Cancer Chemother. Pharmacol. 3, 103–109 (1979)

Cancer Chemotherapy and Pharmacology

Effective Therapy for Burkitt's Lymphoma: High-Dose Cyclophosphamide + High-Dose Methotrexate with Coordinated Intrathecal Therapy

Plasma and Cerebrospinal Fluid Methotrexate Levels

Irma Ramirez[1], Margaret P. Sullivan[1], Yeu-ming Wang[2], R. G. Martin[3], and J. J. Butler[4]

Department of [1]Pediatrics, [2]Experimental Pediatrics, [3]Surgery, and [4]Pathology,
University of Texas System Cancer Center MD Anderson Hospital and Tumor Institute
Houston, Texas 77030, USA

Summary. *A new treatment for Burkitt's lymphoma (BL) has been devised with coordinated intrathecal (IT) methotrexate (MTX) + high-dose intravenous (IV) MTX with citrovorum factor (CF) rescue and high-dose Cytoxan (CYT). Six patients have been entered on the study. Five patients continue in complete remission at 13+—31+ months (median, 29+ months). One died of septicemia during myelosuppression. Only minor toxicity was seen in four patients. Two patients had severe metabolic disturbances following initial CYT therapy; one of these patients also had reversible, moderately severe hepatorenal MTX toxicity. No neurotoxicity was observed. Results of therapy are impressive in this limited patient group, four of whom were poor-prognosis (Stage C or D) and two of whom were good-prognosis patients (Stage B or AR). The potential for severe toxicity is great; adherence to the criteria for drug administration and close surveillance of the patient in the post-treatment period are mandatory.*

Plasma and cerebrospinal fluid (CSF) MTX pharmacokinetics were studied in three patients. CSF MTS levels exceeded 10^{-6} M with coordinated IT—IV MTX (≥ 150 mg/kg body wt.) With MTX infusions at the 200 mg/kg level, therapeutic concentrations were maintained in the CSF for approximately 60 h. Plasma MTX concentrations exceeded 10^{-6} M at all infusion dose levels, the duration of the therapeutic concentration increasing with the dose level. Priming IT MTX followed in 24 h by IV MTX, 200 mg/kg assured therapeutic concentrations in plasma and CSF of sufficient duration to cover two generation times of the BL cell.

Introduction

LSA_2-L_2 therapy, an antileukemic regimen with added high-dose cyclophosphamide (Cytoxan, CYT), has been strikingly successful in the treatment of non-Hodgkin's lymphoma in children, with the noteworthy exception of those with diffuse, undifferentiated (DU) histology [22, 23]. The high failure rate in this disease category was confirmed in children with DU lymphoma, Burkitt's type (BL), in the MD Anderson Hospital and Tumor Institute (MDAH) LSA_2-L_2 field trial (A. Frias, unpublished data). A new treatment regimen for Burkitt's tumor was then devised in an effort to meet the need for truly effective therapy for this category of lymphomatous disease.

CYT has an established role in the treatment of BL; apparent cures have followed a single dose of the drug in African patients with localized disease [8]. Methotrexate (MTX) therapy in African children with BL showed an effectiveness similar to that of CYT if the tumor burden was small [9]. The American or 'abdominal' presentation of BL has been thought to respond less well to therapy than the African disease, an overall survival of 26% being reported for American children, in contrast to a 55% survival in African children [15, 26]. Recently, similar responsiveness has been reported for African BL and the American disease when the latter was treated with combination chemotherapy [vincristine sulfate (VCR), CYT, and MTX, with or without prednisolone (COM-COMP)] and radiotherapy [24]. In our treatment program initiated July 1976, CYT was given first, to effect the rapid reduction in tumor volume thought to be a prerequisite for maximum MTX effect. Intrathecal (IT) MTX therapy was coordinated with intravenous (IV) MTX infusions so that the systemically administered drug would sustain the cerebrospinal fluid (CSF) levels obtained by priming injections of MTX into the lumbar sac. Therapeutic responses of six patients and a detailed analysis of MTX levels in the CSF following IT MTX adminstration to the first three pilot patients are reported in this paper.

Reprint requests should be addressed to: Margaret P. Sullivan

0344-5704/79/0003/0103/$ 01.40

Table 1. Clinical presentations and therapeutic responses of six children given high-CYT + high-MTX therapy

Pt	Age (years)/ sex	Diagnosis[a]	Extent of disease at diagnosis (ABCDAR Stage[9])	Surgical procedures	Degree[b] and duration of response to chemotherapy (months)
1	13½/F	DU BL	Jejunum, mesentery, mesenteric lymph nodes, tumor cells in ascitic fluid, ovaries, fallopian tubes (C)	Bilateral salpingo-ophorectomy; small-bowel resection, partial (< 90%) excision of pelvic mass	CR[c] 31+
2	5/M	DU[d]	Ileum, mesentery, gallbladder wall (C)	Small-bowel resection; partial (< 90%) excision of mesenteric mass	CR[c] 29+
3	9/M	DU BL	Right axilla and right talus (B)	Excision biopsy axillary mass	CR[c] 29+
4	15½/M	DU BL	Ileum, mesentery, omentum; peripheral, mediastinal and abdominal nodes; tumor cells in pleural fluid; liver (D)	Small bowel resection (ileum)	Clinical CR: expired during induction
5	3½/M	DU BL	Cecum (AR)	Bowel resection (right ileocolectomy)	CR 13+
6	14/M	DU BL	Stomach; omentum; cervical, supra-clavicular, axillary, inguinal, and abdominal nodes (D)	Gastric resection	CR[c] 13+ Maintenance therapy in progress

[a] DU, Diffuse undifferentiated lymphoma; BL, Burkitt's lymphoma
[b] CR, Complete remission
[c] Confirmed by second-look surgical exploration
[d] Tissue distortion prevented further characterization

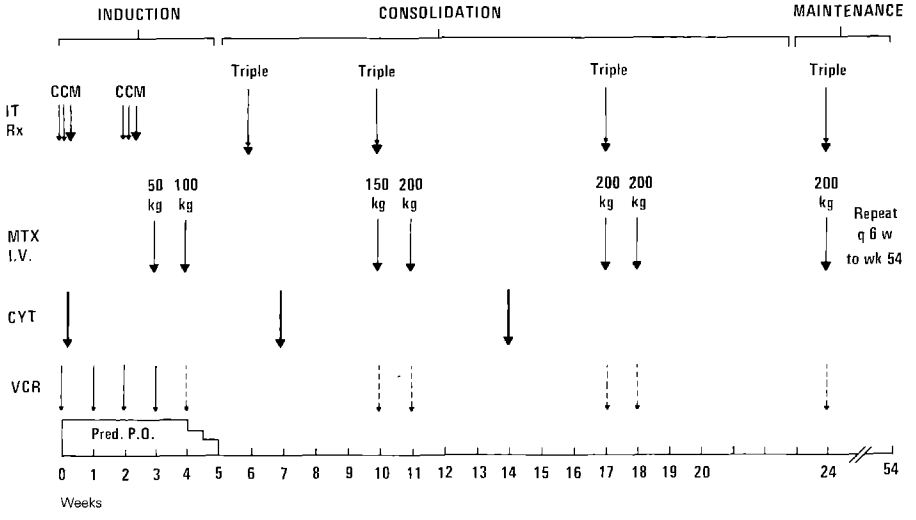

Fig. 1. Treatment plan for high-dose Cytoxan + high-dose MTX therapy with coordinated IT MTX

Patients and Methods

Consecutive, newly diagnosed patients with BL who were less than 18 years of age were entered in our high-dose CYT-MTX protocol study. All tissue diagnoses were reviewed as shown in Table 1 (by JJB) in the Department of Pathology, MDAH. The histologic criteria for diagnosis were those listed in *Histopathological Definition of Burkitt's Tumor*, issued by the World Health Organization, Geneva, 1969. Imprints were not available for study. Mandatory pretreatment studies included: (1) hematologic evaluation [complete blood count including differential white blood cell (WBC) count and platelet count, examination of bone marrow smears and clot sections for tumor cell], (2) radiologic survey (posteroanterior and lateral chest films, intravenous pyelography, and skeletal survey), (3) CSF examination (WBC and red blood cell counts, cytocentrifuge smear examination for tumor cells, protein and glucose levels), (4) blood urea nitrogen, uric acid, creatinine, calcium, phosphorus, albumin, alkaline phosphatase, lactic dehydrogenase, serum glutamic oxaloacetic transaminase (SGOT), (5) routine urinalysis, and (6) creatine clearance.

The ABCDAR stage [24] for each patient is shown in Table 1. None of the patients had involvement of the bone marrow or me-

ninges at diagnosis, and none has subsequently developed involvement at these or any other new site.

A determined effort was made to start therapy within 72 h of admission. Hydration and alkalinization of the urine were accomplished in that period, and allopurinol therapy was initiated 24 h before treatment.

Chemotherapy was administered in accordance with the schema shown in Figure 1. CYT, 1200 mg/m^2 was given IV on day 1 of therapy and repeated on the first day of weeks 7 and 14. VCR, 2.0 mg/m^2 was administered IV beginning on day 2 or 3 for a total of 4 weekly doses. Prednisone, 60 mg/m^2 was given daily PO for 28 days from the time of the first VCR dose. The fourth dose of VCR preceded the first MTX infusion by 1 h; thereafter, VCR, 1.0 mg was given IV 1 h prior to each MTX infusion. Beginning week 3, 10, and 17, two weekly 6-h infusions of MTX[1] were given. The starting MTX dose level of 50 mg/kg body wt. was increased by 50 mg/kg increments to a dose level of 200 mg/kg, which was used throughout the remainder of the treatment course. Citrovorum factor (CF) was given after each MTX infusion as follows: 15 mg IV every 3 h for nine doses, followed by 15 mg PO every 6 h for eight doses.

A prophylactic CNS regimen employing cytosine arabinoside (CA), 45 mg/m^2 IT on days 1 and 2, and MTX, 15 mg/m^2 (maximum dose 15 mg) IT on day 3 was given twice during remission induction. This regimen was modeled after the most successful IT regimen devised for meningeal BL [25]. Subsequently drugs were given simultaneously IT before the first MTX infusion, with doses as follows MTX, 15 mg/m^2 (maximum dose 15 mg), hydrocortisone, 30 mg/m^2, and CA, 60 mg/m^2. Coordination of IT-IV MTX therapy was continued in the consolidation and maintenance regimens with the administration of IT MTX as a component of 'triple' IT therapy 24 h prior to the 6-h MTX infusions (Fig. 1). Radiotherapy was not a component of CNS prophylaxis [16].

Complete remission (CR) was defined as disappearance of all evidence of disease. Children who failed to achieve CR or relapsed were to be removed from the study as treatment failures. Patients achieving continuous CR were taken off therapy after 1 year.

Patients with residual abdominal tumor following primary surgical therapy had 'second-look' abdominal explorations on completion of consolidation therapy, to remove any resectable residual tumor and to mark nonresectable tumor with silver clips for 'target' radiotherapy.

MTX plasma levels were to be obtained with each MTX infusion at the following times: 0, 6, 24, and 48 h. CSF MTX levels were to be determined at −24, 0, 6, 24, and 48 h when coordinated IT-IV MTX was given. Determination of MTX in the plasma and CSF was carried out by an enzyme kinetic method described previously [21].

Written informed consent of the parents was obtained for treatment and the associated procedures.

Results

Response to Chemotherapy

The responses of the six children given high-CYT + high-MTX therapy are presented in Table 1. Patients 1, 2, 3, and 5 have been taken off therapy after completing 1 year in continuous CR; none has relapsed. Survival with no evidence of disease (NED) for the children off therapy is 31+, 29+, 29+, and 13+ months. Surgical exploration of the abdomen in Patients 1, 2, 3, and 6 during consolidation demonstrated freedom from tumor. Patient 3 was explored surgically as the intravenous pyelogram at diagnosis had shown displacement of the right ureter; this deviation was shown to be a variant of normal. No patient has required radiotherapy to any site at any time. Patient 4 expired with septicemia, but had no palpable tumor at the time of death; postmortem examination was not permitted. Patient 6 is disease-free 13+ months from the time of diagnosis and will complete maintenance therapy in 6 weeks.

Side Effects and Toxicity of Chemotherapy

Following the first dose of CYT, Patient 1 developed metabolic complications consisting in hyperuricemia with azotemia, hypocalcemia, hyperphosphatemia, and elevated SGOT and serum glutamic pyruvic transaminase (SGPT) levels. Congestive heart failure and a seizure disorder followed. Recovery was complete except for residual minor electroencephalographic changes. Subsequently, the following evidence of MTX toxicity was exhibited at the 200 mg/kg level: mouth ulcers, skin eruption, elevated BUN (25 mg%), elevated uric acid (8.0 mg%), SGOT level exceeding 250 μg/ml, and total bilirubin of 2.3 mg%. The plasma concentration of MTX 48 h after infusion was 5.9×10^{-5} *M* (the 48-h 'safe' level at this hospital is less than 4.5×10^{-6} *M*) [21]. Intravenous CF was continued until a safe plasma MTX level was attained. High-dose MTX was not given to this patient again and CYT, 1200 mg/m^2 was substituted for the two remaining maintenance infusions rather than discontinuing therapy 3 months earlier than planned.

In Patients 2, 3, 5, and 6, toxicity to high doses of MTX has been limited to mild nausea in each; mild diarrhea and abdominal pain in one patient; and transient liver enzyme elevations. Symptoms of leukoencephalopathy have not occurred. Patient 5 has had transient gross hematuria, thought to be related to CYT therapy.

Patient 4 developed septic shock when pancytopenic. Blood cultures prior to death were reported positive for four different organisms.

MTX Levels in Plasma

Plasma levels were determined in Patients 1, 2, and 3, insofar as possible, at the time intervals described in Methods. Refusal on the part of Patient 1 resulted in incomplete data in her case. Information from studies on Patients 2 and 3, shown as mean values in Table 2, has

1 Provided by the Division of Cancer Treatment, National Institutes of Health

Table 2. Lumbar CSF and plasma MTX concentrations in two patients after priming IT MTX, 15 mg/m² followed in 24 h by 6-h MTX infusions at 50 mg/kg body wt., 150 mg/kg body wt., and 200 mg/kg body wt.

Time (h)	Concentration (mol/liter)		50 mg/kg[a]	150 mg/kg[a]	200 mg/kg[b]
−24	CSF	(10^{-7})	0.55	2.75	2.33 ± 1.60 (9)
	Plasma	(10^{-7})	–	< 0.55	–
0	CSF	(10^{-6})	1.20	6.60	3.70 ± 3.69 (4)
	Plasma	(10^{-7})	< 0.55	< 0.55	2.20 ± 1.37 (6)
6	CSF	(10^{-5})	0.11	1.15	2.54 ± 1.99 (4)
	Plasma	(10^{-3})	0.03	1.20	1.05 ± 0.24 (4)
24	CSF	(10^{-6})	0.94	1.25	3.40 ± 2.37 (6)
	Plasma	(10^{-6})	0.29	5.30	3.93 ± 2.74 (4)
48	CSF	(10^{-7})	< 0.55	–	6.15 ± 2.25 (6)
	Plasma	(10^{-7})	< 0.55	7.40	9.40 ± 6.90 (7)

[a] Mean values of two observations

[b] Mean value ± one standard deviation. Figures in parentheses indicate number of observations used to derive mean value in each case

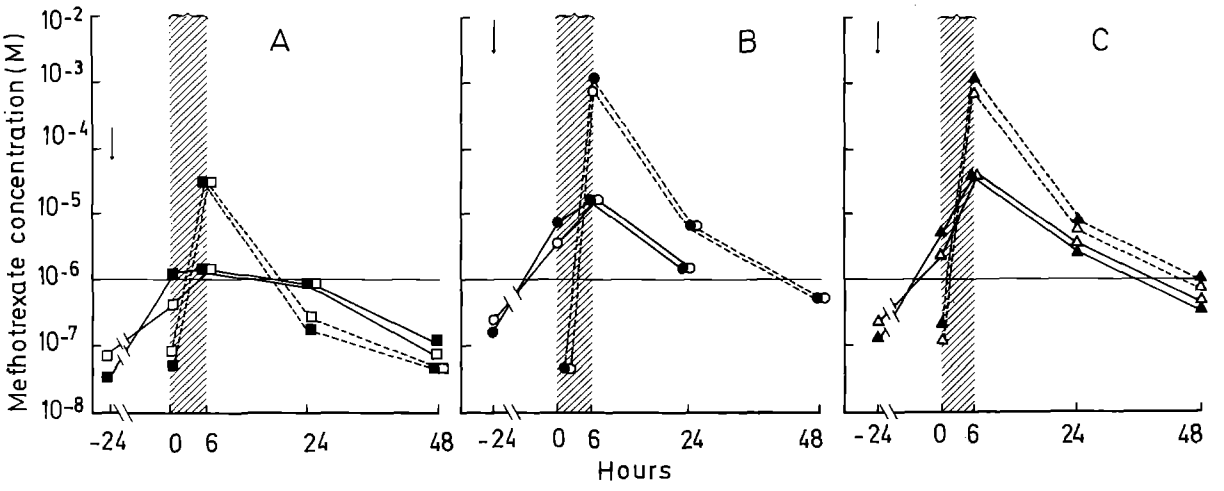

Fig. 2. Lumbar CFS (—) and plasma (– – –) MTX concentrations of Patients 2 (*open symbols*) and 3 (*solid symbols*) after priming IT, MTX, 15 mg/m² (arrows) followed in 24 h by 6-h MTX infusions (▨) at 50 mg/kg body (**A**, *squares*), 150 mg/kg (**B**, *circles*), and 200 mg/kg (**C**, *triangles*)

been used individually to construct the curves for three MTX dose levels (see Fig. 2). At the completion of MTX infusions at the 50 mg/kg dose level, plasma levels were 3.0×10^{-5} *M* and 2.8×10^{-5} *M*. 'Therapeutic concentrations' as defined for acute leukemia [13], i.e., greater than 10^{-6} *M*, were sustained for approximately 18 h. At the 150 mg/kg dose level, plasma levels immediately upon completion of the infusions were markedly increased, to 0.99×10^{-3} *M* and 1.4×10^{-3} *M* for Patients 2 and 3, respectively, therapeutic levels were sustained for approximately 36 h. Similar plasma levels were obtained immediately after infusion at the 200 mg/kg dose level; therapeutic concentrations were maintained for approximately 42–46 h.

MTX Levels in CSF

Figure 3 shows pooled CSF levels for Patients 2 and 3. IT MTX, 15 mg/m² followed 24 h later by an IV infusion of 50 mg/kg resulted in a therapeutic CSF concentration of 1.2×10^{-6} *M* at the end of the infusion period; this level, however, was poorly sustained. At the 150 mg/kg MTX infusion dose level, coordinated IT-IV MTX therapy resulted in a postinfusion peak CNS value of 1.2×10^{-5} *M*. A therapeutic concentration [13] was present at 24 h. At the 200 mg/kg MTX infusion level, CSF concentration was 2.54×10^{-5} *M* on completion of the IV infusion. The therapeutic level was sustained well beyond 24 h. The total period of therapeutic

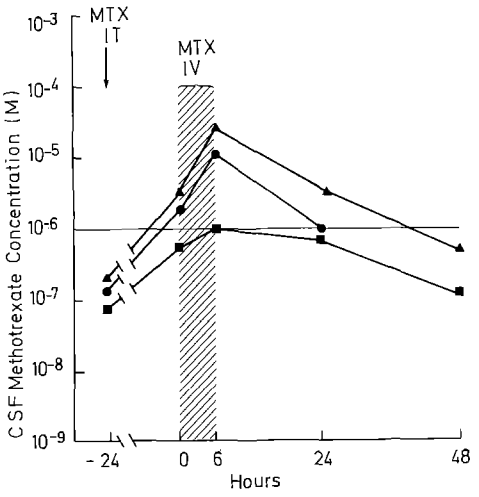

Fig. 3. Pooled lumbar CSF MTX concentrations after priming IT MTX followed in 24 h by 6-h intravenous MTX infusions at 50 (■, $n = 2$), 150 (●, $n = 2$), and 200 (▲, $n = 9$) mg/kg body wt.

concentration in the CSF thus approached 60 h. Increasing CSF retention of MTX at 0 h was documented with the higher dose MTX infusions. Reasons for this build-up in the CSF were not apparent.

Discussion

The effectiveness of CYT in treating BL has been increased considerably by incorporating CYT into the COM-COMP chemotherapy regimens that include MTX[2]. An overall 2-year actuarial survival of 54% has been achieved with these regimens; disease extensions to the CNS are an important cause of treatment failures [24].

The occult CNS disease of newly diagnosed acute leukemia is now being treated with an ingenious regimen in which VCR, dexamethasone, IT MTX, and L-asparaginase induction therapy is 'consolidated' with three treatments employing IT MTX early during 24-h MTX infusions at a moderate dose level of 500 mg/m² [11]. The therapeutic concentration for leukemic cells, 10^{-6} *M*, is maintained in the serum throughout the infusion. An injection of IT MTX into the lumbar space produces a peak CSF MTX level of 5.5×10^{-5} *M*. The therapeutic concentration persists in the CSF throughout the remainder of the infusion.

The therapeutic concentration of MTX for BL has not been clearly defined for either serum or CSF. Data from three children with BL, included with a group of seven with acute leukemia, show that extracellular levels of 10^{-6}–10^{-5} *M* are required to reach the plateau of deoxyuridine (UdR) incorporation; one of the three BL patients showed a significant change in UdR incorporation at the 10^{-5} increment [3]. Therapeutic levels for BL would be expected to be similar to those for acute leukemia or even higher. The potential doubling time for Burkitt's tumor cells has been reported as 24 h, and the growth fraction as being high [25].

Available data suggest that COMP therapy, recently reported to produce 54% survival in BL, produces MTX serum levels of 10^{-7} *M* on the days when MTX is given PO in a dose of 12.5 mg/m² [20]. On alternate days, when MTX, 12.5 mg/m² is given IT, ventricular MTX levels as high as 2.2×10^{-5} *M* might be anticipated, with a therapeutic CNS level persisting for less than 24 h [18]. While such CNS levels might be adequate for the treatment of meningeal disease if the treatment schedule were appropriate, serum levels do not appear to be high enough or to persist long enough to be effective in treating systemic disease. In the treatment regimen we report, IV MTX infusions at the 200 mg/kg dose level resulted in peak plasma levels in the 10^{-4}–10^{-3} *M* range, with therapeutic plasma concentrations persisting for 48 h. The administration of a CNS loading dose of IT MTX, 15 mg/m², 24 h prior to IV infusion results in a therapeutic CSF concentration that is sustained for a period of approximately 60 h. CSF MTX curves following coordinated IT-IV MTX therapy have been presented that reflect the IT-administered drug and the dose-related augmentation produced by infused MTX that passed the blood-brain barrier. The therapeutic responses of the six children treated with this regimen have been excellent; five are living in continuous complete remission 13+–31+ months after diagnosis. None of the patients has developed symptoms or findings of disease extension to a sanctuary site.

Therapy has been discontinued after 1 year of continuous CR in four patients. This cut-off time was based on the observation that among 26 COM-COMP BL patients in continuous CR for more than 6 months, no relapses were encountered [24]. We have continued chemotherapy beyond this period of risk in our patients and this tactic has now been proposed as a means of reducing the COM-COMP failure rate of 46% [24].

The treatment regimen presented in this report has a high risk of toxicity. The metabolic changes secondary to rapid tumor lysis are well described [1, 2, 6, 10]; inappropriate antidiuretic hormone secretion has also been reported [7]. Initiation of CYT therapy requires knowledge of expected complications and adequate preparation of the patient with hydration, alkalinization of the urine, and control of hyperuricemia. Subsequent treatment with CYT carries little risk to the patient,

2 COMP: CYT, 1000 mg/m², day 1; VCR, 1.4 mg/m², day 1; MTX 12.5 mg/m², IV, days 1, 3, and 4; MTX 12.5 mg/m², IT, days 2 and 5; prednisolone, 1000 mg/m², IV, days 1–5; repeat in 2 or 3 weeks. After 2nd course, CYT, 1200 mg/m², IV, daily × 2 and MTX, 12.5 mg/m², IT, single dose. Maintenance therapy given to only 2 of 26 patients continuing in CR

other than hemorrhagic cystitis and transient bone marrow suppression. The potential for serious toxicity with MTX infusions at any dose level is real [4, 12, 14, 17, 19]. Criteria for administering the drug to these children were: WBC > 3000/mm^3, absolute granulocyte count > 1500/mm^3, corrected creatinine clearance > 100 cm^3/min, and normal SGOT, SGPT, and bilirubin levels. As with CYT, pretreatment hydration and alkalinization of the urine were mandatory [5]. CF was given strictly on schedule; additional doses were given, in some instances, until a safe plasma MTX level was documented. With these management plans and precautions, serious toxicity has been encountered in only two patients. Prior MTX toxicity resulted in the substitution of CYT for the last two maintenance courses in Patient 1. Patient 4 expired with evidence of marrow, liver, and renal toxicity.

Neurotoxicity has been described in patients given IT MTX with or without IV MTX plus radiotherapy [5]. The occurrence of leukoencephalopathy has been reviewed recently, and predisposing factors have been identified [14]. Leukoencephalopathy has not been encountered in our patients or in patients with acute leukemia treated with high-dose MTX infusions [11].

According to the presently advocated ABCDAR clinical staging system, COM-COMP therapy resulted in a 24% relapse rate for stages A, B, and AR (extra-abdominal presentations and abdominal presentations in which the tumor mass had been reduced 90% by surgery) [24]. Stages C and D (all other abdominal disease) had a failure rate of 58%; the overall failure rate was 46%. Young age (< 12 years) was found to be an independent variable reflecting a good prognosis. Among the 54 COM-COMP entries, 17 (32%) had Stage A, B, or AR disease with good prognosis; 37 (68%) had Stage C or D disease with poor prognosis. The MDAH material is similar, for two of six, (33%) had B or AR disease with good prognosis, and 4 (67%) had Stage C or D disease with poor prognosis. Among our six patients reported in this paper none has relapsed; one has died as a result of myelosuppression, giving an impressive disease-free survival of 83%.

The limited clinical experience with our treatment regimen suggests a high degree of therapeutic efficacy meriting a preliminary report. The risk of serious toxicity with our regimen is real, and rigid adherence to the criteria for drug administration is mandatory.

References

1. Arseneau, J. C., Bagley, C. M., Anderson, T., Canellos, G. P.: Hyperkalaemia, a sequel to chemotherapy of Burkitt's lymphoma. Lancet **1973 I,** 10–14 (1973)
2. Arseneau, J. C., Canellos, G. P., Banks, P. M., Berard, C. W., Gralnick, H. R., De Vita, V. T., Jr.: American Burkitt's lymphoma: A clinicopathologic study of 30 cases. I. Clinical factors relating to prolonged survival. Am. J. Med. **52,** 314–321 (1975)
3. Bender, R. A., Bleyer, W. A., Drake, J. C., Ziegler, J. L.: In vitro correlates of clinical response to methotrexate in acute leukemia and Burkitt's lymphoma. Br. J. Cancer **34,** 484–492 (1976)
4. Bleyer, W. A.: Methotrexate: Clinical pharmacology, current status and therapeutic guidelines. Cancer Treat. Rev. **4,** 87–101 (1977)
5. Bleyer, W. A., Drake, J. C., Chabner, B. A.: Neurotoxicity and elevated cerebrospinal-fluid methotrexate concentration in meningeal leukemia. N. Engl. J. Med. **289,** 770–773 (1973)
6. Block, J. B., Bronson, W. R., Bell, W. R.: Metabolic abnormalities of lactic acid in Burkitt-type lymphoma with malignant effusions. Ann. Intern. Med. **65,** 101–108 (1966)
7. Braine, H., Colvin, D. M.: Water intoxication in man after cyclophosphamide therapy: time cause and relation to drug activation. Ann. Intern. Med. **78,** 861–869 (1973)
8. Burkitt, D.: Long-term remissions following one- and two-dose chemotherapy for African lymphoma. Cancer **20,** 756–759 (1967)
9. Burkitt, D., Hutt, M. S. R., Wright, D. H.: The African lymphoma: Preliminary observations on response to therapy. Cancer **18,** 399–410 (1965)
10. Cadman, E. C., Lundberg, W. B., Bertino, J. R.: Hyperphosphatemia and hypocalcemia accompanying rapid cell lysis in a patient with Burkitt's lymphoma and Burkitt cell leukemia. Am. J. Med. **62,** 283–290 (1977)
11. Freeman, A. I., Wang, J. J., Sinks, L. F.: High-dose methotrexate in acute lymphocytic leukemia. Cancer Treat. Rep. **61,** 727–731 (1977)
12. Goldie, J. H., Price, L. A., Harr, K. R.: Methotrexate toxicity: Correlation with duration of administration, plasma levels, dose and excretion pattern. Eur. J. Cancer **8,** 409–414 (1972)
13. Hryniuk, W. M., Bertino, J. R.: Treatment of leukemia with large doses of methotrexate and folinic acid: Clinical-biochemical correlates. J. Clin. Invest. **48,** 2140–2155 (1969)
14. Jaffe, N., Traggis, D.: Toxicity of high-dose methotrexate (NSC-740) and citrovorum factor (NSC-3590) in osteogenic sarcoma. Cancer Chemother. Rep. **6** (3), 31–36 (1975)
15. Levine, P. H., Cho, B. R., Connelly, R. R., Berard, C. W., O'Connor, G. T., Dorfman, R. F., Easton, J. M., De Vita, T. V.: The American Burkitt Lymphoma Registry: A progress report. Ann. Intern. Med. **83,** 31–36 (1975)
16. Olweny, C. L., Atine, I., Kaddu-Mukasa, A., Katongole-Mbidde, E., Iwanga, S. K., Johansson, B., Onyango, J., Host, H., Norin, T., Willey, B.: Cerebrospinal irradiation of Burkitt's lymphoma. Failure in preventing central nervous system relapse. Acta Radiol. [Ther.] (Stockh.) **16,** 225–231 (1977)
17. Pitman, S. W., Frei, E., III: Weekly methotrexate-calcium leucovorin rescue: Effect of alkalinization on nephrotoxicity; pharmacokinetics in the CNS; and use in CNS non-Hodgkin's lymphoma. Cancer Treat. Rep. **61,** 695–701 (1977)
18. Shapiro, W. R., Young, D. F., Metha, B. M.: Methotrexate: Distribution in cerebrospinal fluid after intravenous, ventricular and lumbar injections. N. Engl. J. Med. **293,** 161–166 (1975)
19. Von Hoff, D. D., Penta, J. S., Helman, L. J., Slavik, M.: Incidence of drug-related deaths secondary to high-dose methotrexate and citrovorun factor administration. Cancer Treat. Rep. **61,** 745–748 (1977)
20. Wang, J. J., Freeman, A. I., Sinks, L. F.: Treatment of acute lymphocytic leukemia by high-dose intravenous methotrexate. Cancer Res. **36,** 1441–1444 (1976)
21. Wang, Y-m., Lantin, E., Sutow, W. W.: Methotrexate in blood, urine, and cerebrospinal fluid of children receiving high doses by infusion. Clin. Chem. **22,** 1053–1056 (1976)

22. Wollner, N., Burchenal, J. H., Lieberman, P. H., Exelby, P. R., D'Angio, G. J., Murphy, M. L.: Non-Hodgkin's lymphoma in children. Med. Pediatr. Oncol. **1,** 235–263 (1975)
23. Wollner, N., Burchenal, J. H., Lieberman, P. H., Exelby, P. R., D'Angio, G. J., Murphy, M. L.: Non-Hodgkin's lymphoma in children: A comparative study of two modalities of therapy. Cancer **37,** 123–134 (1976)
24. Ziegler, J. L.: Treatment results of 54 American patients with Burkitt's lymphoma are similar to the African experience. N. Engl. J. Med. **297,** 75–80 (1977)
25. Ziegler, J. L., Bluming, A. Z.: Intrathecal chemotherapy in Burkitt's lymphoma. Br. Med. J. **3,** 508–512 (1971)
26. Ziegler, J. L., Magrath, I. T.: Treatment of Burkitt's lymphoma. Pathobiol. Annu. **4,** 129–142 (1976)

Received September 6, 1978/Accepted April 5, 1979