TREATMENT OF ACUTE LYMPHATIC LEUKEMIA WITH AMINOPTERIN

RALPH I. COTTLE, M.D. and JOHN D. BATTLE, JR., M.D.
Department of Medicine

THERE are no specific measures for the treatment of acute lymphatic leukemia. A small number of patients experience periods of spontaneous improvement which last for varying lengths of time.[1] The most recent addition to the therapeutic agents employed for the disease has been the folic acid antagonists. Of these preparations aminopterin* has given the most promising results. The present report summarizes the response observed to aminopterin in 12 consecutive cases of acute lymphatic leukemia.

Aminopterin exerts a toxic action not only upon the granulocytic cells of the bone marrow, but also upon the erythrocytic and megakaryocytic constituents. Its effects in any given patient cannot be predicted beforehand. In acute lymphatic leukemia with lymphocytosis, aminopterin usually causes a sharp fall in the total white blood cell count but when there is lymphopenia instead of lymphocytosis the leukocyte count may either fall still further or rise toward normal. Toxic effects include pronounced hypoplasia of granulocytic and erythrocytic precursors in the bone marrow, erythroid maturation arrest at the megaloblast stage, and further suppression of platelet maturation.

The results of treatment with aminopterin are summarized in table 1 and are similar to the results reported by others.[2,3,4,5] In 5 of the 12 patients there was no detectable clinical benefit and no improvement in the blood picture. In the remaining 7 patients, however, both subjective and objective improvement occurred. In these 7 persons there was a decrease in the total number and the percentage incidence of circulating "blast cells," and in most of the patients the systemic symptoms also improved. Unfortunately, in all but one instance the improvement was temporary and persisted only for a few days to 3 months.

All patients who could be traced have since died. Four died within 3 months; 3 within 3 to 6 months; 2 within 6 to 12 months. The most favorable case is summarized in the first of the following case reports.

Case Reports

Case 1. A 28 year old white man was first seen on November 5, 1950, complaining of fever, multiple joint pains and sore throat of 2 weeks' duration. There was a history of acute rheumatic fever at the age of 20 years. Physical examination revealed fever spiking to 101 F., undernourishment, and tenderness of several joints. The heart was slightly enlarged and murmurs indicative of aortic insufficiency and mitral insufficiency and stenosis were present. There were several elevated and tender erythematous lesions

Kindly supplied by Lederle Laboratories, Pearl River, N. Y.

Table 1

Case	Sex	Age	Type of Leukemia	Initial W. B. C.	Initial Hgb. (Gm.)	Differential	Total Dosage Aminopterin (mg.)	Other Treatment	Complications	Results
1	M	28	Acute Lymphatic	96,000	10.5	95% Blasts.	275	2500 cc. Blood	Alopecia	See Case 1
2	M	15	Acute Lymphatic	1,150	6.8*	98% Lymphs; Occ. Blasts.	17	4000 cc. Blood; Cortisone	Oral Ulcers	See Case 2
3	F	47	Acute Lymphatic	3,100	6.3*	40% Lymphs; 27% Blasts.	87	1500 cc. Blood	None	Death, 56 days Subjective Improvement
4	M	17	Acute Lymphatic	2,400	11.5*	79% Lymphs; 6% Blasts.	10	2500 cc. Blood	Oral Ulcers	Death, Without Improvement
5	F	18	Acute Lymphatic	4,850	8.5*	93% Lymphs.	6	Blood	None	Death, Without Improvement
6	M	3	Acute Lymphatic	3,750	9.8	89% Lymphs; Occ. Blasts.	4	400 cc. Blood	None	Death, Without Improvement
7	M	65	Acute Lymphatic	145,000	6.0*	55% Blasts.	13	3500 cc. Blood	Epistaxis	Fall in W. B. C. Present Status not Known
8	F	19	Acute Lymphatic	8,550	6.3*	56% Lymphs; 27% Blasts.	7.5	Blood	Oral Ulcers	Subjective Improvement; Present Status not Known
9	F	60	Acute Lymphatic	1,650	6.7*	26% Blasts.	Approx. 100	1500 cc. Blood	None	Death, 8 months Subjective Improvement
10	F	58	Acute Lymphatic	8,350	9.0	79% Blasts.	29	1500 cc. Blood	Nausea; Stomatitis	Normal W. B. C. Until just before Death
11	M	4	Acute Lymphatic	8,950	13.0*	67% Blasts.	Approx. 150	Blood	None	Death, 4 months Subjective Improvement
12	M	9	Acute Lymphatic	39,500	7.3*	32% Blasts.	Approx. 75	600 cc. Blood	None	Death, 3 months Temporary Improvement

*Transfusions prior to admission.

measuring about 1 cm. in diameter on the skin of the arms and legs. Neither lymphadenopathy nor splenomegaly was present. An initial diagnosis of recurrent acute rheumatic fever and erythema nodosa was made. Hematologic studies, however, revealed the presence of acute lymphatic leukemia. Sternal marrow inspiration disclosed a preponderance of lymphoblasts. After admission to the hospital, 1 mg. of aminopterin was administered orally each day. The hematologic response to the drug is shown in figure 1. Subjective improvement consisting chiefly of decrease of joint pains and improvement in strength began on the fifth day of treatment. The patient was discharged after 14 days, and 1 mg. of aminopterin daily was continued at home. Twenty-five days later he was readmitted for extraction of several infected teeth, and no complications occurred. Aminopterin was reduced to 0.5 mg. daily after the first month of treatment. At the end of 3 months' treatment the patient developed a mild diffuse alopecia which improved in spite of continued use of the drug.

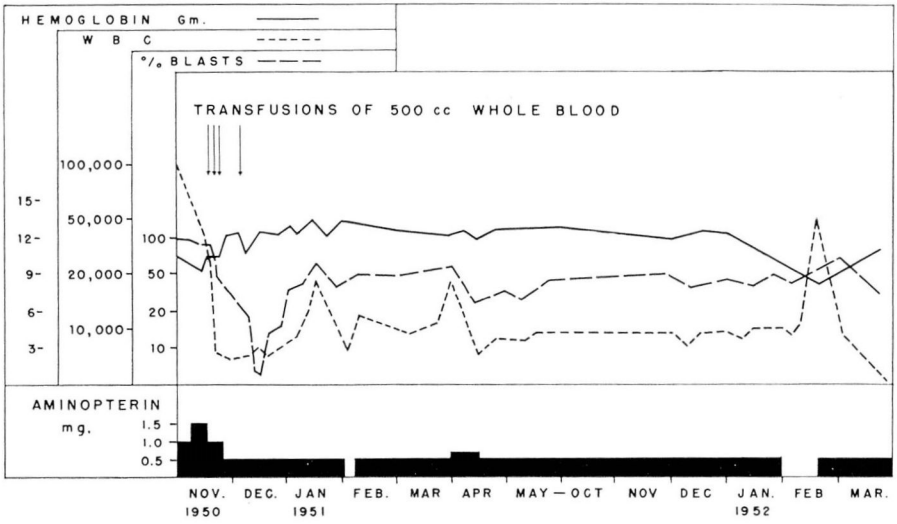

Fig. 1

Fourteen months after continuous aminopterin therapy the patient developed stomatitis, proctitis, and severe alopecia. These toxic effects subsided in 2 weeks after discontinuing the drug. The leukocyte count rose to 94,000 with 87 per cent lymphocytes and the hemoglobin fell to 9 Gm. per hundred cubic centimeters of blood. The resumption of aminopterin therapy (0.5 mg. daily) caused a prompt decrease of the leukocyte count without recurrence of the toxic effects.

The patient has been observed at intervals of 2 or 3 weeks and has worked regularly about 6 hours daily. Repeated blood smears show 10 to 20 per cent lymphoblasts, and marrow aspirations reveal no significant change in the lymphoblastic infiltration.

The course of this patient had been unusual in several respects. At no time has splenic enlargement been demonstrated, and the hemoglobin level has fallen below 11 Gm. only once in the 14 month period of observation. No blood transfusions were given except in the first 6 weeks of treatment.

The more common type of response to aminopterin is illustrated in the following case report (fig. 2).

Case 2. A 16 year old boy was first observed on November 18, 1950 complaining of weakness and fatigue of 18 months' duration. Bone marrow and peripheral blood studies demonstrated acute leukopenic lymphatic leukemia with severe anemia. Treatment with 1.0 mg. of aminopterin orally each day was started 3 days after admission. The fever subsided promptly but the blood picture remained unchanged. He was discharged after 10 days but was readmitted 4 days later because of gingival bleeding. The white blood cell count was 250 per cu. mm. and no platelets were seen. Aminopterin was stopped and antibiotics and transfusions of fresh whole blood were given. The patient's condition deteriorated rapidly in spite of these measures and he became semicomatose with a temperature of 105 F. The parenteral administration of 100 mg. of cortisone every 6 hours resulted in dramatic clinical improvement. The temperature fell to normal. The leukocyte count rose to 2500 and platelets reappeared in the blood smears within 36 hours. The leukocytes reached normal levels on the fifth day of cortisone therapy. Transfusions of whole blood, formerly of little benefit in raising the hemoglobin level, returned the hemoglobin to 11 Gm. per hundred cubic centimeters of blood. The patient continued a maintenance dose of 150 mg. of cortisone daily upon discharge from the hospital and improvement persisted for 6 months. At the end of this time he suddenly became worse and died. The details of the final days of his illness could not be obtained.

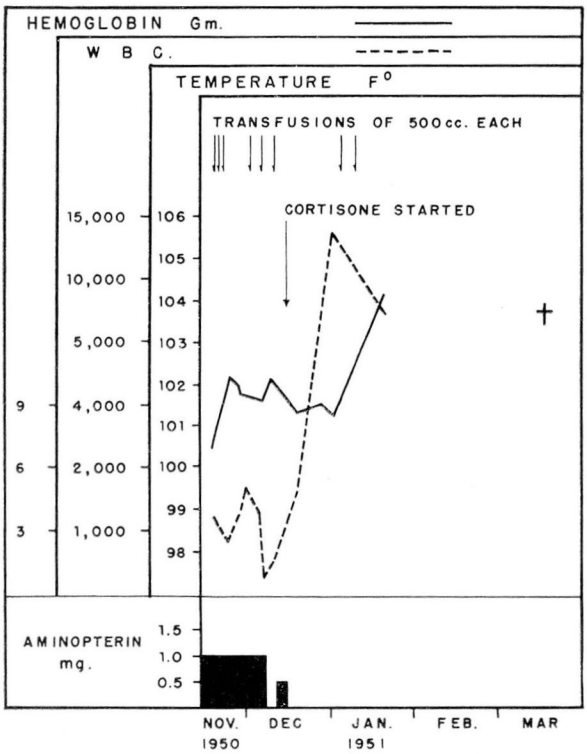

Fig. 2

Discussion

No final conclusions regarding the benefit of aminopterin in acute lymphatic leukemia can be drawn from such a small number of patients. The response observed in the 12 consecutive patients is comparable to the reported results in large series of patients.[6] The experience of most investigators indicates that total improvement which includes complete remission, partial remission, or clinical improvement, occurs in about 50 per cent of patients treated with the drug for a minimum of 3 weeks. The fact that a reversal effect can be obtained in acute leukemia, which was formerly classified as a completely irreversible disorder, offers encouragement for future research.

Summary

1. The effects of aminopterin in 12 consecutive cases of acute lymphatic leukemia are summarized.

2. Six of the patients derived temporary benefit from its use, the improvement lasting from a few days to 3 months.

3. One patient obtained a partial remission which persisted for 14 months after aminopterin therapy was started.

4. Five patients received no benefit from the use of the drug.

5. The striking, but temporary, beneficial effects of cortisone in a patient who had received no help from aminopterin are briefly presented.

References

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