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

Plasma and Cerebrospinal Fluid Methotrexate Levels

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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 MTX levels exceeded \(10^{-6}\) M with coordinated IT–IV MTX \((\geq 150\ \text{mg/kg body wt.})\) 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

LSA2-L2 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DU lymphoma, Burkitt's type (BL), in the MD Anderson Hospital and Tumor Institute (MDAH) LSA2-L2 field trial (A. Frias, unpublished data).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 administration to the first three pilot patients are reported in this paper.

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

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

**Legend:**
- DU, Diffuse undifferentiated lymphoma; BL, Burkitt's lymphoma
- CR, Complete remission
- Confirmed by second-look surgical exploration
- Tissue distortion prevented further characterization

**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-