering the FACT-CNS scale at both study entry and the end of the induction period. The FACT-CNS scale consists of the Functional Assessment of Cancer Therapy-General Scale plus an “additional concerns” scale containing 12 supplementary items designed specifically for use in patients with neoplastic meningitis (29). The trial prospectively documented adequate internal consistency of this instrument and its sensitivity to the response attained by the patient.

Statistical Procedures. The primary analyses were performed on all 61 randomized patients using an intent-to-treat model. All study end points, analyses, and statistical tests used were prospectively defined. Proportions of responders in the two treatment arms were compared using Fisher’s exact test. Survival, neoplastic meningitis-specific survival, duration of cytological response, and time to neurological progression were estimated using Kaplan-Meier methods and compared with a log-rank test. A log-rank test was also used to compare survival times of responders and nonresponders. Changes in FACT-CNS scores from baseline to the end of the induction period were analyzed using an ANOVA model. Evaluation of patient characteristics for potential influence on progression-free survival was performed using proportional hazards regression analysis. First, a univariate analysis was performed for each of the potential predictors recorded in Table 1. A stepwise analysis...
procedure was then used to develop a multivariate model for evaluating the predictors jointly. Treatment variables (randomization group, concurrent systemic chemotherapy, and concurrent radiation) were forced into the multivariate model. For all analyses, \( P \leq 0.05 \) was considered statistically significant.

**RESULTS**

**Patient Characteristics.** Between March 14, 1994 and May 8, 1996, 61 patients were randomized to receive either DepoCyt (31 patients) or methotrexate (30 patients). Baseline clinical characteristics of the two groups are summarized in Table 1. The treatment arms were well balanced with respect to demographic and disease-related variables of potential prognostic importance (30–35), including age, KPS, tumor type, presence of cranial nerve deficits, duration of leptomeningeal disease before randomization, presence of progressive systemic cancer, number of extraneural metastatic sites, presence of visible CNS disease, and previous IT therapy. All but three patients (two patients receiving DepoCyt and one patient receiving methotrexate) were treated by the intraventricular route.

The mean number of cycles administered was 3.9 (median, 3.0) in the DepoCyt group and 2.3 (median, 2.3) in the methotrexate group. Nine DepoCyt-treated patients received all six planned cycles of therapy; no methotrexate-treated patients completed all six planned cycles of therapy. All 61 patients are included in the intent-to-treat analyses. Only the 59 patients who actually received at least one dose of IT chemotherapy are included in the toxicity analyses.

**Response.** Response rates, which were calculated on an intent-to-treat basis, were 26% (8 of 31) for patients in the DepoCyt arm (95% confidence interval, 14–50%) and 20% (6 of 30) for patients in the methotrexate arm (95% confidence interval, 6–34%; \( P = 0.76 \)). Cytological responses (without regard to neurological status) occurred in 26% (8 of 31) of DepoCyt-treated and 23% (7 of 30) of methotrexate-treated patients (\( P = 1.00 \)). Table 2 shows response as a function of the histological type of the primary tumor. Median survival from the time of randomization was 105 days in the DepoCyt group and 78 days in the methotrexate group (\( P = 0.16 \); Fig. 2). Thirteen DepoCyt-treated patients (41%) survived for >6 months, and five (16%) survived for >1 year. Among methotrexate-treated patients, five (17%) survived for >6 months, and two (7%) survived for >1 year (\( P = 0.15 \) at 6 months and 0.43 at 1 year; Fisher’s exact test). Time to neurological progression differed significantly between the two groups (log-rank \( P = 0.007 \)); median time to neurological progression was 58 days in the DepoCyt group and 30 days in the methotrexate group (Fig. 3). Duration of response was longer in the DepoCyt group, but not to a statistically significant degree (log-rank \( P = 0.31 \)). Neoplastic meningitis was more frequently the sole cause or a major contributing cause of death in patients receiving methotrexate (16 of 26 patients, 62%) than in those treated with DepoCyt (13 of 28 patients, 46%). Neoplastic meningitis-specific survival also differed appreciably between the DepoCyt and methotrexate arms (log-rank \( P = 0.074 \); median meningitis-specific survival, 343 versus 98 days). These results are summarized in Table 3.

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DepoCyt (( n = 31 ))</th>
<th>Methotrexate (( n = 30 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range; yr)</td>
<td>49 (19–74)</td>
<td>49 (29–72)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>KPS distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>2 (6%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>60%</td>
<td>15 (48%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>70%</td>
<td>3 (10%)</td>
<td>8 (27%)</td>
</tr>
<tr>
<td>80%</td>
<td>4 (13%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>90%</td>
<td>4 (13%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>100%</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Tumor type(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>SCLC</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>NSCLC</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Primary brain</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Other(^b)</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Median duration of meningeal disease before entry (days)</td>
<td>41 (1–382)</td>
<td>37 (2–291)</td>
</tr>
<tr>
<td>Presenting symptoms of neoplastic meningitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered mental status(^c)</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Cranial nerve deficits</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Spinal cord dysfunction</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Progressive systemic disease at study entry</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>No. of extraneural metastatic sites</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>1–3</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>&gt;3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Visible disease on CT(^d)/MRI scan anywhere in neuraxis</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Previous IT therapy</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Previous cranial or spinal radiation therapy</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Concurrent systemic chemotherapy</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Concurrent cranial or spinal radiation therapy</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^a\) SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

\(^b\) “Other,” cervical, colorectal, prostate, and carcinoma of unknown primary.

\(^c\) Baseline status was unavailable for two DepoCyt and three methotrexate patients.

\(^d\) CT, computerized tomography.

### Table 2 Responses as a function of histological type of primary cancer

<table>
<thead>
<tr>
<th>Histology of primary tumor</th>
<th>No. of responders/ total no. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DepoCyt</td>
</tr>
<tr>
<td>Breast</td>
<td>2/11</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>0/2</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>0/3</td>
</tr>
<tr>
<td>Melanoma</td>
<td>0/2</td>
</tr>
<tr>
<td>Primary brain</td>
<td>5/7</td>
</tr>
<tr>
<td>Other</td>
<td>1/6</td>
</tr>
<tr>
<td>Total</td>
<td>8/31</td>
</tr>
</tbody>
</table>
Survival varied significantly, depending on response status. Median survival for responders in both treatment arms was 279 days compared with 73 days for nonresponders ($P = 0.0002$). Similarly, median survival for cytological responders was 161 days compared with 73 days for nonresponders ($P = 0.0004$).

When a univariate Cox proportional hazards regression model was applied to the baseline patient characteristics listed in Table 1, two variables were found to be associated with significantly improved progression-free survival: (a) treatment with DepoCyt (RR, 0.44; $P = 0.006$); and (b) longer pretreatment duration of CSF disease (RR, 0.79; $P = 0.02$). In the multivariate model, treatment with DepoCyt remained significant (RR, 0.34; $P = 0.002$). Longer pretreatment duration of CSF disease (RR, 0.64; $P < 0.001$), presence of visible central nervous system disease at diagnosis (RR, 4.87; $P < 0.001$), and a history of intraparenchymal tumor (RR, 0.14; $P < 0.001$) were also significant in this analysis.

Three patients received intralumbar chemotherapy. One DepoCyt-treated patient with breast cancer responded to therapy and survived for 465 days. A second DepoCyt-treated patient with non-small cell lung cancer did not respond and survived for 36 days. One patient with melanoma received intralumbar methotrexate, responded to therapy, and survived for 90 days.

There were no significant differences in any response measure between the tumor types listed in Table 1 or between breast or small-cell lung cancer versus those with other tumor types. There were also no differences in FACT-CNS results between the DepoCyt and methotrexate treatment arms between study entry and the end of induction therapy. Patients in either arm who responded to IT therapy did report an improved quality of life (mean change/SD = +2.0/10.1) compared with patients who did not achieve a response (mean change/SD = −4.8/21.7; $P = 0.30$), although complete data were available for only 10 responders and 15 nonresponders (14 DepoCyt- and 11 methotrexate-treated patients). Neither the Mini-Mental Status Exam score nor KPS changed significantly between the baseline and the end of the induction period in either treatment arm, nor was there a significant change in either measure when looked at separately for responders and nonresponders, regardless of treatment assignment.

**Toxicity.** All patients who received at least one dose of their assigned drug were evaluated for toxicity. Of these 59 patients, 29 received at least one dose of DepoCyt, and 30 received at least one dose of methotrexate. Six patients (four in the DepoCyt arm and two in the methotrexate arm) died before completing induction therapy. Leptomeningeal disease progression was the primary cause of death in two patients (one in each treatment group) and was an important contributing cause in the deaths of the remaining four.

The frequency of CALGB grades 3 and 4 adverse events, by patient and by treatment cycle, are recorded for each treatment arm in Table 4. When examined either by patient or by treatment cycle, only the frequencies of sensory/motor dysfunction ($P = 0.021$) and of visual impairment ($P = 0.066$) differed appreciably between treatment groups. Chemical meningitis of any grade was common and occurred with slightly greater frequency in the DepoCyt treatment arm (23% of treatment cycles) than in the methotrexate arm (19% of cycles; $P = 0.57$). In both treatment arms, the incidence of drug-related meningitis was dramatically higher when dexamethasone prophylaxis was omitted (Table 5). Irrespective of dexamethasone administration, grade 3 or 4 drug-related meningitis was seen in only 5% of DepoCyt cycles and only 3% of methotrexate cycles. There were no drug-related hypersensitivity reactions, hepatic or renal toxicity, or cardiac adverse events, and no adverse events unique to IT DepoCyt. Grade 3 or 4 neutropenia and thrombocytopenia were uncommon occurrences in either treatment group and were attributed to systemic chemotherapy by the individual investigators in all cases. There were four deaths associated with febrile neutropenia (two in DepoCyt-treated patients and two in methotrexate-treated patients). In three of these cases, an underlying pneumonia was diagnosed. In one patient, no clear source of infection was identified. Four patients (three receiving DepoCyt and one receiving methotrexate) developed bacterial meningitis. In one of the DepoCyt group patients, the bacterial meningitis was diagnosed before the first dose of DepoCyt was administered.

![Fig. 2 Kaplan-Meier survival curves for patients treated with DepoCyt and methotrexate.](image1)

![Fig. 3 Kaplan-Meier plots of time to neurological progression for patients treated with DepoCyt and methotrexate.](image2)
Overall, no patient in either group had to delay therapy because of treatment-related toxicity. One DepoCyt-treated patient and one methotrexate-treated patient discontinued therapy because of drug toxicity (drug-related meningitis in the DepoCyt arm and neutropenia due to concurrent systemic chemotherapy in the methotrexate arm).

**DISCUSSION**

Despite therapeutic gains against systemic cancer, treatment for neoplastic meningitis remains inadequate. Occasional patients, usually those with breast cancer or lymphoma, may achieve disease-free survivals of a year or more, but overall median survival for patients with neoplastic meningitis is only 4–16 weeks (30–37). Promising results have been reported occasionally in Phase I trials (38–40), but prospective, randomized studies have failed to show any significant benefit for one type of IT therapy over another (5, 30).

Although progressive systemic disease is sometimes the cause of death in patients with neoplastic meningitis, progressive leptomeningeal cancer is the primary cause in most patients and almost always results in devastating morbidity (11, 22, 30, 34–36). An important explanation for the failure of conventional therapy to improve survival or prevent clinical progression may be the difficulty in maintaining cytotoxic levels of chemotherapeutic agents in the CSF with standard doses and schedules. Whereas pharmaceutically derived dosing regimens demanding multiple IT injections each week do provide prolonged cytotoxic drug levels in the CSF, these regimens are costly and logistically difficult for patients and physicians (17, 24, 25).

In the current study, standard therapy for patients with solid tumor neoplastic meningitis, biweekly IT methotrexate, was compared with bimonthly DepoCyt during the induction phase in the largest prospective, randomized trial yet reported in this setting.
disease. Both treatment groups were comparable with regard to important prognostic factors cited in the literature (30–35). Response, duration of response, cytological response, overall survival, and percentage of long-term survivors were all similar between treatment arms. DepoCyt treatment was associated with a significantly improved time to neurological progression and increased neoplastic meningitis-specific survival.

Toxicity was also similar between treatment arms. Drug-related meningitis is a common (at least 20% of patients) and self-limited toxicity associated with both IT methotrexate (41, 42) and standard IT cytarabine (43, 44). In the absence of dexamethasone prophylaxis, there was a high incidence of drug-related meningitis in both treatment groups, but the incidence was markedly reduced by concurrent oral dexamethasone administration. When symptoms did occur, they were easily controlled in both treatment arms by dexamethasone administration.

The frequency of visual toxicity was higher in the methotrexate group (4 of 30 patients) than in the DepoCyt group (0 of 29 patients). IT methotrexate alone has been associated with visual loss in patients with neoplastic meningitis (45) and may increase the frequency of radiation-related optic neuropathy in patients who have previously received cranial irradiation (46, 47). In this study, the difference between the two treatment groups is probably explained by the more rapid disease progression in the methotrexate group, because visual loss is a common symptom of progressive neoplastic meningitis (11, 22). The development of sensory and motor deficits was significantly more common with methotrexate treatment (10 of 30 patients) than with DepoCyt treatment (4 of 29 patients), but again, this finding probably reflects more rapid CSF disease progression in the methotrexate group rather than direct drug toxicity. More rapid CSF disease progression also accounts for the smaller number of treatment cycles given to patients in the methotrexate arm compared with the DepoCyt arm.

Interestingly, survival was significantly longer in responding patients in both treatment groups compared with nonresponders, regardless of whether overall response or just cytological clearing was considered. Similarly, improved quality of life, as registered by the FACT-CNS questionnaire, was seen in responding patients, but not in nonresponders. Both these findings must be interpreted with caution. Whereas “response” is associated with improved survival, causality cannot be proven. Similarly, changes in the FACT-CNS data are based on a subset of responding (10 of 14) and nonresponding (15 of 47) patients. Nonresponders in particular were often too ill to complete the FACT-CNS questionnaire. Nevertheless, these two findings suggest that “response” and “cytological response,” as defined in this study, are valid study end points. These findings also imply that effective treatment can provide meaningful benefit to a subgroup of patients with neoplastic meningitis.

There were no differences in posttreatment FACT-CNS scores between treatment arms, but the FACT-CNS does not record information about the convenience of or patient preferences for different treatment regimens and was therefore insensitive to a potentially important advantage of DepoCyt over methotrexate. In addition, complete data were available for only a relatively small number of patients.

Knowledge of prognostically important variables in neoplastic meningitis is critical to optimally use effective therapies, provide reliable prognoses, and design valid clinical trials. Multivariate regression analysis of our patients, which included concurrent treatment with systemic chemotherapy, identified three variables predictive of longer progression-free survival: (a) treatment with DepoCyt; (b) longer duration of CSF cancer before starting IT therapy; and (c) a history of intraparenchymal tumor. Presence of visible central nervous system tumor on pretreatment neuroimaging studies was predictive of shorter progression-free survival; however, some patients with normal CSF flow studies and no spinal symptoms did not undergo spinal MRI scanning. As a result, some patients with asymptomatic but potentially imageable spinal leptomeningeal disease may have been missed. Similar findings have been reported by others in both prospective (30) and retrospective (31–35) studies.

Several important aspects of this study require elaboration. First, cytarabine, the active drug in DepoCyt, has not generally shown significant activity against advanced solid tumors when administered i.v. However, cytarabine is effective against a wide spectrum of solid tumors, in both the laboratory and the clinic, when prolonged administration schedules, such as that provided in the current study, are used (48–52). In fact, cytological responses were seen in a variety of tumor types, including small cell lung cancer, non-small cell lung cancer, breast cancer, colon cancer, melanoma, and glioblastoma, both in this study and in an earlier Phase I/II study (28). Second, only patients with malignant cells in the CSF were eligible for this study. In practice, patients with compelling clinical, radiographic, and CSF chemistry evidence of neoplastic meningitis are sometimes diagnosed and treated despite a negative CSF cytology (11, 53, 54). In this trial, however, a positive CSF cytology was required to provide a diagnostically homogenous patient population and an objective treatment outcome measure. We were similarly stringent with regard to the definition of response, insisting on a primary end point that required both clearing of malignant cells from the CSF and stable or improved neurological status. In this regard, we followed the lead of nearly all recent clinical trials in neoplastic meningitis (5, 6, 30, 34, 37, 55–58). Furthermore, in concert with other trials (11, 34, 59–61), we required that all CSF sites (i.e., lumbar and ventricular) that were known to be cytologically positive at the time of study entry be devoid of malignant cells at the time of response evaluation. We also based all assessments of response on the reading of a blinded central neuropathologist. Third, we required the radiographic demonstration of normal CSF flow using a 99technetium or 111indium CSF flow study before patients could be randomized. In practice, CSF flow studies are not always performed before initiating treatment in patients with neoplastic meningitis. However, there is compelling evidence to support this approach (13, 15, 62), regardless of the type of IT chemotherapy used. Finally, extremely ill patients (those with KPS < 60% and expected survival < 2 months) were excluded from this study. Whereas this exclusion is common practice in oncology clinical trials and in the largest previous prospective trial in neoplastic meningitis (33), our results may, as a consequence, not be generalizable to patients with very poor performance scores.

Neoplastic meningitis remains a devastating and ultimately fatal disease. Even in the DepoCyt group, median survival was only 15 weeks. Nevertheless, DepoCyt provides longer progres-
Leptomeningeal cancer in leukemia and solid tumors. 

REFERENCES

ACKNOWLEDGMENTS

Participating institutions and investigators include Brown University (M. Glantz), M.D. Anderson Cancer Center (K. Jaeckle), H. Lee Moffitt Cancer Center (S. Phuphanich), Sidney Kimmel Cancer Center (T. Campbell), University of Massachusetts (L. Recht), New York University Medical Center (J. Allen), Loyola University Chicago (L. Swinnen), University of Florida College of Medicine (B. Maria), Marshfield Clinic (A. Choucair), Cross Cancer Institute (D. Fulton), Ottawa Regional Cancer Center (S. Gertler), University of Michigan (H. Greenberg), Thomas Jefferson University Hospital (R. Aiken), Medical University of South Carolina (C. Brunson), University of California at San Diego Cancer Center (M. Chamberlain), Memorial Sloan-Kettering Cancer Center (L. DeAngelis), Rush Cancer Institute (S. LaFollette), University of Texas Health Science Center at San Antonio (P. New), and Barrow Neurological Institute (W. Shapiro). We also thank Brenda Braun and Betsy Roche for expert assistance in the preparation of this manuscript.

REFERENCES

30. Balm, M., and Hammad, J. L. Leptomeningeal carcinomatosis: present-
carcinomatosis in patients with breast carcinoma. Clinical features, 
prognostic factors, and results of a high-dose intrathecal methotrexate 
32. Jayson, G. E., Howell, A., Harris, M., Morganstern, G., Chang, J., and 
Ryder, W. D. Carcinomatous meningitis in patients with breast cancer. An 
Moonihan, T., and Ettinger, D. S. Randomized prospective 
comparison of intraventricular methotrexate and thiopeta in patients 
with previously untreated neoplasic meningitis. J. Clin. Oncol., 11: 
35. Chamberlain, M. C., and Kormanik, P. A. Prognostic significance of 
coexistent bulky metastatic central nervous system disease in patients 
36. Grant, R., Naylor, B., Greenberg, H. S., and Junck, L. Clinical 
outcome in aggressively treated meningeal carcinomatosis. Arch. Neu-
37. Bokstein, F., Lossos, A., and Siegal, T. Leptomeningeal metastases 
from solid tumors. A comparison of two prospective series treated with 
and without intra-cerebrospinal fluid chemotherapy. Cancer (Phila.), 82: 
38. Bigner, D. N., Brown, M., Coleman, R. E., Friedman, A. H., 
Friedman, H. S., McLendon, R. E., Bigner, S. H., Zhao, X-G., Wilk-
strand, C. J., Pegram, C. N., Kerby, T., and Zalutsky, M. R. Phase I 
studies of treatment of malignant gliomas and neoplasic meningitis with 
111 In-labeled monoclonal antibodies anti-tenascin 81C6 and anti-
chondroitin proteoglycan sulfate Mel-14 F(ab)2: a preliminary report. 
39. Berg, S. L., Balis, F. M., Zimm, S., Murphy, R. F., Holenberg, J., 
Sato, J., Reaman, G., Steinheizt, P., Gillespie, A., and Doherty, K. Phase 
II/II trial and pharmacokinetics of intrathecal diaziquone in refractory 
40. Adamson, P., Balis, F. M., Arndt, C. A., Holenberg, J. S., Narang, 
P. K., Murphy, R. F., Gillespie, A. J., and Poplack, D. G. Intrathecal 
6-mercaptopurine: preclinical pharmacology, Phase II/II trial, and phar-
Neurological Complications of Cancer Treatment. pp. 115–134. Boston: 
42. Geiser, C. F., Bishop, Y., Jaffe, N., Furman, L., Traggis, D., and 
Frei, E., III. Adverse effects of intrathecal methotrexate in children 
Bowman, P. W., and Civin, C. I. Acute neurotoxicity after intrathecal 
1-β-D-arabinofuranosylcytosine in two adolescents with acute lympho-
44. Baker, W. J., Royer, G. L., and Weiss, R. B. Cytarabine and 
45. Boogerd, W., Moffie, D., and Smets, L. A. Early blindness and 
coma during intrathecal chemotherapy for meningeval carcinomatosis. 
46. Glantz, M. J. Diagnosis of radiation-induced nervous system injury. 