Editorial

Therapy of Acute Leukemia, 1965

By William Dameshek, Thomas F. Necheles, Harvey E. Finkel and Donald M. Allen

Despite some rather glowing reports of therapeutic successes, acute leukemia is surely the most feared of the "dread" diseases. Nevertheless, it must be admitted that the last few years have seen an increase in therapeutic options and in some quarters, there is even talk of complete eradication of the leukemic process. Thus, an appraisal of the current situation becomes essential.

Following the introduction of the folic acid antagonists, corticosteroids and 6-mercaptopurine, there occurred an hiatus during which, although many agents, the other parallels recent developments in the use of antibiotics, and chemotherapy of acute leukemia has again advanced, this time in two directions. One has been the introduction of other effective antileukemic agents; the other parallels recent developments in the use of antibiotics, and might be termed "new ways with old drugs." An excellent review by Freireich and Frei of some of these advances has recently appeared.1

Of the newer antileukemic agents, the most noteworthy at present is the plant alkaloid, vincristine.2 In the acute leukemia of childhood, the remission rate with this material appears to approach that obtained with corticosteroids; when these two drugs are used in combination, initial remissions are induced in 80 to 90 per cent of the children.1 There appears to be no cross resistance with other antileukemic agents. Furthermore, toxic effects on the normal bone marrow elements and the gastrointestinal mucosa are relatively minor. Temporary alopecia often occurs with the higher dose ranges, and peripheral neuropathy, usually reversible, is the most frequent limiting factor in extended treatment. Vincristine, alone or in combination with other drugs, is considerably less effective in adults and in acute granulocytic or monocytic leukemia in children.

Cyclophosphamide (Cytoxan), an alkylating agent used in the treatment of Hodgkin’s disease and lymphosarcoma, has also been found to induce remissions in some cases of acute leukemia.1,3 It is often used when resistance to other drugs develops. Hydroxyurea, still undergoing clinical trials, has shown some activity in the blastic phase of chronic granulocytic leukemia.4 It shares with cyclophosphamide the disadvantage of significant myelotoxicity. The mechanisms of action of both hydroxyurea and vincristine are presently poorly understood. Both appear to interfere with DNA synthesis or replication. Possibly, further alterations of the chemical structures of these drugs will provide even more effective antileukemic therapy.

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With respect to the exploration of new ways of using old drugs, trials have taken two forms—(1) alternative methods of administration and (2) combination therapy. Thus, amethopterin (Methotrexate), which had always been given orally (often without any thought that it could be administered in any other way), was tried intravenously. It was soon found that not only could it induce a remission in a fresh case, but what was more striking, remissions could, at times, be induced in cases that had become resistant either to other drugs or even to oral amethopterin itself.5,6 Given intravenously in a dose of 0.5 mg./Kg. of body weight every 4 to 7 days, this drug has proven to be substantially more effective than with the standard oral therapy. Given intrathecally, amethopterin is often effective in suppressing central nervous system infiltration by leukemic cells. Recently, Huguley et al. reported encouraging results using oral amethopterin in courses of divided doses in adult cases.7 Unfortunately, extensive use of this method may be prevented by severe toxic manifestations. Thus, shortly after amethopterin was introduced, we demonstrated that this drug could induce remissions not only in childhood leukemia but in adults as well, providing a sufficient dosage of drug was used and a sufficient degree of toxicity was established.8 Unfortunately, it was necessary almost to kill a patient before remission could develop, and this very limited maneuverability shortly led to its abandonment. In any event, the recent trials have stimulated adventures with other agents; presently, the intravenous use of large doses of 6-mercaptopurine9 and of “shot gun” mixtures of chemicals are being investigated. The regimen employing the simultaneous use of four agents consisting of vincristine, amethopterin, 6-mercaptopurine, and prednisone (“VAMP”) has been used in several medical centers, the rationale behind it being an attempt to eradicate in one fell swoop, as it were, all leukemic cells. Encouraging results have been reported.10,11 However, not only may this method be considered unscientific, but the initial toxic reaction may be lethal, particularly in adults. Furthermore, it has not yet been clearly shown that this treatment program offers a significant advantage over more conservative approaches. In adults, two of the “shot gun” constituents (vincristine, methotrexate) are of doubtful value and may do more harm than good. In order to obtain remissions in a few cases, it is likely that the survival time of a larger number of patients may be distinctly shortened. Our own results using “VAMP” therapy in adults have been quite discouraging. Perhaps better results will be obtained with other variations or combinations of chemotherapy.9 In general, however, they may be thought to represent “gropings” which engender little enthusiasm for long-term advantages.

Closely related in concept, although different in execution, is the “composite cyclic” or sequential therapy as advocated by Zuelzer.12 In this program, used

*Currently under investigation are combinations such as “POMP” (a variation of “VAMP” using massive doses parenterally), “PAP” (“POMP” without vincristine) and “BIKE” (cyclic sequential therapy with high dosage amethopterin, 6-mercaptopurine and cyclophosphamide).
thus far only in acute childhood leukemia, remissions are induced by corticosteroids and 6-mercaptopurine. The patients are then maintained on a regular alternation, at 3-month intervals, of amethopterin and 6-mercaptopurine. Using this therapeutic program, Zuelzer has achieved an impressive series of long-term survivals, up to 5 to 10 years. It should be recognized that long-term survivals have been found in other series and without the use of sequential therapy; unfortunately, although the number of cases reported in this country seems rather large, these represent but a small fraction of the total number treated. It is conceivable that with the addition of vincristine (not available when this study was begun) and the intravenous use of antimetabolites, still better results might be obtained.

Adjunctive therapeutic measures are of considerable importance in tiding patients over the life-threatening complications of bleeding and infection until such time as the bone marrow, under the influence of the antileukemic drug, can itself take over the functions mediated by the formed elements of the blood. The supportive care of the patient with acute leukemia may call for modes of therapy that were once considered to be but heroic gestures. When bleeding due to thrombocytopenia becomes a problem, it can be effectively stopped by the administration of abundant platelets in the form of unfiltered fresh whole blood, platelet-rich plasma or platelet concentrates. In some areas, these platelet supplementations have been used on a regular basis as prophylaxis against a hemorrhagic tendency, although the overall benefits of this practice remain to be determined. In situations in which acute bacterial infections cannot be controlled because of the lack of sufficient functioning granulocytes, and in which a remission might otherwise be induced, the patient may be temporarily provided with such cells. This can be accomplished either by the transfusion of blood with a high concentration of granulocytes, (e.g., from an individual with chronic granulocytic leukemia), or by the use of bone marrow infusions, the marrow being obtained from healthy donors. The latter method may supply from 4 to 10 billion bone marrow cells, most of them early leukocytes, many of them capable of mitosis. It should be noted that the marrow is used simply to transfuse myeloid elements, and not to attempt the establishment of a marrow graft. The experimental attempts to eradicate the leukemic process by irradiation and other means, in conjunction with the administration of normal marrow, have not proved to be successful. Although a few temporary remissions have been achieved, the leukemic process has inevitably recurred.

At times, therapy with cytotoxic drugs may be interdicted by the presence of a hypoplastic marrow in a patient with acute leukemia. In this situation, a trial of androgen therapy (e.g., oxymethalone or testosterone) to stimulate marrow regeneration may be worthwhile, so that antileukemic chemotherapy can be re instituted.

In addition to these practical considerations, Mathé has recently reviewed some of the theoretical aspects of attempts to eradicate acute leukemia. He points out that the usual criteria for "complete" remission in acute leukemia overlook the fact that up to 5 per cent of the cells in the bone marrow may be
leukemic stem cells and that further reservoirs of leukemic cells may persist in such areas as the central nervous system, kidney and liver which may be relatively inaccessible to chemotherapy. He further emphasizes that the host, in this case the patient with acute leukemia, may be particularly susceptible to the leukemogenic effect of the noxious agent (virus?) concerned. The host factor is often overlooked, but it assumes an even greater significance when considered in the light of the relatively high rate of concordance of acute leukemia in identical twins, and the lack of such concordance in non-identical twins. Theoretically, even if the therapeutic program is completely successful in eradicating the leukemic cell population, there is no assurance that persistence of an original presumed noxious agent will not lead to recurrence. Thus, Mathé recommends that thought be given to aggressive attempts to suppress or even eradicate relatively inaccessible groups of leukemic cells in the central nervous system, kidney, etc. This could conceivably be done by x-irradiation of local areas (spine, kidneys, testes) combined with chemotherapy until no further evidence of leukemic infiltrate could be demonstrated by multiple biopsies of these areas. Although such a vigorous approach can hardly be advocated at this time for the usual management of acute leukemia, the rationale behind such a program is obvious. All too often we have had the frustrating experience of having a patient die during a “complete remission” as defined by examination of the peripheral blood and bone marrow, only to find at autopsy evidence of leukemic infiltration in the central nervous system, intestinal tract or other organs.

This brief survey of recent advances in the therapy of acute leukemia indicates some general trends in this field. It is obvious that most of the benefits accrued have been in the treatment of childhood leukemia. Although gratifying results have occurred in individual cases of acute leukemia in adults, it is questionable whether any real progress has taken place. The combination of 6-mercaptopurine and large doses of corticosteroids still appears to be the treatment of choice, but has yielded at best only a 25 to 33 per cent rate of remission.8,16 Indeed, it is likely that many cases of adult leukemia would do just as well with symptomatic care (transfusions, reasonable doses of corticosteroids, antibiotics, etc.), together with the rather “gentle” use of one or another chemical agent such as 6-mercaptopurine. Certainly, this group has the most to gain from continued study.

It is conceivable that in the enthusiasm for the major, and even the minor remissions, that can now be produced in acute leukemia by a variety of agents, perspective may be lost regarding this terrible disease. A moment of thought should quickly set this right: supposing one’s child or grandchild or spouse developed acute leukemia, what would one’s reaction be? The hopeless and frightening aspects of the prognosis would loom large in contrast with the relatively small advances already made. However, to the workers in the field “small advances” may be all-important presages of even greater things to come, and sufficiently encouraging to warrant even greater efforts. There are, furthermore, many indications not touched on here that further insight into the etiology and pathogenesis of human acute leukemia may soon develop.
Glossary of Drugs Useful in Treatment of Acute Leukemia

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name and Manufacturer</th>
<th>Route of Administration</th>
<th>Usual Dose</th>
<th>Predominant Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amethopterin</td>
<td>Methotrexate (Lederle)</td>
<td>(a) Oral, (b) Intravenous</td>
<td>(a) 1.25–5 mg. day (b) 0.5 mg./Kg. q 4–7 days (c) 0.5 mg./Kg. up to 10 mg. q 1–2 days until CSF clears</td>
<td>Effects on G.I. mucosa, myelotoxicity</td>
</tr>
<tr>
<td>Corticosteroids:</td>
<td>Meticorten (Schering)</td>
<td>Oral</td>
<td>2 mg./Kg./day</td>
<td>Hyperadrenocorticism</td>
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<tr>
<td>e.g., Prednisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(other preparations available for parenteral use)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>Purinethol, (Burroughs Wellcome)</td>
<td>Oral</td>
<td>2.5 mg./Kg./day</td>
<td>Myelotoxicity</td>
</tr>
<tr>
<td>Vinceristine</td>
<td>Oncovin (Lilly)</td>
<td>Intravenous</td>
<td>0.075 mg./Kg./wk. for 3–6 doses smaller dose advisable in adults</td>
<td>Peripheral neuropathy, alopecia, myelotoxicity</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Cytoxan (Mead Johnson)</td>
<td>(a) Oral, (b) Intravenous</td>
<td>(a) 2.5 mg./Kg./day (b) 5 mg./Kg./day for 10 days</td>
<td>Myelotoxicity, alopecia</td>
</tr>
<tr>
<td>Androgens:</td>
<td>Anasteron (Syntex)</td>
<td>Oral</td>
<td>1–4 mg./Kg./day</td>
<td>Minimal salt and water retention, mini-</td>
</tr>
<tr>
<td>e.g., Oxymethalone</td>
<td>Adroyd (Parke-Davis)</td>
<td></td>
<td></td>
<td>mal virilization</td>
</tr>
</tbody>
</table>

Thus, with increasing knowledge it is hoped that more rational and effective programs of both prevention and treatment can be developed. In turn, these may serve as models upon which can be built similar achievements relative to other neoplasms. In the interval, as clinicians, we must utilize with circumspection such means as are available, and offer a measure of hope to our patients and their families, and, as investigators, we must continue with open mind to pursue new and more effective agents and methods of treatment.

REFERENCES

6. Selawry, O. S., and Frei, E., III.: Prolongation of remission in acute lymphocytic leukemia by alteration in


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