Hydroxyurea in the Management of the Hematologic Complications of Chronic Granulocytic Leukemia

By Joel H. Schwartz and George P. Canellos

The effect of hydroxyurea in 35 patients with chronic granulocytic leukemia (CGL), who either had entered an accelerated phase of the disease or had experienced excessive myelosuppression following alkylating agents, was studied. By either intravenous or oral administration, the drug was successful in reducing peripheral leukocyte and blast counts in all cases and in reducing splenomegaly in 13 of 17 patients. The median duration of disease control was 75 days in myeloproliferative acceleration and 27 days in frank blastic transformation. Mild nausea and vomiting were experienced by most patients, but reversible bone marrow suppression occurred in only three patients. The drug proved useful in 19 patients who demonstrated myeloproliferative acceleration, especially in controlling excessive leukocytosis and/or thrombocytosis. Rapid reduction of an elevated blast cell count was achieved in nine patients who presented in blastic crisis, in an attempt to eliminate the associated risk of cerebral vascular leukostasis. Five patients who required treatment for their disease following splenectomy in the chronic phase were also well controlled. Hydroxyurea appears to have a definite role in the management of these hematologic complications of CGL.

The first clinical trials of the antineoplastic agent hydroxyurea were conducted early in 1960 after the compound was found to be active in leukemia L1210 and other animal tumors. Initial trials in adults revealed some objective responses in solid tumors, especially liposarcoma, neuroblastoma, and melanoma. Patients with chronic granulocytic leukemia (CGL) were noted to achieve significant hematologic benefit, including a decrease in white blood cell count, increase in platelet count and hemoglobin levels, and decrease in hepatosplenomegaly. Almost all of these patients were in the chronic phase of the disease.

Although an effective agent in the treatment of CGL, hydroxyurea has not replaced busulfan as the primary treatment of choice for this disease. However, patients with CGL can evolve to a busulfan-resistant acceleration of their disease characterized by excessive leukocytosis and/or thrombocytosis with splenomegaly, prior to entering frank blastic transformation. In addition, a minority of patients has an inordinate sensitivity to the myelosuppressive effects of busulfan, resulting in prolonged pancytopenia. It is in the above circumstances that we have found hydroxyurea to be an effective drug in CGL therapy. The subject of this report is the National Cancer Institute experience with hydroxyurea in these complications of the course of CGL.

Materials and Methods

The records of 118 consecutive patients with chronic granulocytic leukemia seen at the National Cancer Institute between 1964 and 1974, in whom the entire course of disease could be evaluated, were reviewed.
The terminal phases of CGL could be divided into two general clinical presentations. The majority of cases developed a gradual myeloproliferative acceleration of the disease with progressive anemia and/or thrombocytopenia, splenomegaly, leukocytosis, or even thrombocytosis refractory to previously effective therapy. Increased numbers of basophils may accompany or precede this phase in many of these patients, and, in most, the number of blast cells in the peripheral blood remains less than 20%. Approximately one-third of the cases presented with an acute transition of abrupt onset befitting the term "blastic crisis," with a rapid increase in the white blood cell count composed mostly of blast cells. In this phase of the disease, displacement or attrition of cells capable of maturation usually results in anemia and thrombocytopenia. Splenomegaly may occur but is not always present. A small number of patients (<10%) present with extramedullary myeloblastic tumors of lymph nodes, bone, or skin which can precede the systemic manifestations of the blastic transformation of CGL.

Courses of therapy where hydroxyurea was used simultaneously with one or more other chemotherapeutic agents or where hydroxyurea was used solely as chronic-phase therapy were eliminated from our study. Hydroxyurea was used as a single agent in the management of 35 patients—20 patients in myeloproliferative acceleration, ten patients in frank blastic crisis, and five patients who had undergone splenectomy because of alkylating agent-induced thrombocytopenia. The latter group consisted of those patients who developed marked myelosuppression on busulfan or dibromomannitol during the chronic phase of CGL. Such patients underwent splenectomy in order to correct persistent thrombocytopenia; chemotherapy other than busulfan or dibromomannitol was necessary to control the subsequent clinical and hematologic manifestations of CGL.

All 35 patients had been previously treated with busulfan and/or dibromomannitol during the chronic phase of the disease before receiving hydroxyurea. More than 70% of these patients received daily oral doses between 0.5 and 3.0 g, with a wide range of 5-80 mg/kg/day. Six of the 35 cases also received intravenous hydroxyurea in a mean daily dose of 4.9 g for 1-7 days: this therapy was administered prior to or in between the oral regimens. The total duration of therapy varied according to responsiveness. Most patients received concomitant allopurinol in a daily oral dose of 300 mg, and no patient was included in more than one of the three previously defined groups.

RESULTS

The results of the use of hydroxyurea in the 35 treated patients, divided into the three groups described above, are given in Table 1. In two cases, the drug was given to reduce spleen size. Of 33 patients to whom 44 courses of hydroxyurea were administered in order to reduce the white and blast counts, all exhibited a decrease in total white blood cell count and percentage of blasts in the peripheral blood, although the dose of hydroxyurea had to be progressively increased in each patient. The mean reduction in white count in these 33 pa-

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<th>Table 1. Hematologic Effects of Hydroxyurea in CGL</th>
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<td><strong>I. Myeloproliferative Acceleration</strong>&lt;br&gt;(n = 20)&lt;br&gt;19/19 86.1 28 8/12 75 days</td>
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<td><strong>II. Blastic Crisis</strong>&lt;br&gt;(n = 10)&lt;br&gt;9/9 69.1 5 5/5 27 days</td>
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<td><strong>III. Post-Splenectomy</strong>&lt;br&gt;(n = 5)&lt;br&gt;5/5 77.3 24 — 413 days</td>
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tients was 76.0°. A decline in white count was usually seen within 3-7 days after the onset of oral therapy and within 24 hr after the onset of intravenous therapy. In addition to decreasing the white and blast counts, hydroxyurea proved remarkably successful in decreasing spleen size—often to normal—as noted for groups I and II in Table 1.

Mild nausea and vomiting were experienced by most patients receiving hydroxyurea, but these symptoms were easily controlled with antiemetics. Three of the 20 patients in the accelerated phase exhibited significant thrombocytopenia (platelet count <20,000/cu mm) unrelated to the development of blastic crisis. These patients had been on oral hydroxyurea therapy (0.5-4.0 g/day) for 37, 31, and 11 days, respectively, before developing thrombocytopenia. After cessation of therapy, the platelet count increased to >50,000/cu mm within 22, 23, and 30 days, respectively, and, in each case, the drug was restarted at 50% of the previous dosage without recurrence of thrombocytopenia.

Group I. Myeloproliferative Acceleration (20 Cases)

One patient received intravenous hydroxyurea in a dose of 6 g on days 1, 5, 7, and 9, with a decrease in white count from 293,000/cu mm on day 1 to 20,000/cu mm on day 9. This patient was then given oral therapy. Nineteen patients received oral hydroxyurea (mean daily dose, 1.9 g) with a significant reduction in white count in all 19. The mean initial white count was 71,636/cu mm prior to treatment. A mean white count nadir of 14,260/cu mm was achieved. The 20th patient received hydroxyurea in an attempt to reduce spleen size in the face of a normal white count. The median duration of therapy and, parenthetically, the median duration of this phase of the disease was 75 days (range, 15-443 days), with two patients still being maintained on hydroxyurea at 38 and 297 days, respectively. Four patients died in this phase without additional intensive therapy. Hydroxyurea therapy was terminated in the remaining 14 patients due to progression to frank blastic transformation.

Group II. Blastic Crisis (Ten Cases)

Five patients received intravenous hydroxyurea (mean daily dose, 4.4 g for 1-7 days). This route of administration was chosen in order to effect an acute reduction of a high leukocyte and blast count, as in the one patient in group I described above. The mean white count of these five patients prior to intravenous therapy was 167,540/cu mm, which was reduced to a mean of 52,180/cu mm following therapy. Four patients were treated with oral hydroxyurea alone. Their mean white count of 62,175/cu mm was reduced to a mean white count nadir of 26,025/cu mm (mean daily dose, 1.75 g). Hydroxyurea was successful in reducing the white count in nine of nine patients. The tenth patient was initially given hydroxyurea for the purpose of reducing spleen size, although the white count was maintained in the normal range throughout the course of therapy. The median duration of therapy in this group was only 27 days (range, 3-238 days), since hydroxyurea therapy was mainly utilized to decrease acutely the elevated blood count, at which point nine of the ten patients were treated with more intensive antileukemic therapy. One patient died of an acute hemorrhage and never received any therapy other than hydroxy-
urea. Two patients were maintained in blastic crisis for long periods of time—107 and 238 days, respectively.

*Group III. Postsplenectomy (Five Cases)*

All five patients received daily oral hydroxyurea for eight courses in a mean daily dose of 1.33 g. Again, hydroxyurea was uniformly successful in reducing the leukocyte counts, with a mean white count of 124,500/cu mm prior to therapy and a mean white count nadir of 16,425/cu mm. These patients had a median duration of therapy of 413 days (range, 41 + 1628+ days), with two patients still being maintained on hydroxyurea at 41 and 1628 days, respectively. Two other patients developed blastic crisis, at which time hydroxyurea was stopped. The fifth patient died of massive gastrointestinal hemorrhage unrelated to blastic crisis.

**DISCUSSION**

In the early trials of hydroxyurea in chronic granulocytic leukemia, a dose of 40 mg/kg/day was effective in controlling the chronic phase of the disease.²⁴ The accumulated experience at the National Cancer Institute was reported in two separate studies. Twenty patients in the chronic phase were treated with various combinations of intravenous or oral hydroxyurea. With either route of administration, hydroxyurea was uniformly effective in decreasing the white blood cell count.⁶⁷ In the second of these studies, hydroxyurea was effective in decreasing spleen size in almost all patients. The platelet count was decreased in one-third of the patients, and in some cases an increase in hemoglobin concentration was attained. The median duration of therapy was 75 days.

In a trial of long-term administration, good results were obtained in nine patients who were treated for a median duration of 17+ mo.⁹ These initial results were confirmed in a larger series of 20 patients. Half of this group had been previously treated with busulfan and demonstrated a median duration of improvement on hydroxyurea of 8+ mo; the remaining patients who had not had previous chemotherapy were treated for a median duration of 41+ mo. All patients exhibited a decrease in white blood cell count, splenomegaly, and platelet count, and three-fourths demonstrated an increase in hemoglobin concentration.⁹ Similar results in the chronic phase of the disease have also been observed by other authors.¹⁰

The use of hydroxyurea in the blastic phase of CGL has also been reported in a few cases, although success, measured in terms of clearing the peripheral blood and bone marrow of blasts and decreasing spleen size, has been very short lived.⁶⁶¹¹ Our experience suggests the utility of hydroxyurea in the treatment of CGL in at least three distinct circumstances. First, patients who demonstrate myeloproliferative acceleration and are thus refractory to the effects of alkylating agents, such as busulfan or dibromomannitol, can be maintained for variable periods of time on oral hydroxyurea. Use of hydroxyurea in this circumstance, beginning with a daily oral dose of 10–20 mg/kg and progressing to higher doses in some cases, is uniformly successful in reducing the white blood cell count in such patients and is only rarely associated with thrombocytopenia. Even when thrombocytopenia occurs, the platelet count will spon-
taneously return to normal following cessation of therapy. Hydroxyurea may then be administered in approximately 50% of the previous dosage. In the rare instance where the white count is >200,000/cu mm in this phase of the disease (blast count usually 20%, but up to 40% of white cell count in our series), intravenous hydroxyurea may be used in the same manner as that described for blastic crisis below. Use of hydroxyurea, either intravenously or orally, appears to prevent the complications of excessive leukocytosis, including bleeding, constitutional symptoms such as fever, massive splenomegaly, and, in some cases, thrombocytosis.

In the so-called blastic crisis of the disease, the drug is very effective in acutely reducing the increasing blast count and thus can prevent its potentially fatal complication of leukostasis in cerebral vessels.12 A daily intravenous dose of 50-75 mg/kg is an effective starting dose for patients whose absolute blast count approaches 100,000/cu mm. When the white blood cell count approaches 20,000/cu mm, oral administration of about one-half the intravenous dose can be continued. For patients with lower initial absolute blast counts, a daily oral dose of 10-20 mg/kg may be administered. Since hydroxyurea itself is unsuccessful in inducing remission in blastic crisis, more intensive antileukemic regimens can then be administered.

Finally, hydroxyurea may be used in CGL patients who have had a splenectomy due to the development of prolonged thrombocytopenia following a course of busulfan and/or dibromomannitol. Two of the four patients in this study demonstrated cross-sensitivity manifested as thrombocytopenia to both of these alkylating agents prior to splenectomy. Hydroxyurea, again at an initial dose of 10-20 mg/kg, offers a definite advantage in these patients post-splenectomy, since it is a distinctly different compound to which alkylating agent-sensitive patients have not demonstrated cross-sensitivity. In addition, as already noted, hydroxyurea may have a platelet-sparing effect while effectively reducing the white blood cell count in these patients.

In conclusion, hydroxyurea appears to have a definite role in the treatment of some cases of CGL and appears to be especially effective for certain hematologic complications of the disease. Its advantages are the ease of administration, short duration of action, and absence of cross-sensitivity and resistance with alkylating agents such as busulfan.

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