Response of Patients with Leukemia to 8-Azaguanine

By Jacob Colsky, Leonard E. Meiselas, Sigmund J. Rosen and Irving Schulman

In recent years numerous compounds which interfere with the utilization of normal metabolites have been investigated for their effect upon various malignant neoplasms in both experimental animals and humans. A number of these compounds have caused retardation or inhibition of growth of some neoplastic processes in the affected animal1, 2, 3, 4, 5, 6, 7 or human.8, 9, 10, 11, 12

8-azaguanine, a compound closely resembling guanine in chemical structure, appears to be competitive with guanine in the metabolism of the living organism.6, 13, 14

This compound has caused retardation of growth of some transplantable malignant neoplasms when administered to tumor bearing animals,15, 16, 17, 18, 19, 20 while other transplantable malignancies do not appear to be affected by this compound.7, 16, 21

8-azaguanine has been administered to patients with a variety of neoplasms, and undesirable reactions, such as skin rashes, nausea, vomiting, diarrhea and pain at the injection site, have followed such treatment, but inhibition of growth of human neoplasms has not been observed.23, 24, 25, 26, 27, 28

The reports of the use of 8-azaguanine in patients have stated uniformly that manifestations of hematopoietic depression did not occur, and in some instances marrow studies revealed no changes after treatment.23, 24, 25, 26, 27, 28 These observations, in addition to the facts that experimental leukemia is retarded by 8-azaguanine14, 16, 22 and that no study on the use of this compound in the treatment of human leukemia has been reported, suggested to us that a study of its effect upon human leukemia was warranted.

We have treated four patients with acute leukemia, one with chronic lymphatic leukemia, and one with lymphosarcoma. The results of administration of 8-azaguanine to these patients are reported.

Methods

A control period of observation of one week or more was obtained in each patient before treatment was instituted. The 8-azaguanine was suspended in a 10 per cent glucose solution and given intravenously. In the previous experience of one of us with administration of this compound in this way, dermatitis did not occur,28 but in the group of patients in the present report, four of the six did develop dermatitis.

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Dr. J. M. Ruegsegger of the Lederle Laboratories Division of the American Cyanamid Company, Pearl River, New York kindly supplied the 8-azaguanine used in this study.
FIG. 1.—Case 1. Hematological response of patient with acute leukemia during therapy with 8-azaguanine.

FIG. 2.—Case 2. Hematological response of patient with acute myelogenous leukemia during 8-azaguanine therapy.
RESULTS

Acute leukemia

Two of the four patients with acute leukemia, in whom leukocytosis, lymphadenopathy, and hepatosplenomegaly were present, showed rapid decrease in the leukocyte count and regression in the size of the lymph nodes, the liver, and the spleen within two or three days after institution of 8-azaguanine therapy (cases 1 and 2, figs. 1, 2, 3, 4).

In case 3, hepatosplenomegaly was not present, but a decrease in the leukocyte count appeared after treatment. Two patients (cases 1 and 3) had previously been treated with Amethopterin, 6-mercaptopurine, and cortisone, and the disease had appeared to be resistant to further treatment with these compounds. One patient (case 4) showed no response to treatment with 8-azaguanine.

Improvement in the hematological status of cases 1, 2, and 3 as evidenced by suppression of the blast percentage of the total white blood count, increased polymorphonucleosis, and elevation of platelet count was observed. Bone marrow
Fig. 4.—Case 2. Regression of enlarged cervical and inguinal lymph nodes one week after treatment with 8-azaguanine.

**Summary of Results of Administration of 8-Azaguanine to Patients with Leukemia**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Daily dose 8-azaguanine mg.</th>
<th>Days treatment</th>
<th>Total dose 8-azaguanine mg.</th>
<th>Hepatosplenomegaly and lymphadenopathy prior to treatment</th>
<th>Regression of liver and spleen</th>
<th>Induced hematological changes</th>
<th>WBC pre-treatment per cu. mm.</th>
<th>Lowest WBC after treatment</th>
<th>Nausea vomiting during treatment</th>
<th>Dermatitis during treatment</th>
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<tbody>
<tr>
<td>Acute leukemia</td>
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<tr>
<td>Case 1</td>
<td>25–1000</td>
<td>24</td>
<td>4825</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>119,000 10,100</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Case 2</td>
<td>100–600</td>
<td>42</td>
<td>4500</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>38,000 1,850</td>
<td>+</td>
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<tr>
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<td>400–600</td>
<td>5</td>
<td>2400</td>
<td>0</td>
<td></td>
<td></td>
<td>8,100 1,200</td>
<td>+</td>
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<td>Case 4</td>
<td>200–100</td>
<td>5</td>
<td>1800</td>
<td>0</td>
<td>0</td>
<td></td>
<td>7,200 5,900</td>
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<tr>
<td>Chronic lymphatic leukemia</td>
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<td>Case 5</td>
<td>100–600</td>
<td>13</td>
<td>2500</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>39,000 12,000</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Lymphosarcoma</td>
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<td>Case 6</td>
<td>400</td>
<td>4</td>
<td>1600</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>13,000 12,200</td>
<td>+</td>
<td>+</td>
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examination after therapy with 8-azaguanine did not show parallel improvement in the marrow components. Two patients (cases 1 and 2) developed a brief period of clinical improvement as evidenced by decrease in temperature to normal and increase in appetite and strength.

**Lymphomas**

The patient with chronic lymphatic leukemia (case 5) and the patient with lymphosarcoma (case 6) responded to treatment with regression in size of enlarged lymph nodes, spleen, and liver, but no effect was noted upon the hematological status, and clinical improvement was slight.

**Case Reports**

**Case 1**

A 5 year old white female was admitted to the New York Hospital on May 11, 1953; a diagnosis of acute leukemia was made. She was treated with ACTH and cortisone with no improvement in her condition. 6-mercaptopurine was given and clinical and partial hematological remission was induced for a period of several months. In December relapse occurred and Amethopterin was given to the patient for a period of one month, but no improvement was noted. On January 18, 1954, the spleen was 10 cm. below the costal margin, and the liver was 4 cm. below the costal margin. Therapy with 6-mercaptopurine was re-instituted for a period of ten days without further improvement. The total white blood cell count and blast percentage remained unchanged, and on February 23rd, the total leukocyte count was 119,000 per cu. mm. with a differential count of 98 per cent blasts and 4 per cent polymorphonuclear neutrophils.

From February 24th through February 26th, 8-azaguanine in a dose of 25 mg. daily was given to the patient. There was rapid decrease in the leukocyte count (fig. 1), the liver decreased in size so that it was just palpable at the costal margin, and the spleen also decreased to one-half its former size. She was given 50 mg. of 8-azaguanine on February 27th and March 1st. The patient became afebrile and was clinically improved. The dosage of 8-azaguanine was increased to 100 mg. on March 2nd, 300 mg. daily on March 3rd through March 9th, 500 mg. on March 12th and March 14th, 1000 mg. on March 17th and March 19th. On March 5th, 6-mercaptopurine in a dose of 50 mg. daily had been inadvertently added to the azaguanine therapy, but only after shrinkage of the liver and spleen and decrease in the leukocyte count had occurred. On March 22nd, the leukocyte count was 10,100 per cu. mm. and the differential count showed 4 per cent blasts, 24 per cent polymorphonuclear neutrophils, and 72 per cent lymphocytes, but bone marrow examination showed complete replacement by leukemic infiltration. On March 23rd, she developed a sudden shock-like state and expired.

Autopsy examination revealed large pulmonary infaracts, the source of which were not determined. In addition, there were leukemic infiltrates in the liver, spleen and bone marrow.

**Case 2**

A 63 year old white male was admitted to Maimonides Hospital on January 20, 1954. Examination revealed generalized lymphadenopathy, the liver palpable 9 cm. and the spleen palpable 6 cm. below the costal margin.

Hematological examination: Hemoglobin 8.2 Gm. percent; red blood count 2.7 million per cu. mm.; leukocyte count 38,000 per cu. mm. Differential: 60 per cent blasts; 8 per cent metamyelocytes, 15 per cent myelocytes, 4 per cent polymorphonuclear leukocytes, 9 per cent lymphocytes, 4 per cent monocytes. A bone marrow smear showed 75 per cent myeloblasts.

8-azaguanine, in a dose of 400 mg., was given to the patient on February 1st and the following day the enlarged lymph nodes, liver and spleen were smaller in size. He was given
600 mg. of 8-azaguanine on February 2nd through February 4th. The spleen was no longer palpable; the liver was 2 cm. below the costal margin, and the previously enlarged lymph nodes were barely palpable (figs. 2, 3, 4).

On February 5th, because of severe nausea and vomiting, 8-azaguanine was discontinued for a period of three days. The leukocyte count was 2,450 per cu. mm. at this time. A blood transfusion of 1000 cc. of whole blood was given because of anemia.

On February 8th through February 10th. The leukocyte count had fallen to a level of 1,850 per cu. mm. but therapy was again discontinued for a period of several days because of the return of nausea.

The white blood cell count began to rise so that on February 18th it was 18,250 per cu. mm. and on February 19th, it had risen to a level of 32,100 per cu. mm. Treatment was re-instituted and the patient received 100 mg. 8-azaguanine beginning on February 18th and continuing through February 26th. On February 26th, the leukocyte count was 6,000 per cu. mm. and the differential showed 18 per cent blasts, 2 per cent myelocytes, 5 per cent metamyelocytes, 19 per cent juvenile polymorphonuclear neutrophils, 25 per cent polymorphonuclear neutrophils, 27 per cent lymphocytes and 4 per cent monocytes. The platelet count was 175,000. Bone marrow examination showed 75 per cent myeloblasts. The dosage of 8-azaguanine was reduced to 100 mg. on alternate days from February 28th through March 6th.

On March 8th, the leukocyte count was 2,500 per cu. mm. with a differential of 56 per cent blasts, 6 per cent myelocytes, 10 per cent juvenile polymorphonuclear neutrophils, 4 per cent polymorphonuclear neutrophils, and 24 per cent lymphocytes.

8-azaguanine dosage was increased to 200 mg. daily for a period of eight days but was again discontinued because of the development of a dermatitis on March 15th. Hematological examination on March 15th showed: Hemoglobin 4.1 Gm. per cent; red blood count 1.3 million per cu. mm.; white blood count 2,100 per cu. mm.; blasts 18 per cent, 2 per cent myelocytes, 6 per cent metamyelocytes, 46 per cent polymorphonuclear neutrophils, 28 per cent lymphocytes.

After the discontinuance of 8-azaguanine on March 15th, the leukocyte count rose to a value of 88,000 per cu. mm. and the differential showed 65 per cent blasts, 16 per cent metamyelocytes, 13 per cent myelocytes, 3 per cent polymorphonuclear neutrophils, and 3 per cent lymphocytes.

On April 1st, therapy with 6-mercaptopurine was begun but no improvement appeared and the patient expired.

At autopsy there were leukemic infiltrates of the liver, spleen and lymph nodes.

Case 3

A 20 year old male patient was admitted to Maimonides Hospital on October 9, 1953 for treatment of acute leukemia. Bone marrow examination showed innumerable myeloblasts and the diagnosis of acute myeloblastic leukemia was confirmed.

The patient was treated with 6-mercaptopurine and Amethopterin with a temporary decrease in the total leukocyte count but with no clinical improvement. He was then given cortisone with a good clinical response and with hematological improvement, as evidenced by elevation of hemoglobin and red blood cell levels but with no effect upon the blast percentage in the peripheral blood. Hematological examination on March 4th: Hemoglobin 11.2 Gm. per cent, red blood count 3.5 million per cu. mm., leukocyte count 16,400 per cu. mm. Differential showed 90 per cent blasts, 16 per cent metamyelocytes, 13 per cent myelocytes, 3 per cent polymorphonuclear neutrophils, and 3 per cent lymphocytes.

In addition to cortisone, 8-azaguanine in a dose of 400 mg. was given on March 9th through March 11th and 600 mg. on March 12th. The next day the patient complained of nausea and skin flushes. 8-azaguanine was discontinued but three days later a morbiliform, erythematous, hemorrhagic eruption appeared over the entire body. This dermatitis disappeared after about one week.

Hematological examination during the period of therapy showed no changes in the
hematocrit, red blood count, or platelet count, but there was a decrease in the total leukocyte count and blast percentage of the differential count, so that on March 26th, the leukocyte count was 1,600 per cu. mm. and the differential count showed 20 per cent blasts, 14 per cent neutrophils, 34 per cent polymorphonuclear leukocytes and 32 per cent lymphocytes.

The patient developed a pyocyanous septicemia and expired on April 2nd, 1954. At autopsy, examination of the liver, spleen, lymph nodes and bone marrow revealed leukemic infiltration.

Case 4

A 20 year old Negro female was admitted to the Maimonides Hospital for treatment of acute leukemia.

On admission there was generalized lymphadenopathy, but hepatosplenomegaly was not noted. Examination of the peripheral blood and of the bone marrow showed innumerable blasts and was consistent with the diagnosis of acute leukemia.

The patient was given a 400 mg. dose of 8-azaguanine on February 19th, and 20th, 200 mg. on February 21st and 400 mg. on February 22nd, and 25th. Following the second dose of 8-azaguanine, she complained of pain and tenderness in the enlarged lymph nodes and after the third injection, the nodes were smaller, but the pain and tenderness persisted. After the fifth dose of 8-azaguanine, severe nausea and vomiting appeared and a diffuse erythematous papular dermatitis was present over the extremities and trunk, necessitating cessation of therapy. No change in the peripheral blood status occurred which could be attributed to treatment.

Following discontinuance of 8-azaguanine, the skin rash disappeared and the nausea and vomiting ceased. Subsequently, Amethopterin given to the point of toxicity and also large doses of mercaptopurine did not alter the clinical course or hematological status of this patient.

Case 5

A 72 year old white female, in whom a diagnosis of lymphosarcoma had been made by lymph node biopsy, was admitted to the Maimonides Hospital because of anemia and hemorrhagic episodes.

Physical examination revealed numerous ecchymoses and petechiae scattered over the body, generalized lymphadenopathy, the liver palpable 5 cm. below the costal margin and the spleen enlarged 9 cm. below the costal margin.

Examination of peripheral blood and bone marrow showed changes consistent with the diagnosis of chronic lymphocytic leukemia.

The patient received a 400 mg. dose of 8-azaguanine on February 23rd, 600 mg. on February 24th and 25th, 400 mg. on February 28th, 200 mg. on March 4th, and 100 mg. daily on March 5th through March 7th.

On February 27th, the spleen had become just palpable at the costal margin, and the liver was now only 2 cm. below the costal margin.

Nausea, vomiting and malaise appeared, and the 8-azaguanine was discontinued on March 8th. Subsequently, the spleen enlarged to 4 cm. below the costal margin but did not return to pre-treatment size. Cortisone was given, but it did not appear to affect the course of the patient's disease and she expired on May 3rd, 1954.

During the period of 8-azaguanine therapy, there was no change in the peripheral blood values attributable to the drug.

Case 6

A 70 year old white female was admitted to the Maimonides Hospital because of weight loss and weakness of six months' duration.

Examination revealed generalized lymphadenopathy, a spleen enlarged to 7 cm. below the costal margin and the liver palpable 6 cm. below the costal margin.

A lymph node biopsy was reported as being consistent with the diagnosis of lymphosarcoma.
Examination of the peripheral blood and bone marrow showed normal findings.

The patient was given 8-azaguanine in a daily dosage of 400 mg. on March 31st through April 3rd. On the second day of treatment, the liver and spleen had decreased to about half the pre-treatment size and the lymph nodes were also reduced in size, some being no longer palpable. On the fifth day of treatment, a diffuse erythematous dermatitis appeared over the body and the 8-azaguanine was discontinued, following which the dermatitis disappeared in about one week.

Repeated examinations of the peripheral blood during and after therapy showed no changes which could be attributed to the treatment. The patient was then treated with nitrogen mustard, (methyl-bis-beta-chloro-ethylamine), without further improvement.

**Undesirable Reactions**

Five of the six patients in this group developed nausea or vomiting and also a generalized dermatitis, characterized by a maculopapular, hemorrhagic eruption, which, in three instances, proceeded to desquamation. Case 3 received cortisone prior to and during therapy with 8-azaguanine, but this did not prevent the development of the dermatitis.

**Discussion**

The response of three of the four patients with acute leukemia and the two patients with lymphomata to the administration of 8-azaguanine is of interest as this is the first reported observation of an inhibitory effect of 8-azaguanine upon human neoplasms.

The response of the patients with acute leukemia differed from the response seen in the patients with the lymphoid diseases. In the patients with acute leukemia, there was a suppressive effect upon the leukocytic cells and associated shrinkage of enlarged liver, spleen, and lymph nodes. This response occurred very rapidly and appeared to be almost specific in effect upon the abnormal leukocytes. In the two patients with lymphomata, there was no effect upon the leukocytic cells despite the rapid shrinkage of the enlarged lymphoid organs. This lack of effect upon the leukocytes, in these patients, parallels the lack of effect upon the leukocytes in non-leukemic patients who received doses of 8-azaguanine as large or larger than those given to the patients with acute leukemia. This would appear to indicate that leukemic cells are more sensitive to 8-azaguanine than their normal counterparts.

The response to 8-azaguanine of two of the patients who had previously become resistant to treatment with Amethopterin and 6-mercaptopurine is of interest as it would appear from this observation that 8-azaguanine affects the leukemic cells in a different metabolic pathway from these compounds.

It has been demonstrated that many resistant tumors in the experimental animal contain an enzyme capable of deaminating 8-azaguanine to 8-azaxanthine. Glioblastoma multiforme contains little of the deaminating enzyme and is suppressed by 8-azaguanine in tissue culture but has not been affected by 8-azaguanine in clinical studies. This may be due to the presence in normal tissues of enough deaminating enzyme to rapidly inactivate the 8-azaguanine. It may be assumed that 8-azaguanine, in the dosage employed in the leukemic patients, either affects the leukemic cells before being converted to 8-azaxanthine or that 8-azaxanthine has antileukemic activity in humans. This latter premise is not likely.
Once the 8-azaguanine has been incorporated into the nucleic acids or the essential enzyme systems of the abnormal cells, further metabolic processes could be interfered with by this unnatural purine and might result in inhibition of growth of the abnormal cells.

Since normal leukocytes in the human have not shown evidence of inhibition by doses of 8-azaguanine as large or larger than doses causing suppression of cells in the leukemic patients, then comparison of the rate and quantity of incorporation of 8-azaguanine into human leukemic cells and normal leukocytes would be of interest, as would studies to determine the presence or absence of azaguanine deaminating enzymes in the normal and abnormal leukocytes.

Numerous investigators have demonstrated that there is synergistic activity between chemotherapeutic agents in the treatment of experimental neoplasms. Shapiro and Dietrich have demonstrated that some pteridine compounds may inhibit the enzyme which converts 8-azaguanine to 8-azaxanthine. They have also shown that combination therapy of experimental animal tumors with 8-azaguanine and these guanase inhibitors may enhance the carcinostatic effect of 8-azaguanine, presumably by blocking the conversion of 8-azaguanine to 8-azaxanthine.

Investigations of the effects of combinations of guanase inhibitors and 8-azaguanine and other antileukemic drugs and 8-azaguanine in treatment of human leukemia are warranted. The total dosage of 8-azaguanine necessary to produce an inhibiting effect upon human leukemia may be lessened when it is used in combination with these other drugs. Simultaneously, with reduction of the dosage level, many of the undesirable reactions of 8-azaguanine may be abolished or decreased in severity.

Conclusions

8-azaguanine exhibited a marked retarding effect upon the leukemic process in three of four patients with acute leukemia. In one patient with chronic lymphatic leukemia and in one patient with lymphosarcoma, regression of lymphadenopathy and hepatosplenomegaly resulted, but no change in the hematologic status occurred.

Undesirable dermatological reactions and development of nausea and vomiting have limited the amount of this drug that can be administered to the individual patient. Cortisone administered concomitantly with 8-azaguanine did not prevent occurrence of the dermatitis.

A study of the effect of combinations of 8-azaguanine with other antineoplastic drugs or with guanase inhibitors in the treatment of human leukemia is warranted.

Summario e Conclusiones in Interlingua

In recente aminos numerose compositos que impedi le utilisatiomi normal del metabolitos ha essite investigate in re lor effectos super varie maligne neoplasmas tanto in animales experimental como etiam in humanos. 8-azaguanina ha causate le retardation del crescentia de certe transplantabile tumores in animales, sed nulle inhibition del crescentia de neoplasmas human ha essite observate como resultato de su administration. Le presente reporto es concernite con le effectos de 8-azaguanina super leucemia human.
In tres inter quatro pacientes de acute leucemia 8-azaguanina havia un
marcate efecto retardative super le processo leucemic. In un paciente con
chronic lymphatic leucemia e in un altre con lymphosarcoma, le efecto esseva
un regression del lymphadenopathia e del hepatosplenomegalia sed nulle cam-
biamo in le stato hematologic.

Indesirabile reactiones dermatologic e le disveloppamento de nausea e vomito
impone un limite al quantitate de iste droga que pote esser administrate al
patiente individual. Cortisona administrate simultaneemente
imposite esser investigate le effectos que resulta del uso, in le tractamento de
Indesirabile reactiones dermatologic e le disveloppamento de nausea e vomito

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