Review

Azathioprine: Association with Therapy-related Myelodysplastic Syndrome and Acute Myeloid Leukemia

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ABSTRACT. ***Objective.*** Azathioprine is widely used in patients with autoimmune diseases and after organ allografting. A recognized carcinogen, azathioprine is also associated with the development of therapy-related myelodysplastic syndrome and acute myeloid leukemia (t-MDS/AML).

Methods. In 56 reported cases, azathioprine had been administered for a median of 65 months (range 6–192) to a median cumulative dose of 146 g (range 19–750) before t-MDS/AML developed.

Results. In 11 patients, repeated episodes of cytopenias developed during azathioprine therapy, antedating the development of t-MDS/AML. In 33 cases with successful karyotypic analysis, 26 cases (79%) showed monosomy 7, deletion of the long arm of chromosomes 7 and 5, and rearrangement of chromosome 11q23. These changes were cytogenetic hallmarks of MDS/AML secondary to known leukemogenic agents and radiotherapy.

Conclusion. The observations implicate azathioprine as a leukemogenic agent. It will be prudent to review the need for azathioprine therapy when unexpected cytopenias occur and prescription has been prolonged. (First Release Jan 15 2010; J Rheumatol 2010;37:485–90; doi:10.3899/jrheum.090834)

Key Indexing Terms:
AZATHIOPRINE
ACUTE MYELOID LEUKEMIA
MYELODYSPLASTIC SYNDROME
CYTOGENETICS

Azathioprine is a thiopurine popularized in the 1960s as an immunosuppressive drug in renal allografting[1]. The efficacy of azathioprine as an immunosuppressant soon led to its application in rheumatologic diseases[2]. This was followed by an expansion of its indications to autoimmune blood diseases[3], inflammatory bowel disorders[4,5], and multiple sclerosis[6]. More than 4 decades since its initial use, azathioprine continues to be part of the treatment algorithms of these disorders.

Pharmacology and metabolism of azathioprine. Azathioprine, 6-mercaptopurine (6-MP), and 6-thioguanine (6-TG) constitute the thiopurine group of antimetabolites (Figure 1)[7]. Azathioprine is converted by glutathione to 6-MP[8]. 6-MP is converted by hypoxanthine phosphoribosyltransferase to thioinosine monophosphate (TIMP). TIMP is subsequently converted to thioguanosine monophosphate, which is then converted by deoxynucleotide kinases and reductase to deoxythioguanine 5' triphosphate, a substrate for DNA polymerase in DNA synthesis. Azathioprine is catabolized by 2 enzymes: xanthine oxidase, which converts 6-MP to 6-thiouric acid, and thiopurine methyltransferase (TPMT), which converts TIMP to methyl-TIMP.

The biologic effects of azathioprine may be affected by its catabolism. Allopurinol inhibits xanthine oxidase, and its administration increases the effective azathioprine dosage 4-fold. Polymorphic variants of the *TPMT* gene encode proteins with reduced activities. Heterozygotes for these variants require lower doses of azathioprine. Homozygotes may develop serious to fatal marrow toxicity after azathioprine administration[7].

Toxicity of azathioprine. In addition to problems associated with immunosuppression, azathioprine has other adverse effects. Azathioprine-induced pancreatitis is well known[9]. The use of azathioprine in inflammatory bowel diseases may be associated with hepatotoxicity[10,11].

The carcinogenic potential of azathioprine is not as well known. The International Agency for Research on Cancer classified azathioprine as a human carcinogen[12]. Malignancies attributed to azathioprine therapy are in general rare tumors[13], and during oncogenesis other co-carcinogenic factors, such as graft-vs-host disease after allogeneic hematopoietic stem cell transplantation, may be involved[14]. However, recent data have shown an association between

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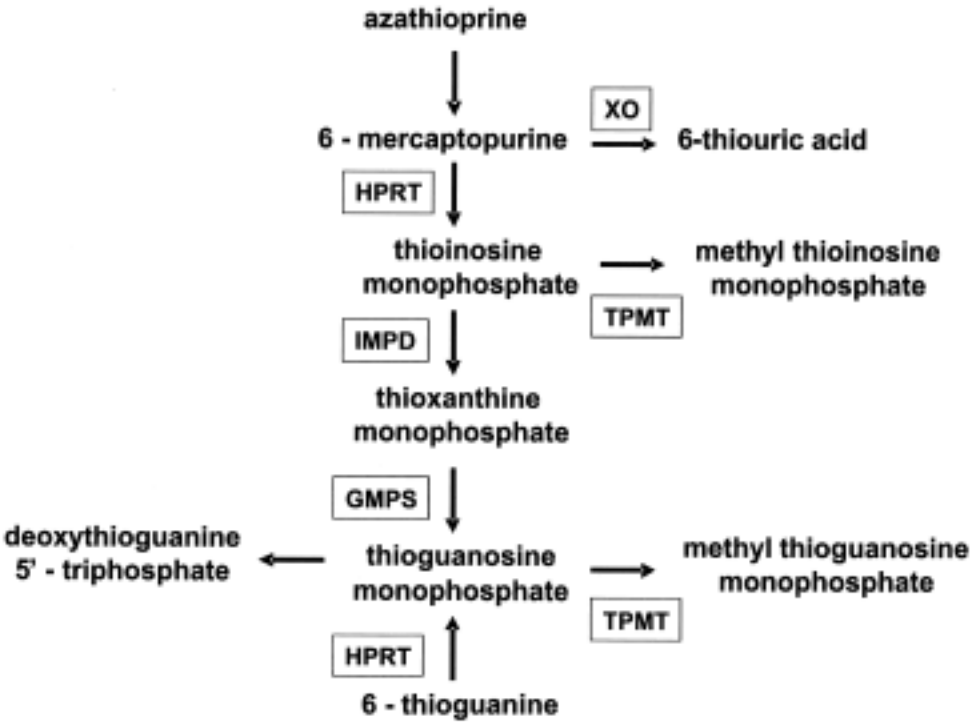

Figure 1. Metabolism of azathioprine and the other thiopurines. HPRT: hypoxanthine phosphoribosyltransferase; XO: xanthine oxidase; TPMT: thiopurine methyltransferase; IMPD: inosine monophosphate dehydrogenase; GMPS: guanine monophosphate synthetase.

azathioprine treatment and therapy-related myelodysplastic syndrome and acute myeloid leukemia (t-MDS/AML), a complication unknown to most prescribing physicians.

The development of t-MDS/AML when azathioprine is used to treat nonmalignant diseases is catastrophic. Therefore, the association between azathioprine and t-MDS/AML must be critically appraised, in order to define risk factors that may predispose patients to this fatal complication.

MATERIALS AND METHODS

English publications indexed in Medline were searched using the key words azathioprine, secondary, therapy-related, myelodysplasia, myelodysplastic syndrome, and acute myeloid leukemia. Articles with complete patient demographics, diagnosis, and treatment outcome were reviewed. References in these publications were also scrutinized to ensure that all relevant articles were included.

RESULTS

Patients. A total of 56 patients were identified[15-42]. Their characteristics are described in Table 1. Details for each patient are given in the Appendix. The underlying indications for azathioprine treatment were autoimmune diseases in half of the cases, and solid-organ allografting in the other half. Men and women were equally affected.

Azathioprine treatment. In organ allograft recipients, azathioprine was part of the triple therapy that included

Table 1. Characteristics of 56 patients with therapy-related myelodysplastic syndrome/acute myeloid leukemia, after azathioprine treatment.

Clinicopathologic Characteristics	No. (% of total)
Sex	
Men	28 (50)
Women	27 (48)
Not available	1
Median age (range), yrs	45 (19–74)
Indications for azathioprine	
Autoimmune diseases	27 (48)
Systemic lupus erythematosus	6
Rheumatoid arthritis	6
Multiple sclerosis	3
Primary chronic polyarthritis	3
Polymyositis	2
Wegener's granulomatosus	2
Crohn's disease	1
Psoriatic arthropathy	1
Dermatomyositis	1
Autoimmune hepatitis	1
Hypereosinophilia, vasculitis	1
Type of organ allograft	29 (52)
Kidney transplant	19
Heart transplant	7
Lung transplant	2
Liver transplant	1
Azathioprine treatment	
Median duration (range), mo	65 (6–192)
Median cumulative dose (range), g	146 (19–756)

cyclosporine and prednisolone. For the remaining patients, azathioprine was the only relevant medication in 25% (10/41) of cases. Five patients had received other medications, including cyclophosphamide (n = 4), gold (n = 2), penicillamine (n = 1), and levamisole (n = 1). Of all the medications accompanying azathioprine therapy, only cyclophosphamide is known to be potentially leukemogenic. The median duration of azathioprine therapy was 65 months (range 6–192), at a median cumulative dose of 146 g (range 19–750).

Hematologic toxicity of azathioprine. Of 27 cases where information on hematologic toxicity during azathioprine therapy was available, 11 patients developed cytopenias before the development of t-MDS/AML (Table 2). The presentation included anemia, leukopenia, thrombocytopenia, or their combinations. The cytopenias necessitated a reduction of dose or temporary cessation of azathioprine. However, in all cases azathioprine was readministered after the cytopenias recovered. Although the cytopenias were attributed to marrow toxicity of azathioprine, in 1 case it was associated with the concomitant use of allopurinol[33].

Table 2. Clinicopathologic features of 56 cases of therapy-related myelodysplastic syndrome/acute myeloid leukemia, after azathioprine treatment.

Features	No. (% of total)
Cytopenia preceding t-MDS/AML	
Not available	29 (51)
Nil	16 (29)
Present	11 (20)
Anemia	2
Leukopenia	2
Thrombocytopenia	1
Anemia and leukopenia	2
Leukopenia and thrombocytopenia	1
Pancytopenia	3
Hematologic diagnoses	
Acute myeloid leukemia	31 (55)
Myelodysplastic syndrome	25 (45)
Refractory anemia	3
Refractory anemia with ringed sideroblasts	2
Refractory cytopenia with multilineage dysplasia	2
Refractory anemia with excess of blasts	7
Refractory anemia with excess of blasts in transformation	3
Myelodysplastic syndrome progressing to acute myeloid leukemia	8
Karyotype	
Monosomy 7	15 (27)
Deletion of long arm of chromosome 7	7 (13)
Deletion of long arm of chromosome 5	2 (4)
Deletion of long arm of chromosomes 5 and 7	1 (2)
Deletion of long arm of chromosome 20	2 (4)
Aberration of chromosome 11q23	1 (2)
Inversion 16	1 (2)
Normal	2 (4)
Complex	2 (4)
Not available	23
Outcome	
Died of disease	37 (66)
Alive after treatment	12 (21)
Not available	7

t-MDS/AML. AML was the diagnosis in 55% of cases. For patients presenting with MDS, 18 (32%) had excessive leukemic blasts (refractory anemia with excess of blasts, refractory anemia with excess of blasts in transformation) or finally transformed into AML. Hence, 87% of patients presented with a leukemic disease. Only 13% of patients had MDS with a more chronic course (refractory anemia, refractory anemia with ringed sideroblasts, and refractory anemia with multilineage dysplasia).

Karyotypic aberrations. Cytogenetic analysis was performed in 33 cases. Aberrations of chromosome 7, either as monosomy 7 (absence of one of the homologues), or del(7q) (deletion of the long arm), were the predominant abnormalities, occurring in 22 cases (66%). Five other aberrations were found: del(5q) in 3 patients, del(20q) in 2, rearrangement of 11q23 in 1, inversion of chromosome 16 in 1, and complex (≥ 3 abnormalities) in 2. Two patients had normal cytogenetics.

Outcome. Treatment outcome was dismal, with 37 patients (66%) having died of disease at the time of reporting.

DISCUSSION

This review identified 56 cases of t-MDS/AML after azathioprine treatment. Although in 31 cases other medications had been used previously or concomitantly, most of the drugs, including cyclosporine, prednisolone, gold, penicillamine, and levamisole, were not known to be oncogenic. Cyclophosphamide was the only medication that might contribute to leukemogenesis, but it was used in just 4 cases. Therefore, azathioprine was the only medication that might be related to the leukemogenesis in the majority of cases.

The duration and cumulative dosages of azathioprine preceding t-MDS/AML were variable. For the cohort, a cumulative dose of 146 g (corresponding to a mean daily dosage of 75 mg) of azathioprine was prescribed and the median duration was 65 months before t-MDS/AML developed. Therefore, azathioprine apparently had to be given for a prolonged period before leukemogenesis occurred.

Although the association between azathioprine and t-MDS/AML appears strong, a causal relationship is more difficult to establish. An inherent risk of malignancies is increased in patients with autoimmune diseases[43] and organ allografts[44]. Chronic inflammation is an important disease component in these disorders. Inflammatory mediators including chemokines, cytokines, and prostaglandins affect numerous tissue and cellular functions, which may contribute to oncogenesis by promoting the growth and survival of transformed cells, increasing angiogenesis, or interfering with effective immunosurveillance[45]. The concomitant use of immunosuppressive drugs also impairs humoral and cel-

lular immune responses against neoplastic cells. Therefore, it is conceivable that these factors may play a co-carcinogenic role, collaborating with azathioprine in leukemogenesis. Another important observation indicating a leukemogenic role of azathioprine was the cytogenetic findings. In 22 patients, monosomy 7 and/or del(7q) was found. These abnormalities of chromosome 7 are highly characteristic of t-MDS/AML secondary to alkylator-based chemotherapy[46,47]. In 4 other cases, del(5q) and rearrangement of chromosome 11q23 were observed. These changes are also typical of t-MDS/AML secondary to leukemogenic agents such as topoisomerase inhibitors and radiotherapy[46-48]. Therefore, of 33 azathioprine-treated patients successfully karyotyped, 26 cases (79%) showed karyotypic aberrations typical of t-MDS/AML secondary to known leukemogenic agents. *In vitro* data have also suggested that azathioprine might select for mismatch repair deficient cells in the bone marrow. t-MDS/AML developing after azathioprine often showed mismatch repair deficiency, as reflected by microsatellite instability[49], again supporting a leukemogenic role of azathioprine. These observations strongly implicate azathioprine as a causative agent in t-MDS/AML.

It is unclear whether the occurrence of t-MDS/AML after azathioprine is dose/duration related, or associated with individual susceptibility. Given that a large number of patients receive azathioprine for various indications, and only a relatively limited number of patients develop t-MDS/AML, risk factors in addition to dose/duration may also be involved. Interestingly, of 27 patients where hematologic toxicity was documented, 11 (40%) of them had cytopenias preceding t-MDS/AML, often by years. The reasons for these cytopenias were not given and might be related to excessive doses of azathioprine. However, problems with azathioprine metabolism might be contributory. In 1 case, concomitant allopurinol was prescribed inadvertently, leading to repeated episodes of pancytopenia before t-MDS/AML finally supervened[33]. Further, genetic variants encoding for low-activity TPMT may lead to undue marrow toxicity when azathioprine is prescribed. It has been estimated that 10% of the population may have a single deficient gene, and 0.3% may be homozygously deficient[50]. Hence, genetic variants of TPMT, by increasing the effective dose of azathioprine, may enhance the genotoxicity of azathioprine and thus predispose to t-MDS/AML. Therefore, whether antecedent cytopenias during azathioprine treatment reflect genetic problems of drug metabolism and may be harbingers of t-MDS/AML will need to be studied. Unfortunately, none of the reported cases of t-MDS/AML after azathioprine treatment were investigated for possible genetic variants of TPMT.

Because a small but significant number of patients treated with azathioprine developed t-MDS/AML, which bears the genetic hallmarks characteristic of leukemogenic agents, precautions are required during azathioprine treatment. Concomitant allopurinol must be avoided. Routine testing for TPMT variants does not appear warranted[50]. However, when unexpected cytopenias develop, and if facilities are available, testing for TPMT variants may provide useful guidance for future dose adjustments. Finally, until more mechanistic data are available on the risk factors or susceptibility to t-MDS/AML in patients treated with azathioprine, it will be prudent to review the need for azathioprine when it has been prescribed for more than 5 years, or for a cumulative dose exceeding 140 g.

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APPENDIX

Supplementary table. Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) in 56 patients treated with azathioprine.

Case	Sex	Age, yrs	Primary Diagnosis	Azathioprine				Blood Disease	Karyotype	Outcome, mo	Reference
				Time, mo	Dose, g	Other Drugs	Cytopenia				
1	M	67	Rheumatoid arthritis	24	77	Cyclo, Pred	WBC, Plat	AML	NA	Dead, 2	15
2	M	32	Kidney transplant	34	153	Pred	Nil	AML	NA	Dead, 5	16
3	M	23	Autoimmune hepatitis	44	NA	Pred	Plat	AML	NA	Alive	
4	F	57	Rheumatoid arthritis	30	109	Au, Cyclo, Pred	NA	AML	NA	NA	17
5	M	68	Rheumatoid arthritis	65	255	Pred	NA	AML	NA	NA	
6	M	37	Kidney transplant	56	NA	Nil	NA	AML	NA	NA	18
7	F	38	Kidney transplant	57	NA	Nil	NA	AML	NA	NA	
8	M	23	Rheumatoid arthritis	10	52	Pred	Nil	AML	NA	Died, 2	19
9	F	73	Rheumatoid arthritis	36	92	Nil	Nil	RAEB	NA	Dead, 0.5	20
10	M	47	Kidney transplant	6	19	Nil	NA	AML	NA	NA	21
11	M	53	Kidney transplant	36	NA	Pred	Nil	RAEB → AML	Complex, del(5q)	Dead, 1	22
12	F	16	SLE	70	150	Nil	NA	AML	NA	NA	23
13	F	30	SLE	65	273	Pred	RBC, WBC, Plat	AML	NA	Dead, 3	24
14	M	34	Kidney transplant	78	390	Pred	RBC, WBC, Plat	AML	NA	Dead, 12	25
15	M	35	Kidney transplant	46	NA	Pred	RBC, WBC, Plat	RAEB	NA	Dead, 10	26
16	M	36	Kidney transplant	22	107	Pred	Plat	RAEB-T	Complex	Dead, 5	
17	F	36	Kidney transplant	54	200	Pred	Nil	RAEB-T	NA	Dead, 7	
18	M	22	Kidney transplant	84	290	Pred	Nil	RAEB-T	NA	Dead, 9	
19	F	24	Kidney transplant	108	NA	Nil	Nil	AML	Complex, –7	Dead, 9	27
20	M	52	Polymyositis	108	565	Nil	Nil	AML	Complex, del(5q), del(7q)	Dead, 2	28
21	F	72	Rheumatoid arthritis	86	260	Au, Pen, Lev	RBC, WBC	AML	del(7q)	Dead	29
22	F	19	Kidney transplant	72	127	Pred	Nil	RCMD	–7	Alive	30
23	F	41	Kidney transplant	156	NA	Pred	Nil	AML	Complex	Dead, 4	31
24	F	45	Kidney transplant	192	NA	Pred	RBC	AML	–7	Dead, 1	
25	M	39	Kidney transplant	NA	NA	CsA, Pred	Nil	AML	inv(16)	Alive, 11+	32
26	F	44	SLE	17	37	Cyclo, Allo	RBC, WBC	AML	–7	Dead, 2	33
27	F	41	SLE	84	89	Pred	WBC	AML	–7	Alive, 2+	
28	F	66	Dermatomyositis	24	109	Pred	WBC	AML	Complex, –7	Dead, 5	34
29	M	56	Lung transplant	NA	NA	CsA, Pred	Nil	AML	NA	Dead, 10	35
30	M	72	Liver transplant	NA	NA	CsA, Pred	Nil	AML	Normal	Dead, 1	
31	M	74	Kidney transplant	NA	NA	CsA, Pred	Nil	AML	t(9;11)(p21;q23)	Dead, 10	
32	M	59	Heart transplant	48	146	CsA, Pred	NA	AML	Complex, del(7q)	Dead, 1	36
33	M	54	Heart transplant	92	NA	CsA, Pred	NA	AML	NA	Dead, 1	
34	M	60	Heart transplant	32	72	CsA, Pred	NA	RAEB	–7	Alive, 32	
35	F	62	Heart transplant	67	96	CsA, Pred	NA	AML	NA	Dead, 8	
36	M	28	Heart transplant	66	124	CsA, Pred	NA	AML	Complex, –5, –7	Dead, 1	
37	NA	63	Heart transplant	132	400	Nil	Nil	RARS	Complex, del(7q), –17	Dead, 24	37
38	M	63	Primary chronic polyarthritis	24	108	NA	NA	RA → AML	Normal	Dead	38
39	M	49	Heart transplant	64	49	NA	NA	CMML → AML	Complex, del(7q)	Dead	
40	F	33	Polymyositis	72	520	NA	NA	CMML → AML	–7	Dead	
41	F	62	SLE	48	136	NA	NA	RAEB-T → AML	NA	Dead	
42	M	45	Kidney transplant	118	576	NA	NA	RA → AML	NA	Dead	
43	F	66	Psoriatic arthropathy	168	360	NA	NA	RAEB → AML	NA	Dead	
44	F	72	Wegener's granulomatosis	82	147	NA	NA	RA	del (5q)	Dead	
45	M	43	Primary chronic polyarthritis	168	379	NA	NA	RAEB	–7	Alive	
46	F	57	Wegener's granulomatosis	34	135	NA	NA	RA	Complex, –7	Dead	
47	M	42	Kidney transplant	84	756	NA	NA	RARS	–7	Dead	
48	F	46	Multiple sclerosis	96	146	NA	NA	RAEB	–7	Alive	
49	M	71	Primary chronic polyarthritis	24	27	NA	NA	RAEB	NA	Dead	
50	F	41	SLE	132	657	NA	NA	RAEB → AML	–7	Alive	
51	F	37	Multiple sclerosis	123	627	NA	NA	RAEB	Complex, del(7q)	Alive	
52	F	39	Multiple sclerosis	98	657	Nil	NA	AML	NA	Alive	39
53	F	48	Kidney transplant	53	480	CsA, Pred	RBC	RCMD	del(20q)	Alive, 100+	40
54	M	53	Lung transplant	15	45	CsA, Pred	Nil	RA	del(20q)	Alive, 14+	
55	F	64	Hypereosinophilia, vasculitis	36	263	Cyclo	Nil	AML	del(7q)	Dead, 1	41
56	F	21	Crohn's disease	36	109	Nil	Nil	AML	Complex, –7	Dead, 3	42

Time: total duration of treatment (months); cytopenia: types of cytopenia preceding development of MDS and AML; RAEB: refractory anemia with excess of blasts; RAEB-T: refractory anemia with excess of blasts in transformation; RA: refractory anemia; RARS: refractory anemia with ringed sideroblasts; RCMD: refractory cytopenia with multilineage dysplasia; CMML: chronic myelomonocytic leukemia; NA: not available; complex: 3 or more karyotypic aberrations; –7: monosomy 7; Pred: prednisolone, Au: gold; Pen: penicillamine; Lev: levamisole; CsA: cyclosporin A; Cyclo: cyclophosphamide; Allo: allopurinol; RBC: red blood cells; WBC: white blood cells; Plat: platelets.

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