USE OF ALLOPURINOL IN PREVENTING HYPERURICEMIA IN LEUKEMIA AND LYMPHOMA

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The treatment of leukemia and lymphoma with cytotoxic agents often leads to the overproduction of uric acid due to the rapid breakdown of cellular nucleic acids. This may result in precipitation of uric acid in the urinary tract with severe, sometimes fatal, urinary obstruction. The methods previously available to prevent or treat this complication have not always been adequate. Allopurinol [4-hydroxypyrazolo (3,4-d) pyrimidine] is an inhibitor of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine and xanthine to uric acid. In man it causes marked inhibition of uric acid production with a decrease in serum and urine uric acid. It has been used in 75 patients with leukemia or lymphoma treated with cytotoxic agents and has consistently prevented or reversed hyperuricemia. No uric acid nephropathy has occurred in this group of patients and allopurinol has caused no significant toxicity. The accumulation of the oxypurines, hypoxanthine and xanthine has been much smaller than the decrease in production of uric acid and no evidence of urinary precipitation of these oxypurines has been seen. The author concludes that allopurinol is an effective and useful agent in reducing the hazard of uric acid nephropathy in patients with leukemias and lymphomas in whom rapid lysis of cells may be expected as a result of therapy.

THAT MARKED ELEVATION OF SERUM URIC acid levels may occur in association with leukemia and lymphoma has been known for almost 100 years.[16] Since the advent of successful methods of destroying tumor cells, hyperuricemia has occurred more frequently and several authors[7, 8, 11, 12, 18] have noted the occurrence of uric acid nephropathy as a complication of the treatment of leukemia and lymphoma. The destruction of neoplastic cells may be followed by liberation of nucleic acid purines and the oxidation of those purines to uric acid which is an end product of purine metabolism in man. It is poorly soluble and, when present in high concentrations in the serum, it can precipitate in the urinary tract with severe, sometimes fatal, urinary obstruction.

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Allopurinol (4-hydroxypyrazolo (3,4-d) pyrimidine), an isomer of hypoxanthine, is one of several purine analogs which Elion et al.[23] found to inhibit xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine to uric acid. In man allopurinol causes marked inhibition of uric acid production, with a decrease in serum and urine uric acid.[15] Several investigators[14, 20] have studied allopurinol in the treatment of gout, concluding that it is an effective measure in the treatment of chronic tophaceous gout and in at least some instances in the management of inter critical gout.

The present study was designed to determine the value of allopurinol in preventing the marked hyperuricemia often seen in patients with leukemia and lymphoma in whom uric acid nephropathy had developed or was considered to be a potential hazard. A previous report[10] described the effects of allopurinol in the first 15 patients of that type to be treated in this center.

MATERIALS AND METHODS

Allopurinol has been administered to date to more than 100 patients with established

diagnoses of advanced neoplastic diseases, principally leukemia or lymphoma, who were hospitalized in Memorial or James Ewing Hospital. In the initial studies daily complete urine collections were made and the urine was analyzed for uric acid and non-uric-acid oxypurines. As experience with the use of allopurinol was gained, serial observations were made of serum uric acid and blood urea nitrogen levels but it was not deemed necessary to measure urinary uric acid and non-uric-acid oxypurines in each patient.

Serum uric acid determinations were performed by the colorimetric method of Archibald.[4] Urine uric acid was measured by ultraviolet spectrophotometry using the method of Dubbs, Davis and Adams.[1] In selected urine specimens total non-uric-acid oxypurines were determined by measuring the increase in absorbance at 292 mμ after treatment with xanthine oxidase. This procedure has been described in detail in a previous report.[10]

Allopurinol was given orally in 100 mg tablets in doses of 100 to 200 mg 3 or 4 times daily. Specific chemotherapy or radiotherapy was given as shown in Table 1.

RESULTS

The oral administration of 300 to 800 mg daily of allopurinol produced a decrease in serum uric acid in all but one patient* and a fall in urine uric acid in those patients in whom that measurement was made. When a patient responded to specific chemotherapy or radiotherapy while being treated with allopurinol the serum and urine uric acid levels continued to fall even though there was, in some cases a marked decrease in leukemic or lymphomatous cells. Urinary oxypurines were increased during the administration of allopurinol but to a much lesser extent than the decrease in urine uric acid.

CASE REPORT

M.G., a 16-year-old girl, was admitted to James Ewing Hospital with splenomegaly and pallor. The hematologic findings were characteristic of chronic granulocytic leukemia with an average total WBC of approximately 175,000. Her serum uric acid was 5.6 mg/100 ml and her mean daily urinary uric acid 674 mg. Urinary oxypurines averaged 10 mg daily. Treatment was started with allopurinol and on the fifth day she was given x-ray therapy to the spleen, 300 rads midplane dose. This resulted in a fall in WBC to 24,200 and a decrease in spleen size from 17 to 10 cm below the costal margin during the next 2 weeks.

In spite of that marked lysis of leukemic cells her serum uric acid fell to a mean of 2 mg/100 ml and her daily urine uric acid to 218 mg. The urinary oxypurines rose to an average of 230 mg daily. She was discharged 2 weeks following the radiotherapy and followed in the outpatient department. There was continued regression of the spleen and further fall of the WBC to 6,000. Allopurinol was discontinued 3 weeks after her discharge from the hospital when her WBC appeared to have stabilized at a normal level (Fig. 1).

DISCUSSION

The occurrence of marked hyperuricemia and uric acid nephropathy may be more frequent than commonly is realized. In a review of more than 200 patients with all kinds of leukemia who died on the Chemotherapy Service of Memorial and James Ewing Hospitals between 1956 and 1960[10] that nearly 25% had serum uric acid levels of more than 12 mg/100 ml at some time during the course of the disease. Uric acid lithiasis and uric acid gravel occurred commonly in this group of patients and, in at least 4, uric acid nephropathy with urinary obstruction was a direct or contributing cause of death. Several methods have been used in an attempt to avoid this problem. These include:

1. Cautious institution of therapy with x-rays or drugs in those patients whose disease might be very sensitive to these measures;

2. Vigorous administration of fluids to dilute the excreted uric acid in as large a urine volume as possible;

3. Administration of alkali or acetazolamide in an attempt to alkalinize the urine, thus increasing the solubility of uric acid;

4. Hemodialysis using an artificial kidney to remove uric acid from the blood in

* The single exception was a patient with renal insufficiency and intestinal obstruction which leads to doubt about the absorption of the allopurinol and about possible alteration in extrarenal disposition of uric acid in that patient.

TABLE 1. Patients Treated with Allopurinol

Patient	Age (yr.)	Sex	Diagnosis	Serum uric acid: Before allopurinol	Serum uric acid: During allopurinol	Other therapy	Comment*
H.W.	44	M	Hepatoma	14.7	11.6	X-ray to liver	Died 4 days after starting
M.G.	16	F	Chronic granulocytic leukemia	5.6	1.3	X-ray to spleen 300 R	WBC 180 → 21 Spleen 15 cm → 10
C.M.	63	F	Multiple myeloma	13.5	1.9	Prednisone	No response
S.F.	18	M	Acute leukemia	11.9	2.3	Prednisone	WBC 86.0 → 1.3, partial remission
M.N.	54	F	Polycythemia vera	8.5	2.5	None	Secondary gout, exacerbation with start of allopurinol
T.C.	26	M	Acute leukemia	10.8	4.0	Prednisone	Leukopenia throughout; marrow remission
L.M.	80	F	Endometrial ca	13.2	10.4	None	Allopurinol given for only 2 days
G.B.	48	F	Ca stomach	12.4	3.7	BrMeOFUdR	BUN 32 → 7
F.G.	22	M	Acute leukemia	15.3	4.4	Daunomycin, x-ray	No antitumor effect
M.S.	67	F	Multiple myeloma	23.1	16.2	Prednisone	Died of disease 12 days after start of therapy
S.H.	59	M	Chronic pyelonephritis, gout	11.4	5.9	Colchicine	No improvement in uremia
S.B.	60	M	Reticulum cell leukemia	10.4	8.7	Cytosine arabinoside, prednisone	WBC 65 → 1.6
R.C.	26	M	Hodgkin's disease	9.4	3.1	Prednisone, thio-TEPA	No clinical response
G.S.	64	F	Chronic lymphocytic leukemia	14.8	4.4	None	No clinical response
				18.9	3.2	prednisone, x-ray	No clinical response
A.S.	51	M	Chronic granulocytic leukemia	9.1	3.1	No therapy during this period	
S.D.	60	F	Gout	8.4	5.5	None	Gradual decrease in tophi
J.G.	72	M	Hodgkin's disease	12.3	5.5	None	Died 20 days later of resp. insufficiency
L.D.	57	M	Lymphosarcoma	11.3	4.6	Methylhydrazine	Leukopenia
L.S.	63	F	Ca colon	23			Died on first day of allopurinol
H.M.	73	F	Lymphosarcoma	9.2	3.3	Cyclophosphamide	Decrease in nodes
A.W.	79	F	Lymphosarcoma	19.3	5.7	X-ray	Decrease in tumor mass
H.D.	57	M	Chronic lymphocytic leukemia	8.3	4.0	X-ray, prednisone	Decrease in nodes
G.Z.	69	F	Chronic lymphocytic leukemia	12.3	4.2	X-ray, periaortic nodes	WBC 220 → 42
B.L.	59	F	Ca breast	6.4	1.7	Methotrexate	Mild rash
J.C.	58	M	Lymphosarcoma	9.8	3.4	Vincristine, prednisone	No response to therapy
W.G.	63	F	Chronic granulocytic leukemia	11.1	3.3	No specific therapy	Uric acid urolithiasis
L.S.	58	F	Ca breast	7.7	3.2		Allopurinol given for metabolic study
H.B.	36	F	Acute leukemia	11.7	2.8	Prednisone, x-ray, vincristine	No response
S.P.	62	M	Acute myelocytic leukemia	10.1	2.9	Cytosine arabinoside, x-ray to neck	No response
H.Z.	54	M	Primary gout	12.9	5.9	None	Good control
F.S.	44	F	Lymphosarcoma	12.8	2.3	X-ray to abdomen	Decrease in abdominal mass
S.C.	14	F	Lymphosarcoma	8.6	2.1	X-ray to mediast., thio-TEPA	Decrease in mediastinal mass
N.L.	66	M	Lymphosarcoma	9.6	4.0	X-ray to abdomen	Decrease in abdominal nodes
M.S.	69	F	Lymphosarcoma	9.2	6.1	Prednisone	No response
L.L.	49	F	Lymphosarcoma	14.0	1.9	Vincristine, x-ray to mediastinum	Subjective improvement
A.L.	75	F	Reticulum cell sarcoma	11.1	4.5	X-ray to neck and abdomen, cyclophosphamide	No response

TABLE 1. (*Continued*)

Patient	Age (yr.)	Sex	Diagnosis	Serum uric acid: Before allopurinol	Serum uric acid: During allopurinol	Other therapy	Comment*
C.C.	64	F	Hodgkin's disease	8.0	4.4	Nitrogen mustard	Decrease in nodes
E.M.	60	F	Reticulum cell sarcoma	10.6	3.5	X-ray to chest, vincristine	No response
M.G.	59	M	Reticulum cell sarcoma	15.6	4.4	X-ray to abdomen	Good response
J.D.	39	M	Reticulum cell sarcoma	18.3	8.6	Cyclophosphamide, x-ray to tumor mass	No response; died $\bar{p}$ 4 days allopurinol
M.G.	62	F	Ca colon	13.8	14.2	Supportive	Oliguria plus bowel obstruction
R.J.	45	M	Reticulum cell sarcoma	9.6	6.2	None during this time	
A.J.	67	F	Ca liver	12.6	5.5	X-ray to liver	Subjective improvement
				12.9	4.0	X-ray to liver	Subjective improvement
R.C.	49	F	Reticulum cell sarcoma	26.8	6.0	X-ray to neck and abdomen, vincristine	Maculopapular rash
G.B.	31	M	Reticulum cell sarcoma	10.1	4.3	Vincristine, x-ray to mediastinum	No response
A.H.	55	M	Ca bladder	16.8	6.0	X-ray to abdomen	No response (UA rise due to uremia, BUN 150)
B.U.	53	M	Ca liver	25.5	12.9		UA rise due to kidney disease, BUN 117
S.R.	62	F	Ca thyroid	9.3	4.5	Thio-TEPA, prednisone	No response
B.L.	78	M	Reticulum cell sarcoma	6.9	2.2	Cyclophosphamide, x-ray to periaortic nodes	Subjective improvement
J.C.	58	F	Lymphosarcoma	12.9	2.5	X-ray to abdomen	No response
M.W.	67	F	Acute lymphocytic leukemia	15.3	4.0	Methylhydrazine	No response
K.A.	53	F	Lymphosarcoma	7.6	Not done	X-ray to brain and abdomen, prednisone	No response; died $\bar{p}$ 4 days allopurinol
M.W.	54	F	Acute lymphocytic leukemia	18.0	4.0	X-ray to spine, 6-MP	WBC 103 → 5.6
D.M.	56	M	Melanoma	11.8	4.0	X-ray to abdomen	Decrease in abdominal nodes
J.B.	46	M	Chronic granulocytic leukemia	6.8	3.4	Thio-TEPA	WBC 166 → 94
A.G.	64	M	Reticulum cell sarcoma	18.0	12.0	None	Therapy with allopurinol for 3 days; died of uremia, not uric acid nephropathy
D.S.	43	M	Hodgkin's disease	20.4	Not done		Died 2nd day of allopurinol
C.M.	60	M	Reticulum cell sarcoma	8.5	3.2	Cyclophosphamide	Regression of nodes
F.P.	63	M	Chronic lymphocytic leukemia	8.4	3.4	Prednisone	Regression of nodes
J.T.	56	F	Reticulum cell sarcoma	12.8	4.0	Pelvic x-ray	Decrease in abdominal mass
				12.8	4.7	Vincristine, mediastinal x-ray	No response
E.K.	28	M	Hodgkin's disease	9.7	6.4	X-ray to abdomen and mediastinum	Lymph node regression
C.D.	64	M	Reticulum cell sarcoma	15.9	3.5	X-ray to abdomen, cyclophosphamide	No response
M.A.	70	M	Ca rectum, primary gout	14.7	4.7	Supportive	
M.N.	54	F	Ca lung	12.8	4.3	Thio-TEPA	No response
B.K.	52	F	Reticulum cell sarcoma	15.6	5.5	X-ray to abdomen	No response

TABLE 1. (*Continued*)

Patient	Age (yr.)	Sex	Diagnosis	Serum uric acid: Before allopurinol	Serum uric acid: During allopurinol	Other therapy	Comment*
W.L.	51	M	Reticulum cell sarcoma	11.8	2.3	Cyclophosphamide	Rash due to allopurinol; decrease in nodes
F.G.	36	M	Lymphosarcoma	11.8	3.5	Cyclophosphamide, prednisone, x-ray to abdomen	No response
A.A.	15	F	Acute lymphocytic leukemia	21.6	5.0	6-MP, vincristine, prednisone	WBC ↓ 203.0 → 1.0
M.B.	68	F	Reticulum cell sarcoma	20.8	8.3	Nitrogen mustard	No response
B.H.	59	M	Lymphosarcoma	21.9	3.9	X-ray to abdomen	Marked regression of intra-abdominal tumor
				8.5	3.5	Nitrogen mustard	No response
R.M.	44	M	Chronic granulocytic leukemia	11.6	3.0	X-ray to spleen, methylhydrazine	WBC 118.0 — 5.2
A.B.	58	M	Reticulum cell sarcoma	18.3	2.4	Thio-TEPA, prednisone	No response
L.S.	13	M	Acute leukemia	7.7	1.4	Vincristine SO_4, prednisone	WBC 0.9 → 60.0 → 0.7 mm^3, spleen 4 cm → 14 cm → 5 cm
G.T.	50	F	Lymphosarcoma	13.4	5.2	Nitrogen mustard, x-ray	Regression of nodes and ascites; rash
G.W.	67	F	Acute leukemia	14.7	4.3	Methylhydrazine	No response
E.S.	54	F	Acute leukemia	2.7	1.4	Ethylaminothidiazole	No response
C.C.	20	F	Acute leukemia	7.7	1.3	Vincristine SO_4, prednisone	WBC 358.0 → 3.0 spleen 19 cm → 2 cm
M.B.	13	M	Acute leukemia	9.2	2.2	Vincristine SO_4	WBC 258.0 → 1.2
G.S.	22	M	Chronic granulocytic leukemia	10.6	3.4	Busulfan	WBC 366.0 → 147.0 spleen 8 cm → 4 cm
M.H.	23	F	Chronic granulocytic leukemia	8.2	2.7	Thio-TEPA	WBC 110.0 → 24.0
A.S.	60	M	Lymphosarcoma	10.4	5.0	X-ray, nitrogen mustard	WBC 59.0 → 1.4; lymph nodes decreased
F.P.	76	M	Acute leukemia	20.0	4.6	FUdR	WBC 195.0 → 10.0
L.K.	23	M	Chronic granulocytic leukemia	7.6	3.0	Thio-TEPA	WBC 84.0 → 29.0 spleen 24 cm → 17 cm
D.T.	?	F	Myeloproliferative disease	20.1	3.5	Cyclophosphamide	WBC 160.0 → 11.4
O.B.	?	M	Ca stomach	7.8	3.1	None	None
M.H.	23	F	Chronic granulocytic leukemia	8.3	2.9	Thio-TEPA	WBC 126.0 → 10.0 spleen 22 cm → 14 cm
R.Z.	27	M	Acute leukemia	12.4	2.3	X-ray therapy, thio-TEPA	Regression of mediastinal mass
M.G.	12	M	Acute leukemia	8.4	1.5	Cyclophosphamide, prednisone	WBC 6.4 → 0.3
R.K.	7	F	Reticulum cell sarcoma	48.0	3.8	Cyclophosphamide	WBC 15 → 28.6 → 0.9
P.K.	10	F	Acute leukemia	15.8	1.7	Prednisone, vincristine	WBC 20 → 0.2
S.A.	5	F	Acute leukemia	19.2	2.4	Cytosine arabinoside, prednisone	No response
M.D.	7	M	Emb. rhabdomyosarcoma	18.3	2.9	Vincristine	No response
P.D.	4	M	Lymphosarcoma	4.7	2.1	None	WBC 7.7 → 1.8
T.W.	12	M	Rhabdomyosarcoma	15.3	3.0	X-ray	No response
R.D.	14	M	Reticulum cell sarcoma	12.3	1.83	Vincristine	WBC 11.8 → 5.6
F.C.	4	M	Wilms' tumor	7.8	1.15	Vincristine	No response
R.E.	3	F	Neuroblastoma	9.0	3.13	Vincristine, cyclophosphamide	WBC 18.9 → 22.6 → 1.8
P.S.	7	F	Ewing's sarcoma	7.6	5.5	Vincristine	No response
M.T.	2	M	Acute leukemia	9.3	0.8	Daunomycin, methotrexate, methyl prednisolone	WBC 1.4 → 0.2
D.V.	8	M	Lymphosarcoma	11.1	6.16	Prednisone, vincristine	WBC 9.7 → 13.8→ 0.2

TABLE 1. (*Continued*)

Patient	Age (yr.)	Sex	Diagnosis	Serum uric acid: Before allopurinol	Serum uric acid: During allopurinol	Other therapy	Comment*
D.M.	4	F	Acute lymphoblastic leukemia	11.4	5.35	6-mercaptopurine	WBC 71 → 134 → 85
R.F.	8	M	Emb. rhabdomyosarcoma	9.8	2.25	Vincristine, cyclophosphamide	No response
B.B.	8	F	Lymphosarcoma, acute leukemia	25.0	3.3	Daunomycin	WBC 52 → 102 → 0.4
S.D.	2	F	Lymphosarcoma	12.0	3.03	Methylhydrazine, prednisone, vincristine	No response
G.R.	3	M	Reticular cell sarcoma	9.0	5.4	Prednisone	No response
C.G.	16	M	Neuroblastoma	9.6	2.05	Daunomycin, prednisone, vincristine, cyclophosphamide	No response

those cases in which severe hyperuricemia already has developed.

Although these attempts to prevent or treat uric acid nephropathy can be successful, they are not invariably so and the clinical situations in which they are necessary are often so complex that the outcome may be unsatisfactory. The availability of a compound such as allopurinol which can prevent the formation of uric acid is a more nearly physiological method and a more effective one of preventing hyperuricemia. An additional benefit resulting from the availability of allopurinol appears to be that the decrease in hazard of uric acid nephropathy has encouraged a more vigorous approach to therapy when necessary.

The increase in urinary non-uric-acid oxypurines has been of smaller magnitude than the decrease in uric-acid excretion in those patients in whom these measurements were made. The single exception to this observation in this laboratory has been in the case of patients with chronic tophaceous gout in whom initially the sum of urinary uric acid plus non-uric-acid oxypurines matched the pretreatment urinary uric acid level.

TABLE 2. Solubilities of Purine Bases (mg/ml)

	Water 20C*	Water 20C†	Water 38C*	Urine 38C*
Uric acid	0.04	0.02	0.08	1.4
Xanthine	0.08	0.18	0.1	0.2
Hypoxanthine	0.60	0.70	1.2	1.3

* Determined in this laboratory, all at pH 7.
† From "Properties of the Nucleic Acid Derivatives," California Foundation for Biochemical Research, Los Angeles 1953.

This finding is similar to that reported by Klinenberg and his associates[6] in studies of a small series of patients with chronic tophaceous gout. Although it appeared at first that the difference in oxypurine excretion observed by these investigators may have been due to differences in methodology, it appears more likely at present that the lack of a deficit in oxypurine excretion in patients with tophaceous gout is due to the mobilization of uric acid from tophi during treatment with allopurinol. This maintains a high level of urinary uric acid, resulting in a sustained total oxypurine (uric acid + hypoxanthine + xanthine) excretion.

In gouty patients without tophi or in nongouty patients such as those reported in this study there has been a consistent deficit in oxypurine excretion. The cause of this deficit is still not certain.

The demonstration by Wyngaarden et al.[19] that the ribonucleotide of 4-hydroxypyrazolo (3,4-d) pyrimidine can produce some degree of feedback inhibition of de novo purine biosynthesis may be partly responsible for this deficit; however, this observation does not explain the deficit in this series of patients with leukemia and lymphoma in whom it has been believed that the overproduction of uric acid during cytolytic therapy is due to the degradation of nucleic acids, a mechanism in which feedback inhibition would not be expected to play a role.

Studies in animals[13] have shown that allopurinol can increase the incorporation of C^{14}-labeled hypoxanthine in tumor and liver ribonucleic acid and into tumor deoxyribonucleic acid. These observations may indicate

that allopurinol increases the reutilization of purines for nucleic acid synthesis.

The increase in excretion of hypoxanthine and xanthine in this group of patients led to an examination of the solubilities of these purines. As shown in Table 2, xanthine is somewhat less soluble than uric acid and hypoxanthine is similar to uric acid in its solubility. Both xanthine and hypoxanthine have been reported to be more rapidly cleared by the kidneys than uric acid.[5] This evidence, together with the consistently demonstrated deficit in oxypurine formation, indicates that the block in oxidation of hypoxanthine and xanthine is a favorable one, reducing the hazard of crystallization in the urinary tract of a poorly soluble purine.

Careful studies were done during the initial phase of this investigation for evidence of toxicity to the hematopoietic, gastro-intestinal, hepatic, renal, cardiopulmonary and central nervous systems, with no evidence of toxicity. Previous studies with a pyrazolo pyrimidine in this laboratory[9] and elsewhere[17] had shown 4-aminopyrazolo (3,4-d) pyrimidine to be extremely hepatotoxic. This compound, an isomer of adenine, had been studied as a potential cancer chemotherapeutic agent but its evaluation was curtailed because of its marked hepatotoxicity.

In contrast, 4-hydroxypyrazolo (3,4-d) pyrimidine which bears a similar relation to hypoxanthine (Fig. 2) has produced no toxicity in this series other than the occurrence in 3 patients of a moderately severe erythematous rash. This rash disappeared promply in each patient when therapy with allopurinol was discontinued.

Allopurinol blocks the usual degradative pathway of 6-mercaptopurine to 6-thiouric acid and, therefore, can produce a marked increase in biologic activity of mercaptopurine. This has not resulted in an increase in therapeutic index of 6-mercaptopurine but it can produce a marked increase in bone marrow toxicity; therefore, the dose of 6-mercaptopurine should be reduced to about 25% of the usual dose if both compounds are used together.

CONCLUSION

Allopurinol is a compound with low toxicity which is capable of causing a marked decrease in uric acid production in spite of prompt and marked tumor lysis with various

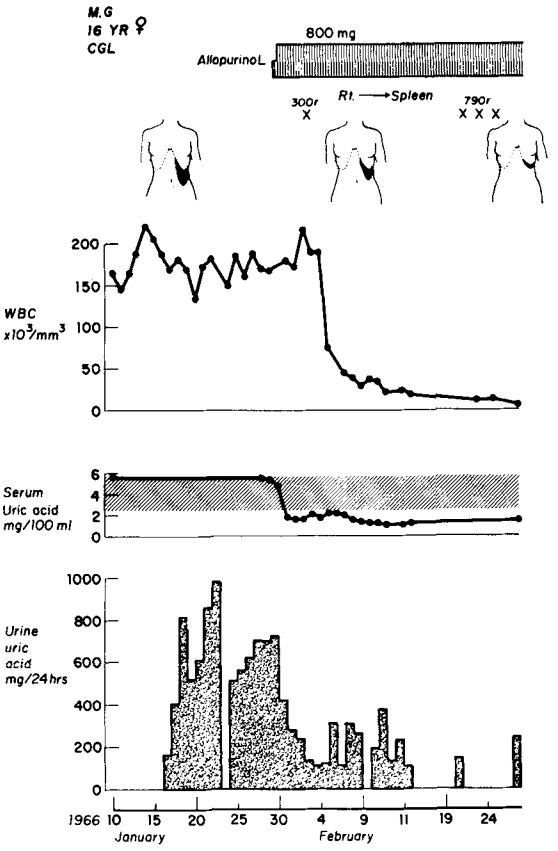

FIG. 1. Clinical course of M.G., a 16-year-old girl with chronic granulocytic leukemia, treated with splenic irradiation and allopurinol.

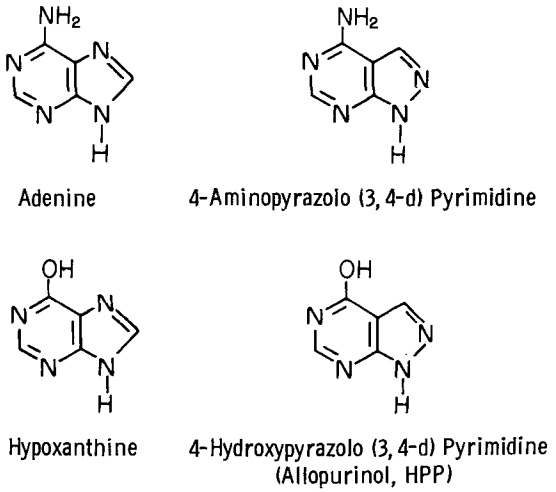

FIG. 2. Structural formulae of adenine and its isomer, 4-aminopyrazolo (3, 4-d) pyrimidine and hypoxanthine and its isomer, 4-hydroxypyrazolo (3, 4-d) pyrimidine (allopurinol).

chemotherapeutic agents and with x-ray therapy; therefore, it has proven to be an effective measure to reduce the hazard of uric acid nephropathy in patients with leukemias and lymphomas in whom rapid destruction of tumor cells can be expected to occur.

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