BRIEF COMMUNICATION

Treatment of Juvenile Chronic Myeloid Leukemia
With Sequential Subcutaneous Cytarabine
and Oral Mercaptopurine

By J. S. Lilleyman, J. F. Harrison, and J. A. Black

Three cases of the juvenile type of chronic myeloid leukemia are described, all of which have shown a clinical and hematologic response to repeated cycles of sequential subcutaneous cytarabine and oral mercaptopurine. It appears that this regime, as described, may afford some control of a disease process previously supposed to be unresponsive to chemotherapy. This control, however, is likely to be reflected in an improvement in well-being, rather than overall survival time. Patient 1 survived 26 mo from diagnosis, and patients 2 and 3 are alive and well 12 and 9 mo from diagnosis, respectively.

WELL-DIFFERENTIATED infantile myelogenous leukemia has been called juvenile chronic granulocytic leukemia,1 juvenile myelomonocytic leukemia,2 and juvenile chronic myelocytic leukemia.3 This heterogenous group of disorders has several features which clearly distinguish it from the adult form of chronic granulocytic leukemia,4 these include absence of the Philadelphia chromosome, a greater tendency towards lymphadenopathy and thrombocytopenia, a raised fetal hemoglobin level, and an increased incidence of infections and skin involvement.

This disease has been described as relentlessly subacute, and though long survivors are recognized,4 the median survival for the group is between 1 and 2 yr. No success has been claimed for any therapeutic regime in this situation, and thus we wish to record our experience with three cases treated with intermittent subcutaneous cytarabine and oral mercaptopurine.

CASE REPORTS

The three children were all female and came to the Children’s Hospital, Sheffield, between 1974 and 1976. Comparable clinical and hematologic findings are shown in Tables 1 and 2.

Case 1

M.F., a girl of 5 mo, presented in February 1974 with a chest infection, generalized lymphadenopathy, hepatosplenomegaly, and the following blood profile: hemoglobin 5.8 g/dl, platelet count 50.0 x 10⁹/liter, and leukocyte count 92.0 x 10⁹/liter: composed of 42%, neutrophils, 11%, eosinophils, 1%, basophils, 16%, lymphocytes, 10%, monocytes, 24%, granulocyte precursors, and 6%, blast cells. The bone marrow showed myeloid hyperplasia with 11%, blast cells, and the neutrophil alkaline phosphatase activity was grossly reduced.

Treatment was commenced with subcutaneous cytarabine, 80 mg/sq m surface area daily for 5 days, with a 5-7-day interval prior to repetition. After four such courses, oral mercaptopurine was added, and thereafter in this case (and the other cases) the course of treatment that evolved...
was as follows: days 1-5 inclusive cytarabine 80 mg/sq m surface area (subcutaneous), day 6 no therapy, days 7-11 inclusive mercaptopurine 70 mg/sq m (oral), the course being repeated with a minimal rest period of 10 days.

This therapy was given for 1 yr and an initial hematologic and clinical response was well maintained at that time, there being no abnormal physical signs, and the blood profile appearing as follows: hemoglobin 10.8 g/dl, platelet count 285.0 x 10^9/liter, leukocyte count 8.0 x 10^9/liter with 68\% neutrophils, 3\%, eosinophils, 16\%, lymphocytes, and 13\%, monocytes. Her bone marrow was reported as normal and the rest interval between courses of therapy was lengthened to 4 wk.

This remission continued for 21 mo, at which time relapse occurred with a clinical and hematologic picture identical to that seen at presentation. (Hemoglobin F, estimated for the first time, was found to be 10.3\%, at this stage.)

Increasing the frequency of courses of cytarabine and mercaptopurine failed to reproduce the previous response, and a slow deterioration occurred over the next few months, punctuated with repeated upper and lower respiratory tract infections. Further chemotherapy, including vincristine, steroids, hydroxyurea, methotrexate, and Adriamycin produced no improvement, and she died 26 mo after diagnosis. The blast cell count rose during the last 3 wk, but was never more than 20\% of the total leukocyte count.

**Case 2**

M.H., a girl of 5 mo, presented in August 1975 with poor feeding. She was found to have generalized lymphadenopathy, hepatosplenomegaly, and a few scattered skin nodules 2-4 mm in diameter. The peripheral blood showed a hemoglobin of 8.8 g/dl, a platelet count of 60.0 x 10^9/liter and a leukocyte count of 32 x 10^9/liter, with 23\%, neutrophils, 47\%, lymphocytes, 10\%, monocytes, 19\%, granulocyte precursors, and 1\%, blast cells. The hemoglobin F concentration was 3.0\%, and biopsy of the skin lesions showed a diffuse sheet of malignant histiocytes. The marrow showed myeloid hyperplasia with 2\%, blast cells, and the marrow karyotype was normal.

No treatment was given until November 1975, when the platelet count fell to 12.0 x 10^9/liter and spontaneous bleeding occurred. At this point cytarabine and mercaptopurine were instituted as in patient 1.

Following this, there was reduction in the liver and spleen size, together with regression of the skin lesions and lymphadenopathy, and over the next few weeks the platelet count rose to normal levels (157.0 x 10^9/liter), as did the hemoglobin (11.4 g/dl), while the leukocyte count fell (17.5 x 10^9/liter), with 55\%, neutrophils, 1\%, eosinophils, 37\%, lymphocytes, and 7\%, monocytes). This change was matched by an objective improvement in well-being and appetite.

This situation has now been maintained for more than 9 mo, and the patient remains well. The interval between courses of therapy has gradually been lengthened to 4 wk.

### Table 1. Summary of Clinical Findings at Diagnosis

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (mo)</th>
<th>Spleen</th>
<th>Liver</th>
<th>Lymph Nodes</th>
<th>Skin Deposits</th>
<th>Purpura</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>++</td>
</tr>
</tbody>
</table>

### Table 2. Hematologic Findings Before Treatment

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Hb (g/dl)</th>
<th>WBC x 10^9/liter</th>
<th>Blast cells x 10^9/liter</th>
<th>Platelets x 10^9/liter</th>
<th>Highest Hbf (%)</th>
<th>Marrow Karyotype</th>
<th>Marrow Karyotype</th>
<th>Serum Lysozyme (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.8</td>
<td>92.0</td>
<td>5.5</td>
<td>50.0</td>
<td>10.5*</td>
<td>46XX10q + *</td>
<td>24*</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8.8</td>
<td>32.0</td>
<td>0.32</td>
<td>60.0</td>
<td>3.0</td>
<td>46XXn.o.d.</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>9.0</td>
<td>42.0</td>
<td>0.42</td>
<td>80.0</td>
<td>5.0</td>
<td>46XXn.o.d.</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

*At time of relapse.*
TREATMENT OF JCML

Case 3

V.O., a girl of 12 mo, presented in December 1975 with a respiratory infection, generalized lymphadenopathy, and hepatosplenomegaly. Her skin was clear. Hematological studies showed a hemoglobin of 9.0 g/dl, a platelet count of $80.0 \times 10^9$/liter, and a leukocyte count of $42.0 \times 10^9$/liter, with $39\%$ neutrophils, $23\%$ lymphocytes, $20\%$ monocytes, $17\%$ granulocyte precursors, and $1\%$ blast cells. The bone marrow showed a normal karyotype and myeloid hyperplasia with $10.5\%$ blast cells. Hemoglobin F concentration was $5.0\%$, and treatment with cytarabine and mercaptopurine was started without delay, as she was fretful and unwell even when her infection resolved.

Following five courses of treatment, there was some regression in the size of the liver, spleen, and lymph nodes, and the leukocyte count fell to $17.4 \times 10^9$/liter, with only $4\%$ granulocyte precursors and no blasts. There was a parallel objective clinical improvement which is maintained at the time of writing, but the mild anemia and thrombocytopenia persist.

DISCUSSION

From many reports, some 75 cases of chronic myelogenous leukemia occurring in children under 5 yr of age have been collected, differing from the adult disease in several ways. The children had more infections, more lymphadenopathy, more skin lesions, and more bleeding, which on investigation were paralleled by a lower total white cell count, thrombocytopenia, and absence of the Philadelphia chromosome. In addition, a high level of fetal hemoglobin (coupled with other fetal red cell characteristics), and raised immunoglobulins were frequently observed.

That this was a heterogeneous group of disorders was suggested by Weisgerber et al. on the basis of scattered survival times, and the recognition of a poor-prognosis subgroup based on age of onset, hematologic picture, and a striking reversion to a fetal pattern of erythropoiesis was indicated by Sheridan et al.

The most consistent feature of previously reported cases has been the poor response to chemotherapy. Ten patients have apparently shown some response to oral mercaptopurine alone, but many have not, and all other agents tried have not apparently been useful. In particular, busulfan has been of no value. The regime used here has been adapted from one employed with some success in acute myelogenous leukemia, and has the advantages of low myelotoxicity, outpatient administration, and preservation of infant veins. Reversible myelosuppression has been the only apparent side effect, and the treatment has been well tolerated by both patients and parents.

With such a small number of cases, it is not possible to assess if this regime affects overall survival. It is likely that it does not, but an improvement in the quality of life is evident. It is suggested that in any given case treatment be withheld until malaise or marrow failure occurs, but in that situation the type of therapy described seems worthy of trial in our present state of knowledge of this group of disorders.

REFERENCES


Treatment of juvenile chronic myeloid leukemia with sequential subcutaneous cytarabine and oral mercaptopurine

JS Lilleyman, JF Harrison and JA Black