Hydroxyurea in the Prevention of the Effects of Leukostasis in Acute Leukemia

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• **Hydroxyurea was administered orally to prevent the effects of leukostasis in adults with acute leukemia who had peripheral blast cell counts greater than 100,000/cu mm. A single oral dose of 50 to 100 mg/kg was given daily until the absolute blast cell count decreased to less than 100,000/cu mm. Hydroxyurea was effective in rapidly lowering the blast cell count by an average of 50% after one dose in each of ten episodes. No patient developed symptoms or signs of the leukostasis syndrome, and no side effects directly attributable to hydroxyurea were observed. The leukostasis syndrome associated with very high blast cell counts in adults with acute leukemia can be avoided by the use of hydroxyurea in the manner described. This treatment can be particularly useful in the interval before consultation or referral and prior to the cytotoxic effect of definitive induction chemotherapy.**

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High concentrations of blast cells in the blood of patients with acute leukemia are associated with intravascular and perivascular accumulation of the leukemic cells.[1] This leukostasis occurs primarily in the small arteries of the lung or brain, but may occur in other organs. The leukemic aggregates are associated with a distinct type of intracerebral hemorrhage that occurs in the white matter of the brain.[2] This peculiar type of intracerebral hemorrhage is related to the elevation of the blast cell count in the blood.[3] Therefore, a means of rapidly lowering blast cell counts in patients with acute leukemia is needed to lower the risk of intracerebral hemorrhage and to prevent the manifestations of leukemic aggregates in other organs. We have reviewed our experience using hydroxyurea to rapidly lower peripheral blast cell counts in order to prevent leukostasis in acute leukemia. We are aware of no systematic study of the use of hydroxyurea to lower peripheral blast cell counts in patients with adult acute leukemia prior to induction therapy.

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METHODS

Since January 1973, we have used this drug to attempt to prevent the clinical manifestations of leukostasis prior to induction therapy of patients with acute leukemia. We elected to treat patients with acute lymphocytic or acute nonlymphocytic leukemia with orally administered hydroxyurea when the peripheral blast cell count was greater than 100,000/cu mm. A single oral dose of 50 to 100 mg/kg was given daily until the blast cells decreased to less than 100,000/cu mm. No patient received cranial irradiation. No patient had definite clinical manifestations of leukostasis at the time of institution of therapy. Induction therapy with other drugs was started at the time of hydroxyurea therapy or soon thereafter. Total peripheral blast cell counts were recorded before and 24 to 40 hours after each dose of hydroxyurea. Serum uric acid levels were monitored. Most of the patients received allopurinol and some were also treated with intravenous fluids and alkalinization of the urine, using either sodium bicarbonate or acetazolamide.

RESULTS

Ten episodes in nine patients with acute leukemia were treated with hydroxyurea to prevent the symptoms of leukostasis in the 42-month period reviewed (Table). Six patients were newly diagnosed and three were in relapse after previous remission. In five instances, only one dose of the drug was required to lower the blast cell count below 100,000/cu mm. The other five episodes required two doses of hydroxyurea for a similar reduction. Thus, in all cases, the blast cell count was lowered to "safe" levels in less than 72 hours. The mean fall in peripheral blood blast cell count after one dose of hydroxyurea was 83,000/cu mm, with a range of 43,900 to 139,000/cu mm. This represented a mean decrease in blast cell count of 50%. None of the patients treated with hydroxyurea developed clinical evidence of intracerebral hemorrhage or leukostasis. Elevation of uric acid

Clinical Data and Response of Blast Cell Counts to Hydroxyurea						
				Blast Cells‡		
Patient/Age, yr/Sex	Diagnosis*	Dose, gm	No. of Doses†	Before	After§	% Decreased
1/26/M	AML	3	1	160	85.6	47
2/76/M	AMML	6	1	120.8	60.5	50
3/62/F	AMML	6	2	157.2	100.3	36
				100.3	55.4	45
4/20/F	AMML	5	1	102.7	58.8	43
5/49/M	AMML	6	2	178.5	109.8	38
				109.8	17.8	84
6‖/47/F	AMML	6	1	186.6	40.0	79
		5	1	182.4	61.6	66
7/46/M	AMoL	6	1	102.6	25.9	75
8/26/M	ALL	6	2	191.7	145.2	24
				145.2	25.5	82
9/18/M	ALL	6	2	285.6	146.6	49
				146.6	45.8	69

*AML indicates acute myeloblastic leukemia; AMML, acute myelomonoblastic leukemia; AMoL, acute monoblastic leukemia; ALL, acute lymphoblastic leukemia.

†Number of doses required to lower blast cell count to less than 100,000/cu mm.

‡Includes only myeloblasts, monoblasts, or lymphoblasts. Values before and after are absolute number of blasts in blood × 10^{-3} per cubic millimeter.

§Twenty-four to 40 hours after first dose.

‖Patient 6 received hydroxyurea on two occasions.

levels did not occur in patients pretreated with allopurinol and/or intravenous fluids with alkalinization of the urine. The patients tolerated hydroxyurea well, and no side effects attributable to the drug were observed. The effect of hydroxyurea on the platelet count could not be ascertained since changes in the platelet counts, as a result of the underlying disease, could not be distinguished from any changes that were due to the drug. In addition, patients who had platelet counts of less than 20,000/cu mm were treated with platelet transfusions. Outcome of remission induction therapy did not seem to be effected by hydroxyurea therapy.

COMMENT

The ability of hydroxyurea to rapidly decrease circulating blast cells was suggested by Fishbein and coworkers[4] in 1965. Four of their patients with acute leukemia who had white blood cell counts between 45,000 and 530,000/cu mm, of which at least 50% were blast cells, received hydroxyurea parenterally combined with steroids and, in two cases, cranial irradiation. Using these multiple modalities of treatment, they reported a decrease in white blood cell count to less than 20,000/cu mm in all cases and survival for at least nine days. Acute Leukemia Group B studied hydroxyurea for the induction treatment of acute myelocytic leukemia. The drug was not effective in inducing remission, but an antileukemic effect was noted.[5] Wiernik and Serpick[6] described an approach for the prevention of intracerebral hemorrhage in patients with acute leukemia and elevated blast cell counts greater than 200,000/cu mm, using hydroxyurea combined with cranial irradiation. No details of individual patient responses were given. Recently, Hoagland and Perry[7] advocated the use of hydroxyurea, 80 mg/kg/day in divided doses every six hours by mouth for two days, in patients with acute nonlymphocytic leukemia and blast cell counts greater than 100,000/cu mm. Although the number of patients treated or individual patient responses were not reported, they indicated that hydroxyurea given in this manner was effective in reducing peripheral blast cell counts in only 30% of patients. Schwartz and Canellos[8] studied hydroxyurea given to patients with chronic granulocytic leukemia blast cell crisis. They reported reduced white blood cell counts in all nine patients treated intravenously with hydroxyurea, using a mean dose of 4.4 gm for one to seven days.

Our experience with hydroxyurea, given orally in the dose range of 50 to 100 mg/kg with a maximum dose of 6 gm, demonstrates that this is an effective, reliable, rapid, and safe method to reduce blast cell counts in adults with acute leukemia. It is suggested that this would be successful in preventing the manifestations of leukostasis. Elevations of the number of blast cells in the blood and the associated leukostasis syndrome must be considered a medical emergency, and all physicians should be aware of the urgency of this situation. Hydroxyurea can be used to rapidly lower blast cell counts and thus prevent the manifestations of the leukostasis syndrome in the interval before consultation or referral, and prior to the cytotoxic effect of definitive induction chemotherapy.

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Nonproprietary Names and Trademarks of Drugs

Allopurinol—*Zyloprim.*
Hydroxyurea—*Hydrea.*

References

1. McKee LC Jr, Collins RD: Intravascular leukocyte thrombi and aggregates as a cause of morbidity and mortality in leukemia. *Medicine* 53:463-478, 1974.

2. Freireich EJ, Thomas LB, Frei E III, et al: A distinctive type of intracerebral hemorrhage associated with "blastic crisis" in patients with leukemia. *Cancer* 13:146-154, 1960.

3. Fritz RD, Forkner CE Jr, Freireich EJ, et al: The association of fatal intracranial hemorrhage and "blast crisis" in patients with acute leukemia. *N Engl J Med* 261:59-64, 1959.

4. Fishbein WN, Carbone PP, Freireich EJ, et al: Clinical trials of hydroxyurea in patients with cancer and leukemia. *Clin Pharmacol Ther* 5:574-580, 1965.

5. Rosner F, Glidewell O, Ellison RR, et al: Failure of hydroxyurea (NSC-32065) and prednisone (NSC-10023) in the treatment of acute myelocytic leukemia. *Cancer Chemother Rep* 55:199-204, 1971.

6. Wiernik PH, Serpick AA: Factors affecting remission and survival in adult acute nonlymphocytic leukemia (ANLL). *Medicine* 49:505-513, 1970.

7. Hoagland HC, Perry MC: Blast cell crisis in acute or chronic leukemia. *JAMA* 235:1888-1889, 1976.

8. Schwartz JH, Canellos GP: Hydroxyurea in the management of the hematologic complications of chronic granulocytic leukemia. *Blood* 46:11-16, 1975.