Prolonged Intravenous Methotrexate Therapy in the Treatment of Acute Leukemia and Solid Tumors

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SUMMARY

Five patients with previously treated acute leukemia received 14 courses of a 24-hr i.v. infusion of a 2 mg/kg dose of methotrexate followed by 6 mg of folinic acid. Four additional leukemia patients, previously treated, and 10 other patients with various metastatic solid tumors, largely choriogonadotropin-producing testicular tumors, received 24 courses of methotrexate at 5 mg/kg, with 60% given as a rapid i.v. injection, followed by the remaining 40% given as a 4-hr infusion. This last regimen was repeated on two consecutive days, and no folinic acid was given. Courses were generally repeated at 2-week intervals. Two of the eight evaluable choriogonadotropin-producing tumors had complete remissions lasting 3 months and 18+ months. Four others responded solely with a decrease in urinary gonadotropin levels, while two more exhibited small decreases in the size of metastatic lesions. No complete remissions were seen in the leukemic population, although marked decreases in the number of peripheral and bone marrow blasts were almost always observed. Two elderly leukemia patients tolerated the 24-hr infusion exceptionally well. No response was seen in a patient with squamous cell carcinoma of the lung.

Leukopenia and thrombocytopenia were more pronounced in the leukemia patients than in those with solid tumors, and platelet transfusions were obligatory in 29% of the courses given to leukemic patients. Hepatic dysfunction and stomatitis, both of which were nearly universal and very severe in the shorter infusion regimen, were relatively mild in the 24-hr infusion. Mild nausea and vomiting and occasional erythrodermic rashes were also observed.

A previously undescribed fever pattern, unassociated with infection, was seen in 55% of all the courses. It generally occurred on the 2nd through the 5th day following the infusions and lysed spontaneously without antibiotic or antipyretic therapy. Possible etiology of this fever is discussed.

INTRODUCTION

Although MTX2 has been in clinical use for over 20 years, investigators still continue to seek the optimal dosage schedule (19). In recent years, a 24-hr infusion of MTX, usually followed by folinic acid (leucovorin) to help minimize toxicity, has been one of the schedules under study. This has been used in attempts to induce remission in adults with acute leukemia (14) and more prominently in the treatment of epidermoid carcinoma of the head and neck (17, 20), as well as mycosis fungoides (18). Although the number of patients responding has not been large, the remissions have often been achieved in patients relatively refractory to other modalities of therapy (20) or to MTX in conventional dosage (8).

Another regimen recently under investigation, principally by Djerassi et al. (7–9), has been a rapidly given i.v. loading dose of MTX followed by a 4-hr infusion. This program has been used mostly in the maintenance of childhood leukemia, and again the results have been encouraging.

We have recently treated 19 patients with intermittent prolonged i.v. MTX infusions. Nine of the patients had acute leukemia, and the other 10 had various advanced solid tumors, largely HCG-producing testicular tumors. This last group of patients was included in the study because of the high degree of success seen with repetitive courses of MTX treatment of HCG-producing trophoblastic tumors in women (13). To our knowledge, this is the first attempt to treat testicular tumors in this manner. In addition to examining the efficacy of these regimens, we have made a detailed study of the toxicities observed.

MATERIALS AND METHODS

MTX (4-amino-N\(^1\)\(^-\)methylpteroylglutamic acid, amethopterin) was administered under 2 different regimens. Regimen A consisted of a 24-hr i.v. infusion at a dose level of 2 mg/kg of body weight. The drug was dissolved in a solution of 5% glucose and water, and each patient received

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2The abbreviations used are: MTX, methotrexate; HCG, human choriogonadotropin; POMP, prednisone, Oncovin (vincristine), methotrexate, and Purinethol (6-mercaptopurine); SGOT, serum glutamic oxaloacetic transaminase.
1500 ml of fluid over the 24-hr period. This was followed by a single i.m. injection of 6 mg of folic acid 4 hr after the cessation of the MTX injection.

Regimen B consisted of a dose of 5 mg/kg of MTX, with 60% (3 mg/kg) given as a rapid i.v. loading dose (at a drug concentration of 50 mg/ml) followed by a 4-hr i.v. infusion of 40% (2 mg/kg) of the drug in 500 to 1000 ml of 5% glucose and water. This regimen was repeated on a 2nd consecutive day, and the 2 days together were considered as a single course. No folic acid was administered to patients receiving this regimen.

In those patients receiving more than 1 course of either regimen, enough time was allowed to elapse between courses to permit adequate recovery from hematopoietic toxicity—usually 2 weeks.

Patients. Five patients with acute leukemia received 14 courses of Regimen A. Four adults had acute myelocytic or myelomonocytic leukemia. One child had acute lymphocytic leukemia (Table 1). Another 4 patients with leukemia received 7 courses of Regimen B (Table 2). In this group, there was also 1 child with acute lymphocytic leukemia, 2 adults with acute lymphocytic leukemia, and 1 adult with acute monocytic leukemia. Patient M. W. did not receive the 2nd day of Regimen B.

An additional 10 patients with solid tumors also received 17 trials with Regimen B. This group included 8 men with various testicular tumors, all of which were producing HCG. There was an additional female patient with choriocarcinoma of trophoblastic origin and one woman with squamous cell carcinoma of the lung (Table 3).

Almost all of the patients treated had far-advanced disease, generally metastatic in the case of the solid tumor patients, and usually refractory to conventional, and often extensive, chemotherapy. Many were considered terminal, but all had normal renal and hepatic function prior to treatment. All of the patients were Caucasian.

RESULTS

Toxicity. Toxicity consisted mainly of bone marrow depression, stomatitis, hepatotoxicity, nausea and vomiting, and fever. Neutropenia and thrombocytopenia were generally pronounced regardless of regimen. Nine of the 14 courses (64%) of Regimen A given to patients with leukemia were associated with neutropenia below 3,000, with a median nadir of the leukocytes of 2,400 (range, 1,200 to 8,300). Ten courses in these patients (71%) had thrombocytopenia (less than 100,000) with a median nadir of 26,000 (range, 23,000 to 94,000). This nadir undoubtedly would have been lower were it not for the intervention of platelet transfusion in 3 courses. In Patient J. L. B., the thrombocytopenia probably contributed to his demise. Anemia was less pro-

### Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
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<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. N. K.</td>
<td>23/M</td>
<td>Acute myelocytic leukemia.</td>
<td>Daunorubicin; POMP.</td>
<td>8 mo.</td>
<td>3</td>
<td>Marrow blasts transiently decreased from 71 to 34%; no peripheral blasts present.</td>
<td>Died 3 mo. later after other therapy.</td>
</tr>
<tr>
<td>J. L. B.</td>
<td>4/F</td>
<td>Acute lymphocytic leukemia.</td>
<td>Prednisone and vincristine; POMP; daunorubicin; cytosine arabinoside 6-mercaptopurine; hydroxyurea; L-asparaginase</td>
<td>18 mo.</td>
<td>1</td>
<td>WBC decreased from 63,500 (64% blasts) to 3,200 (51%); no follow-up marrow.</td>
<td>Patient was terminal when treated and died 8 days after starting MTX.</td>
</tr>
<tr>
<td>A. I. A.</td>
<td>27/F</td>
<td>Acute myelomonocytic leukemia.</td>
<td>POMP; daunorubicin; cytosine arabinoside; methylglyoxal-bis-guanylylhydrazone.</td>
<td>23 mo.</td>
<td>4</td>
<td>WBC decreased from 21,600 (63% blasts) to 1,200 (32%); decrease in marrow blasts from 98 to 66%.</td>
<td>Died 7 wk after start of MTX after refusing further therapy.</td>
</tr>
<tr>
<td>E. J. C.</td>
<td>77/M</td>
<td>Acute myelocytic leukemia.</td>
<td>Hydroxyurea.</td>
<td>1 mo.</td>
<td>1</td>
<td>WBC decreased from 22,400 (83% blasts) to 7,700 (75%); decrease in marrow blasts from 90 to 70%.</td>
<td>Died 6 wk after other therapy in another hospital.</td>
</tr>
<tr>
<td>A. D. T.</td>
<td>70/F</td>
<td>Acute myelocytic leukemia.</td>
<td>Hydroxyurea.</td>
<td>10 days</td>
<td>5</td>
<td>WBC decreased from 20,000 (97% blasts) to 1,800 (0%); decrease in marrow blasts from 95 to 42%.</td>
<td>Died 10 wk after start of therapy.</td>
</tr>
</tbody>
</table>

*In POMP, MTX is given at a dose of 5 mg/sq m every day for 5 days, repeated 4 times.*
considerably less hematopoietic toxicity. Only 8 of the 15
but the median leukocyte nadir of 1,400 (range, 400 to 77,000) and only 2 courses
(53%) were associated with leukopenia with a median nadir of
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J. P. M. and C. M. (Table 3). Seven of the 15
WBC with the lymphocytes decreasing relatively little.
granulocytes accounted for most of the depression in the
was clinically insignificant.
Thrombocytopenia was seen in all 7 courses, and the median
platelet nadir was 33,000 (range, 15,000 to 80,000). As with
Regimen A, 3 courses required platelet transfusions. Hemo-
globin depression (median nadir, 9.9 g; range, 6.3 to 11.3 g)
was clinically insignificant.
The patients with solid tumors receiving Regimen B had
considerably less hematopoietic toxicity. Only 8 of the 15
(53%) courses were associated with leukopenia with a median
nadir of 77,000 (range, 600 to 5,700) was considerably lower than the nadir in Regimen A.
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considerably less hematopoietic toxicity. Only 8 of the 15
(53%) courses were associated with leukopenia with a median
nadir of 77,000 (range, 600 to 5,700). The fall in
granulocytes accounted for most of the depression in the
WBC with the lymphocytes decreasing relatively little. Granulocytopenia played a significant role in the deaths of Patients J. P. M. and C. M. (Table 3). Seven of the 15 courses (47%) had thrombocytopenia with a median nadir of 77,000 (range, 17,000 to 236,000), and only 2 courses required platelet transfusion. The median hemoglobin nadir of 9.9 g (range, 8.5 to 11.5 g) was again of little signifi-
cance.

In both regimens, the nadirs of the formed elements were
reached early in the 2nd week following therapy. Recovery
generally occurred between the 2nd and 3rd weeks, with an
occasional overshoot in the platelet count noted.

Hepatotoxicity was quite common, occurring in 86% of all
evaluable trials. In Regimen A, the toxicity was mild, as
evidenced by a median zenith in SGOT of 73 Karmen units
(range, 55 to 265; normal, <45) and only 2 minimal total
bilirubin elevations to 1.3 mg/100 ml. In Regimen B, the
elevation of SGOT was more pronounced (median zenith, 163; range, 55 to 940) and hyperbilirubinemia was noted in
10 of 19 courses (median zenith, 3.1 mg/100 ml; range, 1.3
to 9.8 mg/100 ml). The peak elevations of SGOT and
bilirubin occurred at the end of 1st week after therapy with a
return to normal by the end of the 2nd week, except in 4
patients (all of whom had received Regimen B) who
developed severe long-lasting hepatic dysfunction. In Patient
W. M. P. (Table 3), a chronic biopsy-proven toxic hepatitis
developed which persisted for 8 months despite cessation of
MTX. Liver failure contributed to the death of Patient J. P.
M. and hepatotoxicity necessitated stopping therapy in
Patient A. E. A., whose leukemia had otherwise been
responding (Table 2).

Nausea and vomiting, which were usually mild, occurred in
53% of the trials and were slightly less in the 24-hr infusion
regimen. Stomatitis was seen in 69% of the trials but was
nearly universal in Regimen B, where it was extremely severe
in almost all patients. In Regimen A, the stomatitis tended
to be limited to several buccal ulcerations; while in Regimen
B the entire mouth, tongue, and often throat were involved.

In 17 of the trials (55%), a definite fever pattern not
attributable to infection was seen. The median maximum
temperature was 102°F (range, 100-102.6°F rectally). The
febrile episodes had their onset on the 2nd or 3rd day
following therapy in 13 courses (range, Days 1 to 5) and
lasted a median of 2 days (range, 1 to 7 days). Vigorous
attempts to find infection, including physical examination,
chest X-rays, and multiple bacterial and fungal cultures of all
body orifices and fluids were unrewarding. Patients had none
of the stigmata of viral infection, such as coryza or myalgia,
and fevers lysed spontaneously without antibiotic or antipy-
retic therapy. The fever pattern was seen in both regimens

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<tbody>
<tr>
<td>J. O. H.</td>
<td>17/M</td>
<td>Acute lymphocytic leukemia (transformation of Burkitt's lymphoma).</td>
<td>Cobalt to neck; Cytoxan.</td>
<td>5 mo.</td>
<td>1</td>
<td>No peripheral blasts; 95% marrow blasts decreased to 10% blasts at autopsy.</td>
<td>Patient terminal when treated; died 1 wk after MTX with sepsis and granulocytopenia. Hepatotoxicity; patient terminal when treated; died 9 days after MTX. Severe liver toxicity; on other drugs for last 2 mo. of life.</td>
</tr>
<tr>
<td>M. R. W.</td>
<td>19/M</td>
<td>Acute lymphocytic leukemia.</td>
<td>Daunorubicin; POMP; cytosine arabinoside; glutamate; L-asparaginase.</td>
<td>9 mo.</td>
<td>1</td>
<td>WBC decreased from 7,400 (57% blasts) to 1,800 (30%); no follow-up marrow.</td>
<td>Hepatotoxicity; patient terminal when treated; died 9 days after MTX. Severe liver toxicity; on other drugs for last 2 mo. of life.</td>
</tr>
<tr>
<td>A. E. A.</td>
<td>17/F</td>
<td>Acute monocytic leukemia.</td>
<td>Hydroxyurea; daunorubicin; cytosine arabinoside; POMP.</td>
<td>3.5 mo.</td>
<td>2</td>
<td>WBC decreased from 24,800 (46% blasts) to 1,600 (10%); no change in marrow blasts (90%).</td>
<td>Regimen used as maintenance; remission lasted 8 mo.</td>
</tr>
<tr>
<td>K. A. W.</td>
<td>7/F</td>
<td>Acute lymphocytic leukemia.</td>
<td>POMP.</td>
<td>3.5 mo.</td>
<td>3</td>
<td>No peripheral blasts; marrow blasts remained less than 5%.</td>
<td></td>
</tr>
</tbody>
</table>
with roughly equal frequency and, although occasionally annoying, it was never debilitating.

Other side effects included an erythrodermic rash in 5 patients, jaundice in 4, anorexia in 4, and diarrhea in 1. Phlebitis at the site of injection was not observed.

**Therapeutic Effects**

**Regimen A: Leukemia Patients.** All patients showed at least a transient decrease in the percentage of peripheral and/or marrow blasts. The best response was seen in Patient A. D. T., a 70-year-old woman with acute myelocytic leukemia, whose peripheral blood was cleared of blasts (having started therapy with a WBC of 20,100, of which 97% of the cells were myeloblasts). The presence of blasts in her marrow decreased from 95 to 42% by her 4th course, and her clinical well-being also improved. Unfortunately, both peripheral and bone marrow blasts began to rise during her 5th course, and she died of her disease 10 weeks after starting MTX therapy (Table 1).

In those courses associated with blasts in the peripheral blood, the median absolute decrease was 7,760 (range, 660

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Table 3

Patients with solid tumors receiving Regimen B

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
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</tr>
</thead>
<tbody>
<tr>
<td>J. P. M.</td>
<td>24/M</td>
<td>Choriocarcinoma of testis.</td>
<td>Cobalt to lungs.</td>
<td>3 wk</td>
<td>1</td>
<td>94% decrease in HCG titer; no other improvement.</td>
<td>Patient died 11 days after MTX with rapidly progressive disease and liver toxicity.</td>
</tr>
<tr>
<td>F. E. N.</td>
<td>24/M</td>
<td>Cancer of testis (teratocarcinoma predominating).</td>
<td>None.</td>
<td>3 wk</td>
<td>1</td>
<td>74% decrease in HCG titer; no other improvement.</td>
<td>Died 10 mo. later; refused further MTX.</td>
</tr>
<tr>
<td>W. M. P.</td>
<td>26/M</td>
<td>Cancer of testis (embryonal cell carcinoma predominating). Cancer of testis (embryonal cell carcinoma predominating).</td>
<td>Mithramycin; cobalt to lungs and abdomen.</td>
<td>6 wk</td>
<td>2</td>
<td>15% decrease in size of lung metastasis; no other improvement.</td>
<td>Severe toxic hepatitis died 10 mo. later.</td>
</tr>
<tr>
<td>C. M. M.</td>
<td>30/M</td>
<td>Cancer of testis (embryonal cell carcinoma predominating).</td>
<td>Mithramycin; daunomycin; 5-fluorouracil Cytosan, vincristine, and low-dose MTX (7.5 mg/sq m i.v. twice weekly for 2 mo.).</td>
<td>16 mo.</td>
<td>1</td>
<td>60% decrease in HCG titer; no other improvement.</td>
<td>Died 3 mo. later at home.</td>
</tr>
<tr>
<td>F. A. M.</td>
<td>32/M</td>
<td>Cancer of testis (teratocarcinoma predominating).</td>
<td>Mithramycin; actinomycin D.</td>
<td>3 mo.</td>
<td>3</td>
<td>Disappearance of HCG titer and lymph node metastasis for 3 mo. 94% decrease in HCG titer but lung metastasis increased.</td>
<td>Died 22 mo. later at home.</td>
</tr>
<tr>
<td>D. E. A.</td>
<td>23/M</td>
<td>Choriocarcinoma of testis.</td>
<td>Mithramycin; actinomycin D; low-dose MTX (15 mg p.o. daily for 5 days).</td>
<td>1 mo.</td>
<td>1</td>
<td>Disappearance of HCG titer and lymph node metastasis.</td>
<td>Died 8 mo. later.</td>
</tr>
<tr>
<td>D. T. S.</td>
<td>16/M</td>
<td>Cancer of testis (embryonal cell carcinoma predominating).</td>
<td>Mithramycin; actinomycin D.</td>
<td>2 mo.</td>
<td>1</td>
<td>Disappearance of HCG titer and lymph node metastasis.</td>
<td>Multiple courses of actinomycin D D and mithramycin given shortly after MTX; patient in remission for 2 yr. Died 10 mo. later.</td>
</tr>
<tr>
<td>E. M. M.</td>
<td>38/F</td>
<td>Choriocarcinoma of trophoblastic origin.</td>
<td>MTX (15 mg p.o. daily for 5 days) intermittently for 5 mo.; actinomycin D. Imidazole carboxamide.</td>
<td>4 yr</td>
<td>3</td>
<td>75% decrease in HCG titer and 25% decrease in lymph node metastasis for 10 wk.</td>
<td>Not evaluable.</td>
</tr>
<tr>
<td>C. M.</td>
<td>43/F</td>
<td>Squamous cell carcinoma of lung.</td>
<td></td>
<td>3 mo.</td>
<td>1</td>
<td>75% decrease in HCG titer and 25% decrease in lymph node metastasis for 10 wk.</td>
<td>Patient terminal when treated; died 7 days after MTX.</td>
</tr>
</tbody>
</table>
to 39,800), occurring a median of 6 days after the MTX infusion. The median fall in marrow blasts was 35% (range, 20 to 53%). Some of the responses were clinically useful, as they were accompanied by a definite increase in well-being.

**Regimen B: Leukemia Patients.** The best response was seen in Patient A. E. A. (Table 2), a 17-year-old girl with fulminant, chemotherapy-resistant acute monocytic leukemia. Peripheral blasts were reduced from 40% of a WBC of 24,800 to 10% of a WBC of 1,600, but no bone marrow improvement was seen. Severe hepatotoxicity and mucositis prevented repeating the MTX in this patient. A 2nd patient, K. A. W., was treated with this regimen as part of a maintenance protocol. Her remission lasted 8 months, but she received different drugs for the last 5 months of this remission because of the toxicity of the MTX, resulting mainly in stomatitis.

In those courses associated with blasts in the peripheral blood, the median absolute decrease was 2,620 (range, 1,100 to 10,600) occurring on Day 8. Follow-up bone marrow was possible during life only in Patient A. E. A.

**Regimen B: Solid Tumor Patients.** Two of the 10 patients had complete responses. The first occurred in Patient F. A. M. (Table 3), who had an HCG-producing teratocarcinoma. His lymph node metastases and urinary HCG titer completely disappeared for 3 months following 3 courses of MTX. When disease recurred, it was refractory to multiple chemotherapeutic regimens, and the patient died 22 months after first receiving MTX therapy.

The 2nd complete response occurred in Patient J. H. U., a 50-year-old man with HCG-producing embryonal cell carcinoma of the testes. This patient’s inguinal metastases and his urinary HCG titer completely disappeared after 1 course of therapy. This patient still remains free of disease 18 months after receiving MTX. A 3rd patient (D. T. S.) showed a complete response, but it is likely that mithramycin and actinomycin D, administered shortly after MTX, were contributory in achieving this remission. This patient has therefore been considered only in the toxicity studies.

In addition, 6 other patients showed some signs of response. Patient E. M. M. showed a 25% decrease in size of metastatic nodules, as well as a decrease in her urinary HCG titer and an increase in well-being, which lasted 10 weeks before tumor regrowth started. In 4 patients, response was manifested solely by a decrease in urinary HCG titer. A 6th patient (W. M. P.) had a small decrease (<15%) in metastatic pulmonary nodules, but his urinary HCG titer rose slightly. No response was seen in the single patient with lung cancer (Table 3).

Thus, in 8 evaluable patients with HCG-producing tumors, there were 2 complete remissions and 6 other responses, albeit only 1 of the latter was clinically useful. These responses were generally seen in patients who had been refractory to several other drugs, notably mithramycin and actinomycin D, and 3 were refractory to MTX in conventional dosage [Patients J. H. U., C. M. M., and E. M. M. (Table 3)].

**DISCUSSION**

When MTX was first introduced by Farber et al. for the treatment of acute leukemia, a daily p.o. dosage was used (10), and this became the most common regimen for remission induction of leukemia with MTX (11). Burchenal et al. (5) administered 24-hr i.v. infusions of MTX over several days, but found that severe toxicity resulted. Nevertheless, some studies showed that the prolonged exposure of leukemic cells to MTX did produce remission in patients already refractory to conventional daily dosage (9).

Bertino et al. attempted to take advantage of the added efficacy of the increased length of exposure of tumor cells to MTX, while at the same time, by utilizing repeated injections of folinic acid, they tried to minimize toxicity to the host. They studied both leukemic patients (14) and patients with epidermoid carcinoma of the head and neck (17, 20) with 24-hr infusions of MTX, followed by 4 to 6 doses of folinic acid, compared to our single dose. Their studies showed that the administration of folinic acid was able to decrease toxicity without decreasing the effectiveness of the chemotherapy. There was one-half the incidence of mucositis and one-fifth the incidence of leukopenia in those patients receiving folinic acid compared to those who did not receive this agent, while the overall response rate in head and neck cancer was the same in both treatment regimens (17). Later studies with spaced, repeated courses of MTX produced 47% objective responses in head and neck cancer (20) and 57% complete or partial remission in adult leukemia (14). Toxicity was similar to that reported in our patients receiving Regimen A, with 2 exceptions. Our patients had a high incidence of hepatotoxicity and fever, while Hryniuk and Bertino (14) reported few MTX-associated temperature elevations and no liver toxicity. This may in part be due to their utilizing more folinic acid than was administered in our study. We were also able to confirm the study of Hryniuk et al. (15) showing that a rapid fall in peripheral blasts can be expected with prolonged MTX infusions. Two of our patients were in their 70's and tolerated this regimen with minimal toxicity, which suggested that 24-hr i.v. MTX infusions may be a promising therapeutic regimen in this age group, which is considered an extremely difficult age to treat (4). The hematopoietic depression, although considerable, was relatively well tolerated in these elderly patients, and the hepatotoxicity and stomatitis observed were clinically insignificant.

Another factor, in addition to duration of drug exposure, that may influence the degree of response seen is the concentration gradient of the drug in the plasma versus the leukemic cells. In an attempt to both increase exposure time, as well as increase the concentration gradient, Djerassi et al. treated a group of leukemic children in remission with a regimen virtually identical to our Regimen B. They found the regimen extremely tolerable with minimal mucosal ulceration and elevation of SGOT, and all abnormalities returned to normal within 2 weeks after MTX administration (9).

Our results with leukemic patients treated with Regimen B were somewhat disappointing. The 2 patients in whom promising responses were seen [A. E. A. and K. A. W. (Table 2)] were both severely incapacitated by toxicity, necessitating discontinuance of the regimen. Although a fall in peripheral blasts always occurred, the toxicity that we
observed, unlike that reported by Djerassi, was severe and debilitating. Part of the observed differences in toxicity may be accounted for by the fact that Djerassi et al. (9) were studying leukemia in children in remission, while 3 of our 4 patients were adults in relapse. More encouraging results occurred in the solid tumor patients. Two complete remissions were seen, and a fall in HCG titer was observed in 5 other patients.

Since Regimen B produced considerably more liver toxicity and mucositis and since the therapeutic results in the leukemic patients in both regimens were similar (albeit the differences in the ages and types of leukemia in the 2 patient populations made significant comparisons difficult), it would seem that, in treating leukemia, Regimen A would be preferred. Perhaps if the patients given Regimen B had also received folinic acid, this increased toxicity would not have occurred, and the therapeutic usefulness of this regimen in treating leukemic patients might have been increased.

One of the most curious toxicities noted was the definite fever pattern occurring on the 2nd or 3rd day following administration of MTX. The temperature lysed spontaneously after several days and was not associated with any documentable infection. Fever of unexplained etiology associated with MTX administration has been noted by other observers (1, 21); however, this particular temperature pattern has not been described before, perhaps due to the infrequency with which these regimens have been tried by other investigators. Clarysse et al. (6) reported fevers associated with possible hypersensitivity-related pulmonary disease in 7 patients receiving MTX, but only after 12 to 100 days of biweekly p.o. or i.m. MTX therapy for leukemia in remission. No pulmonary disease attributable to MTX was noted in our patients.

Attempts by other investigators to correlate fever of non-infectious origin with the activity of the neoplastic process, with tumor necrosis, or with the level of granulocytopenia have been unsuccessful (2, 3). MTX is not currently thought to be metabolized significantly by man (12, 16), ruling out a drug metabolite as a probable cause of the fever. The possibility exists that some as yet unknown antimetabolic effect of MTX is the cause of the temperature pattern observed.

Although we were unable to produce any complete remissions in our leukemic patients with the 24-hr MTX infusions, we were able to reduce peripheral and bone marrow blast counts significantly. Furthermore, 2 of our patients in their 70's tolerated this regimen extremely well, one with the therapy of folinic acid and solid tumor patients are in progress.

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REFERENCES


Prolonged Intravenous Methotrexate Therapy in the Treatment of Acute Leukemia and Solid Tumors

Jeffrey A. Gottlieb and Arthur A. Serpick


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