Status of Present Treatment for Acute Leukemia in Children

WATARU W. SUTOW, MARGARET P. SULLIVAN, AND GRANT TAYLOR
Section of Pediatrics, The University of Texas, M. D. Anderson Hospital and Tumor Institute, Houston, Texas

SUMMARY

A review of the present status of clinical management of children with acute leukemia has been presented. The literature on acute leukemia and its therapy has been critically surveyed with respect to (a) use of specific chemotherapeutic agents, (b) supportive treatment, and (c) the management of complications of the disease and of drug toxicity. Progress in more effective handling of the leukemic patient has been indicated by an increase in the number of useful drugs, prolongation of survival statistics, and better control of central nervous system involvement and hemorrhage.

Many recent publications (20, 21, 47) provide a review of cancer chemotherapy in general and of chemotherapy for acute leukemia in children specifically (8, 19, 76, 125). Symposium reports indicate the scope and intensity of research concerned with basic and clinical aspects of chemotherapy (118, 123, 136, 142, 153, 171-174). This report is a limited survey of the voluminous literature on acute leukemia and its therapy.

The treatment of children with acute leukemia can be discussed from 3 aspects: (a) specific chemotherapy, (b) supportive care, and (c) management of leukemic complications and of drug toxicity. The present-day score (Table 1) shows no cures induced, minimal success with long-term control of the disease, achievement of short-term palliation in most patients, and no information on preventive approaches. Drug-related complications often limit therapy, incapacitate children, and sometimes prove fatal.

THERAPY

Specific chemotherapy.—Steroids, folic acid antagonists, and purine analogs remain the most widely used chemotherapeutic agents for the specific treatment of children with acute leukemia. Recently, vincristine and cyclophosphamide have shown sufficient anti-leukemic activity to be included in the chemotherapist’s armamentarium.

Assessment of the relative effectiveness of the chemotherapeutic agents is difficult. The value of each drug depends upon its successful performance in spite of important limiting factors (Table 2). The most persistent obstacle in the treatment of children with acute leukemia has been the development of drug resistance. With the exception of adrenocortical steroids, 2nd responses to the same agent are rare once resistance has developed during drug administration. Cross-resistance among related compounds has prevented effective exploitation of more than 1 agent from a group in a given patient. Maintenance of an optimal balance between the therapeutically effective dose and tolerable dosage is complicated by the varying biologic responses in each patient. Another limiting factor is the relative ineffectiveness of the compounds. The patient's clinical status and the inherent pattern of the disease contribute to the lack of therapeutic response, but these cannot be predetermined.

The pooled clinical data permit tabulation of expected performance in terms of remission rates for a number of drugs (Chart 1). However, the validity of such data is uncertain because of variability in (a) completeness of reported information, (b) criteria for assessment of response, (c) intensity of supportive care, (d) adequacy of drug dosages, and (e) the nature of leukemia. Despite these known biases, the determination of the number, extent, and duration of responses to each of several drugs provides the basis for comparisons.

Folic acid antagonists.—In 1948, Farber et al. (45) first reported remissions in children with acute leukemia treated by aminopterin (154). Since then, extensive literature on the use of folic acid antagonists for leukemia has accumulated (19, 31, 47, 82, 136, 142, 146). Although many related analogs have been tested (31, 47, 62, 151), the 4-aminopteroylglutamic acid compounds (aminopterin, methotrexate, and dichloromethotrexate) have been the most successful in the treatment of children. Currently, methotrexate is the most widely used (31). Clinical studies with dichloromethotrexate are being conducted (62, 151, 189). Extensive research in the biochemistry and metabolism of folic acid has focused on the relation of the drug to activities of specific enzymes (5, 31, 82, 138, 184, 188).

Sampey (146) reviewed the world literature on the use of folic acid antagonists in 3117 patients. The response rate was estimated at 45%. Though such data suffer from the qualitative deficiencies mentioned earlier, the response rate is comparable to that in controlled studies. Holland (82) found that of 627 children adequately treated with folic acid antagonists 34% had complete remissions and an additional 20% had partial remissions. In most patients with acute granulocytic or monocytic leukemia, the anti-folic compounds have been relatively ineffective, the remission rates being in the order of 0-6% (8, 82).

In a prospective study, the effectiveness of methotrexate...
TABLE 1
OBJECTIVES AND RESULTS OF CHEMOTHERAPY IN ACUTE LEUKEMIA

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Present achievement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td>None</td>
</tr>
<tr>
<td>Long-term control (5 years or more)</td>
<td>Fraction of 1% treated</td>
</tr>
<tr>
<td>Short-term palliation</td>
<td>Complete or partial remissions in 88% treated; survival over 12 months in 40—50% treated</td>
</tr>
<tr>
<td>Repair of iatrogenic complications</td>
<td>Recovery in 98% (?)</td>
</tr>
<tr>
<td>Prevention</td>
<td>No data</td>
</tr>
</tbody>
</table>

TABLE 2
RATING (ESTIMATED ON 0 TO 4+ SCALE) OF DRUGS IN RELATION TO VULNERABILITY TO LIMITING FACTORS

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Development of clinical resistance</th>
<th>Frequency of intolerable toxicity</th>
<th>Relative effectiveness of drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folic acid antagonists</td>
<td>4+</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>Steroids</td>
<td>3+</td>
<td>1+</td>
<td>3+</td>
</tr>
<tr>
<td>Purine analogs</td>
<td>4+</td>
<td>1+</td>
<td>2+</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>4+</td>
<td>3+</td>
<td>1+</td>
</tr>
<tr>
<td>Vincristine</td>
<td>4+</td>
<td>3+</td>
<td>2+</td>
</tr>
</tbody>
</table>

Cancer therapy.—On the basis of experimental data demonstrating lympholytic action of adrenocortical steroids (36, 77, 103, 185), treatment of lymphoma and acute leukemia with ACTH and cortisone was begun in 1949. Beneficial effects were reported by Pearson et al. (131) and Farber et al. (46).

The use of cortisone and adrenal corticosteroid analogs in the management of acute leukemia is widespread, particularly during the induction phase of therapy. Inadequate clinical reporting and pooling of all patients with acute leukemia impede accurate evaluation of the agents in this group.

Responses of children with acute leukemia to ACTH and adrenal corticosteroids are shown in Table 3. All dosages were in the conventional range, e.g., prednisone, 2.0—2.5 mg/kg of body weight daily. Few children were included in the massive-dose (1.0 gm/24 hr) steroid studies (10, 81, 141, 158). Continuous, prolonged therapy failed to increase the response rate significantly (87). To minimize side effects, short-term therapy, i.e., 28 days, was used by most investigators. The remission rates reported with initial courses of steroid varied between 39 and 86% (Table 3). The median remission duration was 6—9 weeks (89, 134, 169). The median time required to achieve the best response was 27—30 days (Table 4) (142). In comparison, a median of 73 days was needed to obtain complete remission in children receiving 6-MP (168).

The patient's ability to respond to re-treatment with a steroid has been documented. Second courses of the drugs have produced remissions in 46—70% of children (Table 3). The duration of remissions averaged 4—9 weeks. A longer period (median 28 days) was necessary to obtain maximum benefit from the second courses.

Purine analogs.—The predicted effectiveness of the anti-purines (37, 39) at the 1954 (118) symposium on 6-MP has been substantiated. At the symposium, analysis of pooled data on the early use of 6-MP in managing acute leukemia in children indicated that the drug produced a remission in 36% of 332 children (12, 18). Sampey (146) calculated a “good and fair” remission rate of 54% in 2027 acute leukemia patients of all ages treated with this drug. This reflects a minimum estimate of the response rate, since the inclusion of adults in many reports tends to decrease rather than increase the rate.

Data obtained by more uniform methods from medical centers showed response rates of 50—70% in children with stem-cell or acute lymphoblastic leukemia (8, 76). In controlled cooperative studies the incidence of complete and partial remissions combined ranged from 41 to 84% (54, 80, 168, 169).

Although 6-MP is the purine antagonist most widely used, other anti-purine compounds have been synthesized and investigated (14, 16, 29). Aminonucleoside (14), 2,6-diaminopurine (14, 17), and 8-azaguanine (18, 23) were not sufficiently active to sustain clinical interest. 6-Chloropurine (127), 6-thioguanine (127), 6-methylmercaptopurine (16, 73), thioguanosine (16, 98, 99), and 2-amino-6-(1-methyl-4'-nitro-5'-imidazolyl)thiopurine (40) were effective only in children with acute leukemia previously untreated by an anti-purine compound. These drugs showed no significant advantages over 6-MP (76). Cross-resistance precluded their administration to patients who
6-MP might be highly effective (88). However, a cross-sensitivity between the anti-purines and the folic acid antagonists and steroids (8, 54, 76).

Some data indicated that large, intermittent doses of 6-MP might be highly effective (88). However, a comparative study using a high loading schedule of 3 times the usual dosage failed to produce results superior to the usual daily dose regimen (168).

**Combination therapy.**—The experimental basis for clinical treatment of patients with malignant disease by means of combinations of chemical agents has been reviewed by Goldin and Mantel (69). Theoretically, combinations of drugs can achieve therapeutic synergism (69, 80, 168), delay the development of drug resistance (54, 69), permit the use of drugs below the separate maximum tolerated levels (69), or combine the unique desirable characteristics of the drugs (13, 59, 108, 200).

When 6-MP was combined with the glutamine antagonists, azaserine (80) or 6-diazo-5-oxo-L-norleucine (168), there was no significant improvement over the use of 6-MP alone. The concomitant administration of 4-hydroxyprazolo(3,4-d)-pyrimidine, an inhibitor of xanthine oxidase, has altered the catabolism of 6-MP and has resulted in potentiation of the therapeutic activity of thiopurines (38). In a controlled study, the combination of methotrexate with 6-MP produced more remissions than either drug alone (54). Although no difference was noted in the median survival, more patients who received the combined drugs obtained prolonged remissions. Zuelzer and Flatz (200) have published data showing an impressive number of long-term survivors among children with acute lymphocytic leukemia, in whom the response was first induced by prednisone and 6-MP and then maintained by cyclic continuous therapy with 6-MP and methotrexate rotated at regular (12-weeks) intervals. An increase in frequency of 4-year survivors has also been reported among leukemic children who were treated cyclically with prednisone, methotrexate, and 6-MP, each given successively for 6-week periods (13). Though steroids have been used together with anti-metabolites, including 6-MP (13, 108, 147, 157, 200), methotrexate (108, 147, 200), cyclophosphamide (157), hydroxyurea (157), and vincristine (157), the relative value of such combinations remains to be established.

**Cyclophosphamide.**—Cyclophosphamide, synthesized in 1958 (3), has produced beneficial responses in a significant number of children with acute leukemia who had become resistant to other therapy. The Southwest Cancer Chemotherapy Study Group reported complete remissions in 8 (18%) and partial remissions in an additional 5 (11.4%) of 44 children treated (48). Tan et al. (175) obtained similar results, i.e., remissions (complete and partial), in 35% of 40 children. Yessayan et al. (196) obtained 20% complete remissions in 100 children previously treated by other agents.

Bone marrow depression with severe leukopenia, distressing gastrointestinal symptoms, and hemorrhagic chemical cystitis (48, 133, 175, 196) are serious side effects of cyclophosphamide therapy. Although the clinical performance of this compound has not been as consistent (83) as that of steroids, folic acid antagonists, or the anti-purines, it promises to be useful. The optimum dose schedule must be more adequately evaluated in clinical trials (101, 181).

**Vincristine sulfate.**—The 4 dimeric compounds containing cantharanthine and vindaline moieties derived from

---

**TABLE 3**

**Response Rate of Children with Acute Leukemia to Therapy with Adrenocorticosteroids**

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Agent</th>
<th>No. of Patients</th>
<th>Incidence of Remissions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>CR*</td>
</tr>
<tr>
<td>Pierce (134)</td>
<td>ACTH</td>
<td>100</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>ACTH Gel, 1st course</td>
<td>37</td>
<td>24</td>
</tr>
<tr>
<td>Sutow et al. (169)</td>
<td>ACTH 1st course</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Pierce (134)</td>
<td>ACTH gel, 2nd course</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td>Fessas et al. (49)</td>
<td>Cortisone, 1st course</td>
<td>27</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Cortisone, 2nd course</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Pierce (134)</td>
<td>Hydrocortisone</td>
<td>22</td>
<td>59</td>
</tr>
<tr>
<td>Sutow et al. (169)</td>
<td>Hydrocorticione</td>
<td>54</td>
<td>39</td>
</tr>
<tr>
<td>Pierce (134)</td>
<td>Prednisone</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>Hyman and Sturgeon (89)</td>
<td>Prednisone, 1st course</td>
<td>21</td>
<td>48</td>
</tr>
<tr>
<td>Freireich et al. (89)</td>
<td>Prednisone, 1st course</td>
<td>92*</td>
<td>51</td>
</tr>
<tr>
<td>Vietti*</td>
<td>Prednisone, 1st course</td>
<td>46</td>
<td>32.6</td>
</tr>
<tr>
<td>Hyman and Sturgeon (89)</td>
<td>Prednisone, 2nd course</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Vietti*</td>
<td>Prednisone, 2nd course</td>
<td>41</td>
<td>24.4</td>
</tr>
</tbody>
</table>

* CR = complete remission; PR = partial remission; BMR = bone marrow remission.
+ Six patients over 15 years of age.
+ Unpublished data, Pediatric Division, Southwest Cancer Chemotherapy Study Group.

---

**TABLE 4**

**Days Required to Reach Best Status with Adrenocorticosteroid Therapy**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Complete Remission</th>
<th>Partial Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Median</td>
</tr>
<tr>
<td>ACTH (169)</td>
<td>21–63</td>
<td>28</td>
</tr>
<tr>
<td>Hydrocortisone (169)</td>
<td>7–144</td>
<td>13–33</td>
</tr>
<tr>
<td>Prednisone, 1st course</td>
<td>13–43</td>
<td>30</td>
</tr>
<tr>
<td>Prednisone, 2nd course</td>
<td>11–84</td>
<td>42</td>
</tr>
<tr>
<td>6-Mercaptopurine (168)</td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

* Unpublished data, Pediatric Division, Southwest Cancer Chemotherapy Study Group.
the periwinkle plant (Vinca rosea Linn; Catharanthus roseus G. Don) were active tumor inhibitors in experimental systems (90). Vinblastine and, later, vincristine were significantly effective against transplanted rodent leukemia (90, 170). Their effectiveness in producing remissions in refractory acute leukemia of childhood was reported in 1962 (155). In previously untreated children, 85% treated with vincristine achieved remissions (43). Clinical remission was obtained within 29 days and marrow remission within 39 days. The mean duration of remissions was 57 days when therapy was discontinued on attainment of remission; it was 125 days with biweekly maintenance therapy (43).

More extensive studies of refractory acute leukemia indicate a remission rate of 54–60% (43, 91, 92). Older patients respond less favorably to treatment with vincristine (91). In children with resistant leukemia, biweekly maintenance therapy failed to lengthen the remissions significantly from the mean value of 55 days obtained with discontinuous therapy (43). A double-blind study on 150 patients with resistant acute leukemia showed little prolongation of remission in those receiving maintenance therapy compared with those given placebo (91).

Prohibitive neuromuscular toxicity appeared at higher dosage levels. Nervous system symptoms were reported in 50% of treated children (43). The full extent of toxicity is indicated in reports of studies of adults and older children who can better express subjective disturbances, such as paraesthesia, neuritis, and dysphagia (9, 112, 156).

Methylglyoxal-bis-guanylhydrazone.—The achievement of complete hematologic remissions after administration of methylglyoxal-bis-guanylhydrazone (51, 115) was reported in 11 of 20 patients with acute myelocytic leukemia. Marrow improvement appeared within 13–58 days (median, 27 days), and the remissions induced lasted from 30 to 205+ days (58, 105). In Me-GAG-treated patients, abnormal cells disappeared more promptly from the bone marrow, and platelets and granulocytes appeared in the peripheral blood earlier than is usual in patients given 6-MP. Megaloblastoid erythropoiesis was not a feature of the Me-GAG-induced remissions (105). Responses were limited to acute myelocytic leukemia. Prohibitive toxicity was not noted (105).

At another institution, no complete remissions were induced by Me-GAG administered to 24 patients with acute leukemia, 19 of whom had a myelocytic type (143). Four patients obtained partial remissions, although they were of short duration and relapsed upon discontinuance of therapy. Toxicity appeared after a median time of 7 days from the beginning of the therapy.

Current investigations.—Current investigations in antileukemic chemotherapy are directed toward appraisal of new compounds and evaluation of dosage regimens and drug therapy patterns (Table 5).

Survival.—Statistics on children with acute leukemia treated before the introduction of folic acid antagonists show a median survival of approximately 4 months (134, 164, 177); 90% died within 11 months (177). Following the introduction of folic acid antagonists and steroids, anti-purines, and other drugs for the treatment of patients with acute leukemia, the median survival figure for children increased to 12–13 months (8, 44, 47, 125, 134). The survival duration was related basically to the number and duration of remissions (8, 60, 75).

The reported incidence of spontaneous remissions ranges from 10 to 14% in children with acute leukemia (34, 164). With present-day chemotherapy the probability of achieving a remission with 1 or more of the drugs is as high as 85% (60). Of particular significance is the increasing number of patients who live from 3 to 4 years or more after the diagnosis of acute leukemia (13, 44, 47, 125, 126, 134, 200). Though not all reported series reflect a longer survival (84, 113, 128), most of the data imply that improvement in survival statistics is attributable to chemotherapy.

**COMPLICATIONS AND TOXICITY**

Management of complications.—Infiltration of organs other than the bone marrow, liver, spleen, and lymph nodes becomes clinically apparent in many patients during various stages of the disease (8, 109). Localized infiltrations often require special treatment, sometimes as an emergency procedure. The most clinically significant of these have been tabulated (Table 6). The recognition of and treatment for the complications have been more successful than the specific control of the basic leukemic process (8, 28).

The extent and degree of visceral invasion are important in distinguishing between the end results of acute leukemia and the results of drug toxicity. Infiltration of an isolated organ in a patient with otherwise completely controlled leukemia stresses the need to improve drug distribution and to prevent, by chemotherapy, leukemic cell dissemination (57). The possibility that the organs may not be

---

**TABLE 5**

<table>
<thead>
<tr>
<th>Variables under Study in Clinical Chemotherapy of Acute Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage regimen</strong></td>
</tr>
<tr>
<td>Continuous</td>
</tr>
<tr>
<td>Intermittent</td>
</tr>
<tr>
<td>Mosaic</td>
</tr>
</tbody>
</table>

**TABLE 6**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system infiltration</td>
<td>Intrathecal methotrexate or aminopterin; external roentgen therapy</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>External roentgen therapy</td>
</tr>
<tr>
<td>Hyperuricemia and nephropathy</td>
<td>Fluid therapy; artificial kidney</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Transfusion of red cells; transfusion of platelets</td>
</tr>
<tr>
<td>Infection</td>
<td>Anti-microbial chemotherapy; white-cell transfusion</td>
</tr>
<tr>
<td>Anemia</td>
<td>Transfusion of red cells</td>
</tr>
<tr>
<td>Skeletal involvement</td>
<td>External roentgen therapy</td>
</tr>
</tbody>
</table>
infiltrated with leukemic cells, even though the patient is totally untreated, further complicates assessment of the effect of therapy or the activity of the disease (11).

**Infiltration of the central nervous system.**—Meningeal leukemia develops in approximately \( \frac{1}{4} \) of the children with acute leukemia (42, 167). Of 32 children with leukemia of the central nervous system, 13 had involvement of the following structures in addition to the meninges: dura, 1; hypothalamus, 4; cerebellum, 2; cranial nerves, 2; cranial and spinal nerves, 2; spinal nerves and nerve roots, 1; and peripheral nerves, 1.

Pathologic features of leukemia of the nervous system have been described in detail (28, 33, 67, 94, 104, 122, 152, 166, 167, 186, 193). Grossly, early changes are minimal, consisting of thickening and opacification of the meninges. Hydrocephalus is associated with more advanced stages of the disease. Diffuse infiltrations of the leptomeninges, choroid plexus, and perivascular spaces are microscopically apparent. Autopsy data on leukemia of the spinal meninges are scant, though reports indicate that infiltrations of this region are not rare (28, 122, 167).

Lumbar tap alone with limited spinal fluid drainage (28, 42), the administration of adrenocorticosteroids (130, 159, 161, 166), external radiation (28, 42, 166, 167), or the administration of methotrexate (42, 125, 192, 195) or aminopterin intrathecally (144, 145) have produced favorable results of varying duration. Controlling leukemia of the central nervous system by drugs given systemically is suggested by the results with 1,2-bis-(β-chloroethyl)-1-nitrosourea (139, 140).

**Renal masses.**—Renal infiltration by leukemia cells has been reported to be as high as 66% (165). The extent of this infiltration may not relate to the clinical stage of the disease. In most cases there is bilateral involvement. The leukemic infiltrate is distributed diffusely throughout the cortex, the medulla being affected to a lesser degree. Renal dysfunction is rare in children, although minimal depression of the glomerular filtration rate, renal plasma flow, and tubular maximum p-aminohippurate secretion have been observed. Episodes of azotemia have also been reported (53, 200).

The kidneys are usually infiltrated late in the course of leukemic disease; however, they may be enlarged at the time of diagnosis (200). Palpable renal masses are ominous signs because of impending uremia, which may seriously inhibit renal excretion of the chemotherapeutic agents (134).

Decrease in the kidney's size, together with improvement in renal function, has been effected by systemic chemotherapy and local irradiation of the kidneys (160, 180, 200). Reports on radiation dosimetry have been scant.

In 1955, enlargement of the kidneys without evidence of leukemic infiltration was reported in 15% of 108 leukemia cases reviewed in a postmortem study (165). Though morphologic explanation for the enlargement was not apparent, renal hypertrophy as a result of pterin therapy was postulated. Renal enlargement, with urographic findings similar to those produced by infiltration, has also been attributed to interstitial edema and to extensive parenchymal hemorrhage in patients with leukemia (110). Correlations between renal and hepatic enlargement and the degree of leukemic infiltration in the other organs were also reported.

In another postmortem study (55), renal or hepatic enlargement, or both, not induced by leukemic infiltration was found in \( \frac{1}{4} \) of 57 leukemia patients. The enlargement was attributed to hyperplasia or hypertrophy of parenchymal cells, or both. The following causative mechanisms were suggested in renal and hepatic hypertrophy: (a) increased metabolic load resulting in compensatory hypertrophy; (b) secretion by neoplastic cells of a product that induces hypertrophy, e.g., toxohormone, derived from tumors in some experimental systems; and (c) homologous or secondary disease following multiple transfusions with fresh whole blood (111).

Evidence of renal dysfunction associated with noninfiltrative enlargement of the kidneys has not been forthcoming, and specific therapy for this phenomenon does not seem to be indicated.

**Hyperuricemia and uric acid nephropathy.**—The increased excretion of uric acid in patients with acute leukemia is well known (148). Hyperuricemia was recently reported in at least 50% of patients with leukemia irrespective of the histologic type (111). The excess uric acid results from nucleic acid metabolism of leukemic cells. Increased cellular destruction incident to effective therapy, especially by steroids, may produce marked hyperuricemia and uric acid nephropathy (33, 97, 114). An internal hydronephrosis follows, manifested by azotemia, electrolyte imbalance, and oliguria. Hyperuricemia may also reflect increased uric acid production associated with the general acceleration of the synthetic pathways of nucleic acid (148).

Hyperuricemia with uremia has been reported in a number of leukemic children (15, 50, 68, 71, 79, 97, 125, 148, 182, 183, 191). The incidence of uric acid nephropathy in children with acute leukemia has not been recorded.

Mannitol has been administered to patients with severe oliguria to produce diuresis (4). Patients with uric acid nephropathy who developed acute renal failure (4, 50, 125) have been treated by peritoneal lavage and extracorporeal hemodialysis. Development of hyperuricemia should be anticipated in therapeutic planning. The report that 4-hydroxy-4H-pyrazolo[3,4-d]pyrimidine, a xanthine oxidase inhibitor, alters the catabolism of 6-substituted purines (38) has led to a study of the practical application of this type of metabolic control in conditions of excessive production of uric acid.

**Infections.**—Infection has been reported to be the principal cause of death of 36% of patients with acute leukemia, and infection combined with hemorrhage has been the cause of death in an additional 6% (122).

Bacterial infections generally with *Micrococcus pyogenes* var. *aureus* and Gram-negative rods, i.e., *Escherichia coli* and *Pseudomonas aeruginosa* are major, often fatal, complications (117, 137, 163). Serious bacterial infections are associated with relapses. The susceptibility of the leukemic patient in relapse to infection by other organisms usually lacking in pathogenicity is documented (7, 32, 117, 163). Recovery from the infection is related to the induction of remissions (6, 72, 117, 163).
Patients with leukemic disease often fail to respond to viral infections in the usual fashion. Measles (41, 119, 120, 121, 129) and chickenpox (129, 135, 178) may follow atypical courses. Vaccination may have adverse effects (30, 96). Cytomegaloviruses have been implicated (70, 74) in unexpected situations.

Secondary mycoses have become increasingly prevalent in children with acute leukemia (26, 72, 85, 93, 163, 179, 194, 197–199). Uncommon infections such as Pneumocystis carinii pneumonia have also been reported (78).

Transfused granulocytes in the control of infections (106, 124), the role of blood γ-globulin levels (116, 163), and the leukemic patient’s capacity for antibody production (100, 102, 117, 149, 150, 162) have recently been investigated.

Hemorrhage.—Cerebral hemorrhage, gastrointestinal bleeding, and massive blood loss from other sites are major causes of death of children with acute leukemia (8). Many determinants of hemorrhage in these patients have been evaluated, including the number of blast cells circulating blood (64), fever (52), fibrinolysin levels (107, 187), and the severity of the illness (107). A direct relationship between the incidence and severity of hemorrhage and the degree of thrombocytopenia has been consistent (35, 66). At thrombocytopenic levels hemorrhage in the leukemic child is a lethal risk inversely proportional to the blood platelet count (66).

Platelet administration as a control for thrombocytopenic hemorrhage has been attempted (27, 63, 65, 136). The recent development of plasmapheresis and platelet transfusion techniques (35, 95) have made the provision of platelets in sufficient quantities to control thrombocytopenia a practical procedure.

Effective hemostasis following the administration of large quantities of platelet material is encouraging (35, 61) and presages a point of attack against 1 of the more dangerous complications of this disease.

Skeletal pain.—About $\frac{1}{4}$ of the children with acute leukemia (176) have severe skeletal pain; in $\frac{1}{3}$, skeletal pain of lesser intensity develops during the course of the disease. The pain is attributed to cortical and periosteal lesions. The incidence and severity of skeletal pain increase as the disease progresses (176). Usually, pain arising from localized skeletal lesions can be controlled by radiotherapy (28).

Gastrointestinal lesions.—Gastrointestinal lesions associated with acute leukemia (106) have not been considered causes of symptoms in the absence of bleeding or hemorrhage (8). Raised leukemic nodules, leukemic plaques, diffuse infiltration, and multiple leukemic polyposis were found at autopsy in 14.8% of 264 cases of leukemia (25). Amromin and Solomon (2) reported necrotizing enteric lesions in 63 of 280 autopsy studies. These lesions were attributed to shock or ischemia, drug toxicity, trauma, and hemorrhage.

Drug toxicity.—The clinician must achieve therapeutic results within the patient’s drug tolerance. The possibility of unexpected or unpredictably severe reaction is always present with chemotherapy. Side effects that have necessitated drastic changes in dose or discontinuance of therapy are tabulated (Table 7) for each of the 5 classes of anti-leukemic agents. With the induction and mainten-


47. Frei, E., III, Fredrick, J., Silver, R. T., Gold, G. L., and Regelson, W. A Comparative Study of Two Regimens of


Status of Present Treatment for Acute Leukemia in Children

Wataru W. Sutow, Margaret P. Sullivan and Grant Taylor

Cancer Res 1965;25:1481-1490.

Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/25/9_Part_1/1481

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.