

Teratogen Update: Azathioprine and 6-Mercaptopurine

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Azathioprine (AZA) and its active metabolite, 6-mercaptopurine (6-MP), are purine analogues that interfere with the synthesis of adenine and guanine ribonucleosides. These ribonucleosides are important precursors of DNA and RNA. Because AZA and 6-MP act predominantly on rapidly dividing cells such as the T lymphocytes, these drugs are not only cytotoxic but also immunosuppressive and anti-inflammatory. The effects are dose-related, small doses of either drug are anti-inflammatory, but larger doses are immunosuppressive and cytotoxic (Goldstein, '87).

6-MP has been used in cancer chemotherapy, primarily in childhood and adult leukemias and usually in combination with other drugs. 6-MP is also used to treat autoimmune diseases, such as inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) (Bermas and Hill, '95; Ramsey-Goldman and Schilling, '97). Initial oral doses for treatment of leukemia range between 2.5–5 mg/kg/d. For maintenance therapy of leukemia, doses range between 1.5–2.5 mg/kg/d. Similar doses (1.5–2.5 mg/kg/d) are used to treat IBD (Present et al., '80; Botoman et al., '98; USP DI, '01), but the use of 6-MP as an immunosuppressant has been largely superseded by AZA, which has been shown to possess a better therapeutic index (Van Scoik et al., '85; Goldstein, '87; Chabner et al., '96). AZA is no longer used as an antineoplastic agent (Østensen, '92), but is employed in the treatment of autoimmune disorders at doses between 1–2.5 mg/kg/d and at doses between 1–5 mg/kg/d as part of immunosuppressive regimens to prevent transplant rejection (Botoman et al., '98; USP DI, '01).

The majority of patients affected by autoimmune diseases are women, in whom the peak incidence occurs between 16 and 55 years of age (Weterman, '89; Brent et al., '97; Esplin and Branch, '97). Successful treatment with cytotoxic and immunosuppressant drugs such as AZA has greatly improved the feasibility of pregnancy in affected women, many of whom must continue to take the medications throughout gestation to prevent relapse. Similarly, women who become pregnant after organ transplantation continue immunosuppressive therapy to prevent rejection if they have been on immunosuppressive therapy before pregnancy. In

some patients who become ill with an immunopathic or malignant disease while pregnant, treatment with 6-MP or AZA may be initiated during gestation.

The use of cytotoxic immunosuppressants during pregnancy raises concern about possible adverse effects in the developing embryo or fetus, but the potential teratogenicity of AZA and 6-MP is difficult to evaluate in humans. These agents are used to treat patients who have severe illness, and it is often impossible to determine if adverse effects that occur in the embryo/fetus resulted from a particular treatment, the maternal illness, or some other factor (Brent et al., '97). Also, because of the severity of the illness and the complications that ensue, combination therapy is common. Use of drug combinations as well as variations in dose further hamper efforts to attribute an observed adverse effect to a particular treatment. This article will review human and animal data regarding the pharmacology of 6-MP and AZA and their adverse effects on the embryo and fetus.

METABOLISM AND PHARMACOLOGY

AZA and 6-MP are structurally very similar, differing only in that AZA has a methyl-nitro-imidazolyl group attached to the sulfur atom at the 6-position of the purine ring of 6-MP (Van Scoik et al., '85; Diasio and LoBuglio, '96). On the average, 47% of an orally-administered dose of AZA is available to the systemic circulation (Van Os et al., '96; Sandborn, '98). AZA is a prodrug that, after absorption, is extensively cleaved to 6-MP in the blood by the enzyme glutathione-S-transferase (Van Scoik et al., '85). More than 80% of AZA is converted to 6-MP (Sandborn, '98; Cuffari et al., '00). AZA may also be metabolized by the enzyme aldehyde oxidase to 8-hydroxyAZA, which in turn is converted to an inactive metabolite, 6-thiouric acid, by xanthine oxidase.

In contrast to AZA, the bioavailability of 6-MP is low and highly variable, with only 16% of an orally-admin-

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istered dose of 6-MP gaining access to the systemic circulation, on the average (Zimm et al., '83). This is because most of an oral dose is metabolized in the intestine and liver by the enzyme xanthine oxidase to the inactive metabolite 6-thiouric acid, which is excreted in the urine (Andersen et al., '98). In addition, the oral bioavailability of 6-MP is inversely proportional to the dose (Sandborn, '98). Relative bioavailability of 6-MP after an oral dose of 500 mg/m² was 55% of that after an oral dose of 75 mg/m² (Arndt et al., '88). Nevertheless, cytotoxic 6-MP plasma levels (>1–10 μmol/L) were achieved in all six patients given 500 mg/m² of 6-MP but in only one of these patients after an oral dose of 75 mg/m².

The half-lives of AZA and 6-MP in plasma are short, ranging from 1–3 hr (Lennard, '92; Gaffney & Scott, '98). Steady state levels of 6-thioguanine in the red blood cells can be reached after 2–8 weeks of oral treatment in most patients (Ewe et al., '93; Sandborn et al., '99); however, therapeutic effects are achieved more slowly, requiring up to 16 weeks in some individuals (Present et al., '80; Lennard et al., '84).

6-MP itself is biologically inactive as an inhibitor of purine synthesis (Van Scoik et al., '85). It must be anabolized by the enzyme hypoxanthine guanine phosphoribosyl transferase to thioguanine nucleotides to exert its cytotoxic effects (Van Scoik et al., '85; McLeod et al., '00). These active metabolites of 6-MP alter cellular metabolism in a number of ways, including inhibition of de novo purine ribonucleotide synthesis and interconversion and incorporation into cellular RNA and DNA. Incorporation of thioguanine nucleotides into DNA is four times greater than into RNA (Tidd and Paterson, '74; Nelson et al., '75), but cell types differ with respect to whether the effect on RNA synthesis or the effect on DNA synthesis is of greater importance to the pharmacologic response. For example, thioguanate incorporation into cellular RNA has a much larger inhibitory effect on bone marrow cells than on circulating T-lymphocytes (Van Scoik et al., '85). Thioguanine nucleotides do not traverse cell membranes, circulate in the plasma, or appear in the urine (Ding and Benet, '79; Kurowski and Iven, '91; Bostrom and Erdmann, '93).

Incorporation of thioguanine nucleotides into cellular nucleic acids is the mechanism of 6-MP's cytotoxicity, whereas inhibition of de novo purine ribonucleotide synthesis and interconversion is responsible for the drug's inhibition of cellular proliferation (Nelson et al., '75; Van Scoik et al., '85). Treatment usually aims to minimize one effect (e.g., cytotoxicity) to achieve the other (e.g., immunosuppression). Because the cytotoxic and immunosuppressive effects of AZA and 6-MP are nonspecific, undesired effects such as bone marrow suppression, hepatotoxicity, and an increased risk of neoplasia may occur with use of these drugs (Van Scoik et al., '85).

Although the half-lives of AZA and 6-MP in plasma are very short, the half-life of thioguanine is quite long, ranging between 3 and 13 days. (Lennard, '92; Sand-

born et al., '95). This delayed clearance of thioguanine from body tissues suggests that active metabolites of AZA and 6-MP may accumulate in cells with chronic administration even if plasma concentrations are low (Chan et al., '90).

After oral administration, 6-MP may be anabolized intracellularly, as described above, or catabolized in the liver, depending on the enzyme and cell type the drug first encounters (Van Scoik et al., '85; Chrzanoska et al., '99). 6-MP can be degraded through two catabolic pathways. One is inactivation by xanthine oxidase to 6-thiouric acid. The other catabolic pathway is through methylation of the 6-MP sulfur atom by thiopurine methyltransferase (TPMT).

There is a wide range of interindividual variability in the activity of TPMT due to genetic polymorphism (Weinshilboum, '92). Approximately 1 in 300 people inherits two nonfunctional TPMT alleles and consequently lacks the enzyme activity altogether. About 5–10% of people are heterozygotes for the nonfunctional TPMT allele and have intermediate enzyme activity (Collie-Duguid et al., '99; Marathias et al., '99; Relling et al., '99). Individuals who carry a variant of TPMT or lack the enzyme altogether can have high cellular concentrations of 6-thioguanine nucleotides and experience severe and sometimes fatal hematopoietic toxicity when given conventional doses of 6-MP or AZA (Lennard, '92).

There is some evidence that the methylated thiopurines produced by the action of TPMT on 6-MP are also capable of inhibiting de novo purine synthesis and may play a role in cytotoxicity (Bokkerink et al., '93; Stet et al., '93; Janka-Schaub et al., '94; Stolk et al., '98). The metabolism of 6-MP in humans is complex, and its role in the production of active drug metabolites remains poorly understood (Rowland et al., '99).

AZA, 6-MP, and their inactive metabolite, thiouric acid, can pass through the human placenta. All three compounds were found in fetal blood after oral administration of radioactively-labeled AZA (³⁵S-AZA) to three women during the 9th, 14th, and 15th weeks of pregnancy in one study (Saarikoski and Seppälä, '73). Higher concentrations of thiouric acid than of AZA or 6-MP were found in placenta, amniotic fluid, and fetal and maternal blood.

ANIMAL TERATOLOGY STUDIES

The teratogenic effects of AZA and 6-MP have been studied in mice, rats, rabbits, and hamsters, but the treatments used in these animal studies differ from those given to pregnant women. Humans usually take AZA or 6-MP orally, whereas most animal studies employ parenteral AZA or 6-MP treatments. As discussed above, the bioavailability of these two drugs is substantially reduced when they are administered orally. In the animal studies reviewed below, parenteral AZA and 6-MP doses are compared to the maximum human therapeutic doses (5 mg/kg/d) adjusted to account for reduced bioavailability (47% for AZA and 16% for

6-MP) after oral administration. Application of these adjustment factors yields a parenteral-equivalent maximum human therapeutic dose of 2.35 mg/kg/d for AZA and 0.8 mg/kg/d for 6-MP. In this adjustment, equivalent bioavailability and activity in both species is assumed.

AZA

Increased frequencies of cleft palate, open-eye, and skeletal anomalies as well as a significant decrease in thymic size were observed in the offspring of mice injected intraperitoneally (i.p.) during the period of organogenesis with the equivalent of 4–13 times the maximum human therapeutic dose of AZA (Githens et al., '65; Rosenkrantz et al., '67). No anomalies were observed in the offspring of mice treated similarly in another study (Tuchmann-Duplessis and Mercier-Parot, '64). The rate of malformations was not increased among the offspring of mice injected i.p. during the period of organogenesis with AZA in doses that were within the human therapeutic range or twice as great, although increased frequencies of fetal loss and growth retardation were observed (Tuchmann-Duplessis and Mercier-Parot, '64; Githens et al., '65; Rosenkrantz et al., '67). Fetal hydrops, anemia, and hematopoietic depression were observed without significant maternal hematopoietic depression in the offspring of mice treated for 3 days during the latter stages of pregnancy with the equivalent of 13 times the maximum human dose of AZA (Rosenkrantz et al., '67).

Increased frequencies of limb malformations, ocular anomalies, and cleft palate occurred among the offspring of pregnant rabbits injected i.p. with AZA in doses equivalent to 2–6 times those used in humans (Tuchmann-Duplessis and Mercier-Parot, '64).

No malformations occurred in the offspring of rats injected i.p. during the period of organogenesis with AZA in doses equivalent to up to four times the human therapeutic dose (Tuchmann-Duplessis and Mercier-Parot, '64). Fetal loss and growth retardation, however, were significantly increased at these doses (Tuchmann-Duplessis and Mercier-Parot, '64; Scott, '77; Fein et al., '83).

6-MP

6-MP is teratogenic in experimental animals at doses similar to or greater than those used therapeutically in humans. An increased incidence of cleft palate, skeletal, and urogenital anomalies, diaphragmatic hernia, and other malformations was observed among fetuses of rats given a single i.p. injection equivalent to 37.5–156 times the maximum human therapeutic dose of 6-MP on the 11th or 12th day of gestation (Murphy, '60; Bragonier et al., '64; Chaub and Murphy, '68; Kury et al., '68; Puget et al., '75). In another study, increased frequencies of fetal death and central nervous system, facial, and limb anomalies were observed among the offspring of rats treated at various times during organogenesis with the equivalent of <1–62.5 times the maximum human dose of 6-MP (Mercier-Parot and

Tuchmann-Duplessis, '67). No malformations were induced in the offspring of rats treated orally at various times during organogenesis with 6-MP at the equivalent of <1–12 times the maximum human dose (Thiersch, '54). A high rate of embryonic death occurred when 6-MP was administered to pregnant rats at the time of implantation at doses equivalent to 2–12 times the human dose; these doses were also toxic to the mothers (Thiersch, '54).

In mice, treatment with 6-MP during the period of organogenesis at doses equivalent to <1–125 times the maximum used in humans induced increased frequencies of fetal death and central nervous system, facial, and limb defects in the offspring (Mercier-Parot and Tuchmann-Duplessis, '67; Puget et al., '75; Reimers et al., '80).

Increased frequencies of fetal death and central nervous system, tail, and limb defects were also observed among the offspring of pregnant rabbits treated with 6-MP at doses within the human therapeutic range (Mercier-Parot and Tuchmann-Duplessis, '67; Puget et al., '75). Cleft palate, facial, limb, and abdominal anomalies were produced in the offspring of pregnant hamsters given a single i.p. injection equivalent to 29–162 times the maximum human therapeutic dose of 6-MP (Shah and Burdett, '79).

Treatment of pregnant mice with 6-MP has been found to impair the reproductive function of surviving offspring (Reimers et al., '80). Decreased fertility occurred among both male and female offspring of mice treated subcutaneously during pregnancy with 6-MP in doses equivalent to <1–4 times those used in humans. Although the external appearance of these offspring at the time of mating was normal, their gonads contained fewer germ cells than expected. In some cases, the gonads were completely devoid of germ cells. The frequency of fetal loss was also increased in the pregnancies of daughters of treated females.

HUMAN STUDIES

AZA

Although controlled epidemiological studies are not available, information regarding the outcome of pregnancy in women who were treated with AZA during pregnancy has been reported in a large number of clinical series (see Table 1). A list of the congenital anomalies described among the infants of women who took AZA during pregnancy is presented in Table 2.

The frequency of congenital anomalies among infants of renal transplant recipients who were treated with AZA throughout pregnancy ranged from 0.0–11.8% in 27 clinical series (Table 1). The number of infants included in each series varies from 6–110. No recurrent pattern of congenital anomalies emerges from these studies (Table 2). The incidence of congenital anomalies did not appear to be increased among 314 infants of female kidney transplant recipients whose pregnancies were reported to the National Transplantation Pregnancy Registry (Armenti et al.,

'94). It is difficult to determine if the rate of congenital anomalies in some of these studies is higher than what would be expected because the mothers usually took other drugs besides AZA and often had azotemia, hypertension, and other illnesses. No congenital anomalies occurred in two small series among ten infants born to heart/lung or liver transplant recipients who were treated with AZA and other immunosuppressants during pregnancy (Talaat et al., '94; Pruvot et al., '97).

One infant with a cardiovascular defect, one with pes equinovarus, and one with undescended testicle were reported among 33 infants born to women who were treated with AZA during pregnancy for rheumatic disease in a study conducted through the Swedish national medical record system (Källén, '98). No congenital anomalies were observed among 17 liveborn infants whose mothers were treated with AZA during the first trimester of pregnancy for severe SLE (Martínez-Rueda et al., '96) or among nine liveborn infants whose mothers were treated with AZA during pregnancy for various immunopathic diseases in other series (Symington et al., '77). The infant of a woman treated with AZA for SLE during the 2nd and 3rd trimesters of pregnancy was reported to have double outlet right ventricle, but this defect is unrelated to the AZA exposure because cardiac development was complete by the time treatment began (Tincani et al., '92). Six normal infants were born to other AZA-treated mothers in this series. No congenital anomalies were seen among 22 infants of women treated with AZA during pregnancy for IBD in two clinical series (Alstead et al., '90; Khan et al., '00) or among 14 infants of women treated with AZA during pregnancy for autoimmune hepatitis (Heneghan et al., '01).

Case reports of 117 infants born to women who were treated with AZA at various times during pregnancy have been published (see Table 3). First-trimester exposures occurred in 96% of the cases. No major congenital anomalies were found in 112 of these infants. Congenital anomalies were observed in two infants of renal transplant recipients who had been treated with AZA during pregnancy (Rasmussen et al., '81; Burleson et al., '83). One of these children, whose mother was not treated with AZA until the second trimester of pregnancy, had an atrial septal defect. The other affected child had a mild combined valvular aortic anomaly, possibly in combination with a ventricular septal defect and delayed psychomotor development (Burleson et al., '83). An anencephalic fetus was delivered to a third renal transplant recipient who was treated with AZA throughout pregnancy but who also had insulin-dependent diabetes mellitus (Vinicor et al., '84). Congenital anomalies were also reported in two infants whose mothers were treated for SLE throughout pregnancy with AZA (Williamson and Karp, '81; Ostrer et al., '84). Preaxial polydactyly was found in one of these infants and microcephaly, facial dysmorphism, and micropenis in the other. In another case report, both infants in a pair of twins born at 32 weeks gestation exhibited dilated heart chambers (Vyas et al., '99). One of the

twins died of cardiomyopathy. The authors attributed the neonatal cardiomyopathy to maternal treatment with tacrolimus, a recognized cause of cardiomyopathy in transplant recipients (Atkison et al., '95; Baruch et al., '96). Five other infants listed among the case reports in Table 3 were either stillborn or died shortly after birth (Lower et al., '71; Zerner et al., '81; Williams and Johnstone, '82; Laifer and Guido, '95). No congenital anomalies were observed in any of these babies.

Maternal AZA therapy early in gestation was associated with an increased frequency of fetal death among women with SLE (Martínez-Rueda et al., '96), but the women in this study had severe SLE, which could account for the poor fetal survival (Georgiou et al., '00). High frequencies of premature delivery, fetal growth retardation and neonatal death have been reported in pregnancies of AZA-treated renal transplant recipients in some series (Penn et al., '80; Registration Committee of the European Dialysis and Transplant Association [EDTA], '80; Pirson et al., '85; Marushak et al., '86; Brown et al., '91; Sturgiss and Davison, '91; Armenti et al., '93, '95; Cararach et al., '93; Pahl et al., '93; Huynh and Min, '94; Källén, '98). The infants of such women often have adrenocortical insufficiency, bacterial infections, or respiratory distress (Penn et al., '80; Pahl et al., '93). Many of these transplant recipients were maintained on cyclosporine and prednisone as well as AZA; therefore it is impossible to separate the effects of AZA from those of other medications or the maternal illness.

Fatal neonatal anemia, thrombocytopenia, and lymphopenia occurred in an infant born to a renal transplant recipient treated with AZA and prednisone during pregnancy (DeWitte et al., '84). Neonatal lymphopenia and thrombocytopenia have been observed in several other children born to women who received similar therapy (Lower et al., '71; Coté et al., '74; Price et al., '76; Rudolph et al., '79; Penn et al., '80; Davison et al., '85; Talaat et al., '94). It seems likely that these hematologic abnormalities resulted from a toxic effect of AZA similar to that which occasionally occurs in adults.

Pregnancy in renal transplant recipients is frequently complicated by hypertension (Armenti et al., '95). Furthermore, immunosuppression by AZA may predispose to bacterial, viral, and fungal infections (O'Donnell et al., '85; Pahl et al., '93; Castiglione et al., '00). These factors may also have adverse effects on the developing fetus.

6-MP

Although 6-MP is effective in the treatment of autoimmune disorders such as IBD and SLE, it is more widely used as an antineoplastic agent, especially in the treatment of leukemia (Goldstein, '87; Pearson et al., '95). Malignancy during pregnancy poses substantial risks to maternal and fetal survival, so treatment with potentially teratogenic drugs is sometimes justified.

TABLE 1. Clinical series reporting outcome of pregnancies in women treated with AZA*

Number of pregnancies	AZA dose	Reason for treatment (number of women)	Trimester of treatment (number of women)	Number of SA	Number of SB or IUD	Number of LB	CA or neonatal problem (number of infants)	Reference
30	50-175 mg/d	RT	1-3	9	1	22 ^a	CA (2); IUGR (6); LBW (14); ND (7) ^a	O'Donnell et al., '85
18	No data	RT	1-3	1	0	17	Hepatoblastoma (1); prolonged fetal heart rate decelerations, umbilical cord obstruction (1); hyperbilirubinemia (4); CA (2)	Pahl et al., '93
26	No data	RT	1-3	3	0	23	Premature delivery (2); acute respiratory distress (1); multiple malformations incompatible with life (1); IUGR (3); ND (2)	Framarino di Malatesta et al., '93
25	No data	RT	1-3?	6	0	20 ^a	Premature delivery (2); ND (2) ^a	Golby, '70
45	37.5-150 mg/d	RT	1-3	1	1	44 ^a	CA (4); respiratory distress syndrome (4); adrenocortical insufficiency, lymphopenia (2); septicemia (2); seizures (1)	Penn et al., '80
27	3 mg/kg/d	RT	1-3	4	1	23 ^a	Premature delivery (13); SGA (2); ND (3)	Brown et al., '91
112 ^b	No data	RT	1-3	13	8	95 ^a	CA (4); premature delivery (28); IUGR (17) SGA (29); ND (3)	Cararach et al., '93
39	No data	RT	1-3	2	0	37	Premature delivery (7); ND (1)	Haugen et al., '94
24	25-125 mg/d	RT	1-3	0	0	24	Premature delivery (8); SGA (4); RDS (1); impaired psychomotor development (1)	Marushak et al., '86
20	1-2 mg/kg/d	RT	1-3	0	1	19	IUGR (8); oligoamnios (4); meconium emission (9); fetal hypoxia (5); SGA (8)	Pirson et al., '85
104	2-3 mg/kg/d	RT	1-3	0	0	110	CA (5); CMV (1); ND, intracerebral hemorrhage (1)	Registration Committee of the European Dialysis and Transplant Association (EDTA), '80
22	<150 mg/d	RT	1-3	0	5	17	IUGR (4); LBW (4); ND (1)	Sturgiss and Davison, '91
12	2.5 mg/kg/d	RT	1-3	1	0	12 ^a	SGA (3), all born to same mother	Sciarra et al., '75
12	2-2.5 mg/kg/d	RT	1-3	3	0	10 ^a	Premature delivery (4) ^a ; premature delivery, diaphragmatic hernia (1); ND (4) ^a	Salant et al., '76
14	No data	RT	1-3	3	0	11	Premature delivery (3); IUGR (4); bronchopulmonary dysplasia (1)	Wong et al., '95
8	No data	RT	1-3	2	0	6	Premature delivery (1)	Vennarecci et al., '97
14	No data	RT	1-3	0	1	13	Premature delivery (1); SGA (9)	Ghahramani et al., '93
22 ^c	No data	RPT	1-3	2	0	20	Premature delivery (14); anemia (2); LBW (18); atrial septal defect that resolved after 1 year (1)	McCrory et al., '99
26 ^d	No data	RT	1-3	3	3	20	Premature delivery (3)	Naqvi et al., '99
14	No data	RT	1-3	1	5	8 ^a	Hydrocephalus, IUD (1); ND (1)	O'Connell et al., '89

22 ^e	2-3 mg/kg/d	RT	1-3	2 ^a	1	20 ^a	1	Cleft palate in stillborn; premature delivery (14); LBW (14); ND (1)	Santamaria Saber et al., '95
35	No data	RT	1-3	2	2	33 ^f	2	Premature delivery (24); growth retardation (24); RDS (4); renal hypoplasia with reflux (1); poliomyelitis-like syndrome (1); ND (1)	Bererhi et al., '97
8	No data	RT	1-3	0	1	8 ^a	1	Premature delivery (1); RDS (2); hypospadias (1)	Ogburn et al., '86
11	100-150 mg/d	RT	1-3	3	2	6	2	Cerebral palsy (1); ND (1); Normal karyotype (4/5); chromosomal complement of 46XX/47XX+2 (1/5);	Williams et al., '83
13	100 mg/d	RT	1-3	0	0	13	0	RDS (2); premature closure of fontanelles, ND (1); umbilical hernia (1)	Hadi et al., '86
30	No data	RT (25) RPT (2)	1-3	0	0	30	0	Premature delivery (13); SGA (4); RDS (1); hypocalcemia (2); thrombocytopenia (1)	Talaat et al., '94
7	No data	LT	1-3	0	0	7	0	Premature delivery (2)	Privot et al., '97
7	100 mg/d	SLE	2-3	0	0	7	0	Neonatal lupus-skin (1); mild respiratory distress (1); SGA (2); double outlet right ventricle (1)	Tincani et al., '92
31	No data	SLE	1	0	14 ^g	17	14 ^g	None reported	Martinez-Rueda et al., '96
9	50-150 mg/d	CAH (4) SLE (4) MCTD (1)	Varying times	0	0	9	0	Premature delivery, CMV (1)	Symington et al., '77
33	No data	RD	No data	-	-	33	-	CA (3)	Källén, '98
14	1-2 mg/kg/d	IBD	1-3 (7) 1 (3)	0	0	15 ^a	0	Cyanosis (1); premature delivery (1)	Alstead et al., '90
8	Mean dose = 1 mg/kg/d	IBD	1-2 (4) 1-3	0	0	8	0	None	Khan et al., '00
15 ^b	1-2 mg/kg/d	AH	1 (2) 1-3 (13)	0	1	14	1	None reported	Heneghan et al., '01

*AH, autoimmune hepatitis; CA, congenital anomalies; CAH, chronic active hepatitis; CMV, cytomegalovirus; IBD, inflammatory bowel disease; IUD, intrauterine death; IUGR, intrauterine growth retardation; LB, liveborn; LBW, low birthweight; LT, liver transplant; MCTD, mixed connective tissue disease; ND, neonatal death; RD, renal disease; RDS, respiratory distress syndrome; RPT, renal-pancreas transplant; RT, renal transplant; SA, spontaneous abortion; SB, stillborn; SGA, small for gestational age; SLE, systemic lupus erythematosus.

^aIncludes one or more set of twins.

^b88% of the women in this series were taking AZA.

^c78% of the women in this series were taking AZA.

^d80% of the women in this series were taking AZA.

^eWith the exception of one, all women in this series took AZA.

^fIncludes one set of triplets, one of which died 3 weeks postdelivery.

^gThis total is for "fetal mortality" and therefore may include SA.

^hMaternal and fetal death occurred at 25 weeks of pregnancy in one patient; 2 early miscarriages (<20 weeks) occurred but it is not known if either of these women were taking AZA.

TABLE 2. Congenital anomalies observed among infants of women who were treated with AZA during pregnancy

Anomaly (number of infants)	Reference
Hydrocephalus (1)	O'Connell et al., '89
Anencephaly (1)	Vinicor et al., '84
Plagiocephaly with neurological damage (1)	Registration Committee of the European Dialysis & Transplant Association, '80
Hemangioma frontalis (1)	Registration Committee of the European Dialysis & Transplant Association, '80
^a Slight impairment in psychomotor development (2)	Rasmussen et al., '81; Marushak et al., '86
Premature closure of fontanelles (1)	Hadi et al., '86
Cleft palate (1)	Santamaria Saber et al., '95
Patent ductus arteriosus (1)	Pahl et al., '93
Mild mitral regurgitation (1)	Registration Committee of the European Dialysis & Transplant Association, '80
Cardiovascular defect (1)	Källén, '98
Atrial septal defect (2)	Burleson et al., '83; McGrory et al., '99
Double outlet right ventricle (1)	Tincani et al., '92
Probable peripheral pulmonary arterial stenosis (mild) (1)	Penn et al., '80
Congenital pulmonary artery stenosis (1)	Penn et al., '80
Mild combined valvular aortic anomaly, possibly in combination with a ventricular septal defect (1)	Rasmussen et al., '81
Deformed left hand (1)	Penn et al., '80
Hypoplasia of left leg (1)	Cararach et al., '93
Hyperflexion of 5 th digits, large toenail deformity (1)	Pahl et al., '93
Polydactyly (2)	Williamson and Karp, '81; Cararach et al., '93
Diaphragmatic hernia (2)	Salant et al., '76; O'Donnell et al., '85
Bilateral inguinal hernia (1)	Penn et al., '80
*Umbilical hernia (2)	Hadi et al., '86; Cararach et al., '93
Undescended testicle (1)	Källén, '98
Hypospadias (3)	Registration Committee of the European Dialysis & Transplant Association, '80; Ogburn et al., '86; Cararach et al., '93
Pes equinovarus (2)	Registration Committee of the European Dialysis & Transplant Association, '80; Källén, '98
Microcephaly, unusual facial features, micropenis (1)	Ostrer et al., '84
"Severe multiple malformations incompatible with life" (1)	Framarino di Malatesta et al., '93

^aSome infants had more than one anomaly.

No congenital anomalies were observed among the infants of 14 women who were treated with 6-MP and other antineoplastic agents during pregnancy in two small series (Pizzuto et al., '80; Aviles et al., '91). Pancytopenia was observed in one infant who died of septicemia at 21 days of age (Pizzuto et al., '80). A second infant in the same series died of gastroenteritis at three months of age. The frequency of congenital anomalies did not appear to be increased among the children of 72 women with IBD who were treated with 6-MP during pregnancy (Francella et al., '96).

Case reports of 53 women who took 6-MP at various times during pregnancy have been published (Table 4). Forty-nine (92%) of these women were treated with 6-MP and other medications for leukemia and the remaining mothers were treated with 6-MP for non-Hodgkin lymphoma (1), SLE (1), or IBD (2). 6-MP treatment occurred in the first trimester in 46% of the pregnancies for which there are data regarding time of exposure. Four (7.5%) of the 53 reported pregnancies resulted in spontaneous abortions; one of the fetuses (a twin) had major malformations. Congenital anomalies were also reported in two (4.1%) of 49 liveborn infants. One child whose mother took 6-MP for leukemia "around conception" and 1 month before delivery was born with bilateral microphthalmia, corneal opacity,

cleft palate, hypoplastic thyroid and ovaries, thoracic kyphosis, and growth retardation (Diamond et al., '60). The infant died at 10 weeks of age. Macrocephaly, hypertelorism, and "probable" phocomelia were observed in one twin infant whose mother took 6-MP for leukemia throughout pregnancy (Sosa Muñoz et al., '83). The other twin was normal. Two of the infants listed in Table 4 were stillborn, and one of these babies had polydactyly (Parekh et al., '59; Mulvihill et al., '87).

Transient neonatal anemia and pancytopenia were observed in three infants of women treated with 6-MP and other antineoplastic agents during pregnancy (McConnell and Bhoola, '73; Okun et al., '79; Pizzuto et al., '80). These short-term effects may be the result of direct drug toxicity.

MECHANISMS OF TERATOGENICITY

The mechanisms by which AZA and 6-MP or their metabolites induce teratogenicity are not known. Two mechanisms have been proposed: 1) inhibition of nucleic acid synthesis, or 2) alteration of maternal zinc metabolism. Laboratory investigations of these mechanisms have focused on the effects of 6-MP, but the conclusions probably apply to AZA as well because AZA is metabolized to 6-MP.

TABLE 3. Case reports of pregnancy outcomes for women treated with AZA*

Number of infants	Dose of AZA	Trimester of treatment (number of women)	Reason for treatment	Maternal complications (number of women)	Infant outcome (number of infants)	Reference
1	2-2.5 mg/kg/d	1-3	RT	None	Normal	Board et al., '67
1	2.5 mg/kg/d	2-3	RT	Cellular rejection, hypertension	Premature, RDS, hyperbilirubinemia, hypothyroidism, atrial septal defect	Burleson et al., '83
1	No data	1-3	RT	Possible rejection	Premature, SGA, IUGR, transient hypotonia	Caplan et al., '70
5	1-1.5 mg/kg/d	1-3	RT	None	Normal	Coulam et al., '82
1	150 mg/d	1-3	RT	None	Normal	Gebhardt, '83
1	75 mg/d	1-3	RT	Not reported	Normal	Kaufman et al., '67
5	25-100 mg/d	1-3	RT	Decline in renal function, preeclampsia (4)	Normal	Merkatz et al., '71
2	75 mg/d	1-3	RT	PROM (1)	Normal	Nolan et al., '74
2	1.2 mg/kg/d	1-3	RT	None	Normal twins	Prieto et al., '89
1	2 mg/kg/d	1-3	RT	Hypertension, hypoparathyroidism	Transient hyperparathyroidism	Rabau-Friedman et al., '82
5	100-150 mg/d	1-3	RT	Graft dysfunction (1)	RDS, severe metabolic acidosis (1); Transient respiratory difficulty (1); Mild combined valvular aortic anomaly, possibly in combination with a ventricular septal defect, delayed psychomotor development (1)	Rasmussen et al., '81
1	50 mg/d	1-3	RT	Preeclampsia	Normal	Westney et al., '84
6	100-150 mg/d	1-3	RT	Severe preeclamptic toxemia (2); renal artery, stenosis, hypertension (1); possible tuberculosis, partial thyroidectomy, hypothyroid, PROM (1); toxoplasmosis (1)	Normal (5); SGA (1)	Whetham et al., '83
2	150 mg/d	1-3	RT	Eclampsia	Stillborn (1); Normal (1)	Williams and Johnstone, '82
2	125-150 mg/d	1-3	RT	IUD failure; PROM	Normal (1); prematurity, failure to thrive (1)	Zerner et al., '81
6	50-100 mg/d	1-3	RT	Severe pregnancy induced hypertension, PROM (1); toxemia (1); premature delivery (2)	Normal (5); cerebral palsy, mild mental impairment (1)	Pilarski et al., '94
1	75 mg/d	1-3	RT	None	Normal	Shigenobu et al., '93
1	100 mg/d	1-3	RT	Renal failure, 35 weeks	RDS	Ersay et al., '95
2 ^a	50 mg/d	1	RT	Hypertension; premature delivery	RDS, dilated cardiomyopathy (both twins); Twin A death, thrombotic cardiomyopathy, Twin B survived but had renal failure, anasarca, poor cardiac function	Vyas et al., '99
1	75-100 mg/d	1-3	RT	Preeclampsia	Transient chromosomal damage in peripheral blood lymphocytes	Leb et al., '71
1	125 mg/d	1-3	RT	None	Normal	Hume et al., '66
2	200 mg/d (1) 50 mg/d (1)	1 (1) 1-3 (1)	RT	None (1) PROM (1)	Normal (1) Normal (1)	Ha et al., '94

5	100-200 mg/d	1-3	RT	SA (1); premature delivery (1)	Normal (4)	Merrill et al., '73
1	150 mg/d	1-3	RT	None	Normal; including normal karyotype	Farber et al., '76
1	3 mg/kg/d	1-3	RT	None	LBW; normal karyotype	Jacob et al., '74
2	3 mg/kg/d (1)	1-3	RT	None	Normal (2)	Saito et al., '93
3	50 mg/d (1)	1-3	RT	None	Normal (3)	Ben Hamida et al., '99
2	125 mg/d	1-3	RT	None	Normal (2)	Grekas et al., '84
2 ^a	75-100 mg/d	1-3	RT	None	Death postdelivery (2); RDS, hypoplasia of lymph system, bone marrow, and adrenal cortex	Lower et al., '71
2	100 mg/d	1-3	RT	Diabetes mellitus	Anencephalic fetus (1); Normal (1)	Vinacor et al., '84
1	150 mg/d	1-3	RPT	None	Normal	Skannal et al., '96
1	150 mg/d	1-3	Chronic renal disease	CMV infection	Normal, CMV infection	Coté et al., '74
1	125 mg/d	1-3	CT	None	Normal	Yuh-Jer Shen and Mansukhani, '97
1	150 mg/d	1-3	CT	Primary genital herpes viral infection; PROM	Normal	Key et al., '89
1	100 mg/d	1-3	CT	Rejection episode, 3 rd trimester	Normal	Kirk, '91
1	100 mg/d	1-3	CT	Gestational diabetes, possible renal insufficiency at 40.5 weeks	Normal	Baxi and Rho, '93
1	50 mg/d	1-3	CT	Asymptomatic bacteriuria	Normal	Morini et al., '98
2	175-250 mg/d	1-3 (1); 1-2 (1)	CT	Preeclampsia (1); Hepatotoxicity (1)	Normal (1); SGA, mild respiratory distress (1)	Scott et al., '93
1	50-75 mg/d	1-3	CT	<i>Herpes genitalis</i>	Normal	Camann et al., '91
1	75 mg/d	1-3	CT	<i>Listeria Monocytogenes</i>	Normal	Camann et al., '89
1	2 mg/kg/d	1-3	CT-LGT	None	Normal	Chinayon and Sakornpant, '94
2	25-75 mg/d	1-3	CT-LGT	None	Normal (2)	Rose et al., '89
2	50-100 mg/d	1-3	CT-LGT	None	Normal (2)	Troché et al., '98
2	50-75 mg/d	1-3 (1); 1 (1)	LT	Severe anemia, oligohydramnios, 37 weeks (1); severe osteoporosis, toxoplasmosis (1)	Normal (2)	Baruch et al., '93
1	50 mg/d	1-3	LT	None	Normal	Myers et al., '80 ^b
1	50 mg/d	1-3	LT	None	Normal	Walcott et al., '78
1	125 mg/d	1-3	LT	None	Normal	Baarsma and Kamps, '93
1	No data	1-3	LT	None	Normal	Laifer et al., '90
1	No data	1-3	LT	Chronic graft rejection, PROM, preterm delivery (23 weeks)	Fetal CMV infection, anemia, death postdelivery	Laifer and Guido, '95
3	No data	1-3	LT	None	Normal	Scantlebury et al., '90

Table 3 continues on next page

TABLE 3. Case reports of pregnancy outcomes for women treated with AZA* (continued)

Number of infants	Dose of AZA	Trimester of treatment (number of women)	Reason for treatment	Maternal complications (number of women)	Infant outcome (number of infants)	Reference
1	No data	1	SLE	Bone marrow suppression; blood transfusion; severe proteinuria, hypertension; preeclamptic toxemia at 32 weeks	Normal	Gillibrand, '66
1	No data	"Early pregnancy"	SLE	None reported	Normal	Levy et al., '91
4	75-100 mg/d	At conception	SLE	Sigmoid vasculitis (1); pneumonitis and nephritis (1); IUD in place (1)	SA (2); normal with pneumothorax and pneumonia (1); normal (1)	Meehan & Dorsey, '87
3	2.5 mg/kg/d	1 (2); 1-3 (1)	SLE	Ruptured ectopic (1)	SA (2); normal (1)	Sztejnbock et al., '71
1	50-150 mg/d	1-3	SLE	Hemolytic anemia	Microcephaly, unusual facial features, micropenis, growth retardation, two <i>de novo</i> chromosomal abnormalities	Ostrer et al., '84
1	200 mg/d	1-3	SLE	Preeclampsia	Preaxial polydactyly	Williamson and Karp, '81
1	10 mg/d	2-3	Anti-Ro (SSA) antibodies	None	Normal	van der Leij et al., '94
1	2.4 mg/kg/d	1-3	Wegener's granuloma colitis	Respiratory tract infection	Normal	Cooper et al., '70
2	No data	2 (1); 3 (1)	Ulcerative colitis	None	Normal (2)	Levy et al., '81
1	2 mg/kg/d	1-3	Crohn's disease	None	Normal	Hanauer and Greenberger, '99
1	75 mg/d	1-3	Idiopathic membranous glomerulonephritis	None	Ventricular parasystole	Blanchard et al., '79
1	50 mg/d	1-3	Chronic, persistent hepatitis	None	Normal	Erkman and Blythe, '72

*CMV, cytomegalovirus; CT, Cardiac Transplantation; IUD, intrauterine device; IUGR, intrauterine growth retardation; LBW, low birthweight; LGT, Lung Transplantation; LT, Liver Transplantation; PROM, premature rupture of membranes; RDS, respiratory distress syndrome; RPT, Renal/Pancreas Transplantation; RT, Renal Transplantation; SA, spontaneous abortion; SGA, small for gestational age; SLE, Systemic Lupus Erythematosus.

^aTwin birth.

^bSecond pregnancy of the same patient reported on by Walcott et al., '78.

Inhibition of Nucleic Acid Synthesis

Numerous *in vivo* and *in vitro* studies have demonstrated that 6-MP is incorporated into the nucleic acids of human and other mammalian cells and that this incorporation is the key mechanism of cytotoxicity (Bieber et al., '61; Elion, '67; Lepage and Whitecar, '71; Tidd and Paterson, '74; Nelson et al., '75; Breter, '85). 6-MP inflicts damage on rapidly dividing cells, such as bone marrow, intestinal epithelium, and the reproductive organs in adults (Sokal and Lessmann, '60). Most embryonic tissues proliferate rapidly, especially during organogenesis, so embryonic tissue would be expected to be particularly sensitive to the cytotoxic actions of 6-MP. Several attempts have been made to test the hypothesis that the teratogenicity of 6-MP results from cytotoxicity caused by an incorporation of 6-thioguanine into the DNA of embryos.

Bragonier and Carver ('68) administered a teratogenic *i.p.* dose of 6-MP to pregnant rats on gestation day 12. Placental purine synthesis was decreased 6 hours after treatment, and fetal DNA content was reduced 48 hr after treatment. No evidence of fetal malformation was seen at this stage of development, but skeletal defects consistently occurred in 20-day-old fetuses after such treatment.

Platzek et al. ('85, '94) found a correlation between incorporation of S³⁵-labeled 6-MP-riboside (an active metabolite of 6-MP) into embryonic DNA and the frequency of skeletal abnormalities in the offspring of pregnant mice treated on the 11th day of gestation. This observation is consistent with the hypothesis that the embryotoxicity of 6-MP riboside is due to its incorporation, probably as 6-thioguanine, into the DNA of the embryos.

In another study, Burdett et al. ('88) found that maternal treatment with the equivalent of 87.5 times the maximum human therapeutic dose of 6-MP on Day 9 of gestation depressed DNA synthesis and reduced mesenchymal cell number and density in the maxillary processes of treated 10–12-day-old hamster embryos. Although these studies provide convincing evidence that 6-MP-induced modifications in DNA are associated with increased frequencies of fetal malformations, they do not prove that the inhibition of DNA synthesis was directly involved in the pathogenesis of the anomalies.

Alteration of Maternal Zinc Metabolism

Zinc is essential to many enzyme systems that influence DNA synthesis, RNA synthesis, and cell division and proliferation (Ploysangam et al., '97; MacDonald, '00). Maternal zinc deficiency decreases fetal incorporation of ³H-thymidine (Swenerton et al., '69; Eckhart and Hurley, '77; Hirsch and Hurley, '78; Shrader et al., '78) and reduces the activity of fetal thymidine kinase and DNA polymerase (Dreosti and Hurley, '75; Duncan and Hurley, '77; Shrader et al., '78). In rats, maternal zinc deficiency can produce fetal anomalies very similar to those caused by maternal treatment with 6-MP

(Hirsch and Hurley, '78). Several studies have found that 6-MP is capable of altering the metabolism of zinc and other minerals in pregnant rats and their fetuses (Hirsch and Hurley, '78; Amemiya et al., '86, '89). Therefore, it has been suggested that the teratogenic effect of 6-MP may be mediated through embryonic zinc deficiency (Amemiya et al., '86, '89; Hirsch and Hurley, '78).

Amemiya and associates ('86) found that the zinc concentrations of whole fetuses and fetal liver were consistently lower after treatment of pregnant rats on gestational day (GD) 11 with a teratogenic dose of 6-MP. The increased rate of fetal anomalies produced by this 6-MP treatment could be partially alleviated by supplementing the maternal diet with zinc. Similar protective effects on embryogenesis were found in another study in which rats were fed diets supplemented with zinc and injected with a teratogenic dose of 6-MP on GD 11 (Hirsch and Hurley, '78). Although it is clear that supplemental levels of zinc in the maternal diet can reduce the teratogenicity of 6-MP in animals, the mechanism by which zinc supplementation does this is poorly understood.

GENETIC EFFECTS OF AZA AND 6-MP

The mechanisms of teratogenicity and mutagenicity, and the risks associated with them, are distinct (Alexandrov, '73; Bishop et al., '97). Teratogenesis occurs when an initially normal embryo or fetus is damaged while it is developing, usually by an exposure that the mother sustains while she is pregnant. Teratogenicity affects many cells of the developing organism, and the incidence and severity of teratogenic effects increase with the dose and the number of cells affected (Brent, '86). Cells that are damaged by a teratogen may be replaced by normal cells in early embryonic development, so a teratogen must damage a threshold number of cells to produce a disruptive effect. Consequently, a threshold dose exists for teratogenic exposures, below which no effect is produced.

In contrast, mutation results from DNA damage within a single cell. Germ cell mutations occur when there is damage to the DNA of the sperm or oöcyte. If an individual is conceived from a sperm or oöcyte containing a mutation, the mutation will be copied into every cell of that individual's body. The likelihood of mutation increases with the magnitude of mutagen exposure, but only a single event is required for mutation to occur. A potential mutagenic risk may therefore exist at any dose, and there is no threshold for a mutagenic effect (Brent '86).

Because AZA and 6-MP interfere with nucleic acid synthesis, treatment with these drugs might produce germ cell mutations as well as teratogenic effects. Mutations that occur in the germ cells of a treated parent could result in constitutional chromosomal abnormalities or new dominant diseases in children who are subsequently conceived. Such effects would be more likely after treatment of a man than of a woman be-

TABLE 4. Pregnancy outcomes for women treated with 6-mp during pregnancy*

Number of Infants	Dose of 6-MP	Reason for treatment	Length of treatment during pregnancy	Maternal complications	Infant outcome	Reference
1	125 mg/d	Leukemia	Around conception and 1 month prior to delivery	Death 1 month postdelivery	Bilateral microphthalmia, corneal opacity, cleft palate, hypoplastic thyroid and ovaries, thoracic kyphosis, disseminated cytomegaly, IUGR; death at 10 weeks of age	Diamond et al., '60
1	100 mg/d	Leukemia	2 nd month to delivery	Premature delivery	Normal	Diamond et al., '60
1	No data	Leukemia	1 st two months	None	Normal	Feliu et al., '88
1	150 mg/d	Leukemia	Entire pregnancy	Death at 23 rd week of pregnancy	Normal fetal morphology	Feliu et al., '88
1	100 mg/d	Leukemia	Entire pregnancy	Premature delivery; death 16 days postdelivery	Micro-angiopathic hemolytic anemia	McConnell and Bhoola, '73
1	No data	Leukemia	Not reported	Premature delivery; death 3 days postdelivery	Normal	Lee et al., '62
1	No data	Leukemia	29 th week to term	Death 3 months postdelivery	Normal	Lee et al., '62
1	No data	Leukemia	Not reported	Premature delivery	Normal	Lee et al., '62
1	75 mg/d	Leukemia	1-4 months	Premature delivery; death 5 days postdelivery	Death 12 hours postdelivery	Rothberg et al., '59
1	25-150 mg/d	Leukemia	5 th -9 th months	None	Normal	Rothberg et al., '59
1	175 mg/d	Leukemia	3 days during 5 th months	Death, cerebral hemorrhage	Postmortem section, death 2 hours later	Rothberg et al., '59
1	50 mg/d	Leukemia	10 days during 7 th month	Premature delivery; death during delivery	Stillborn, 7 months	Parekh et al., '59
1	150 mg/d	Leukemia	Entire pregnancy	None	Normal	Sinykin and Kaplan, '62
1	2.5 mg/kg/d	Leukemia	1-6 months	Premature delivery; death 2 months postdelivery	Death 2 days postdelivery	Merskey and Rigal, '56
1	25-150 mg/d	Leukemia	6-8 weeks; 28 th -31 st weeks	Premature delivery	Normal	Ravenna and Stein, '63
1	50 mg/d	Leukemia	Entire pregnancy	None	Normal	Frenkel and Meyers, '60
1	75-150 mg/d	Leukemia	5 th month to term	Death 7 months postdelivery	Normal	Frenkel and Meyers, '60

1	50-325 mg/d or 0.8-5 mg/kg/d	Leukemia	5 th month to term	Death 4 weeks postdelivery	Normal	Frenkel and Meyers, '60
1	100-250 mg/d	Leukemia	3 weeks during 6 th month	Premature delivery; death 4 months postdelivery	Normal	Frenkel and Meyers, '60
1	7.7 g (total)	Leukemia	4-5 months	None	Normal	Sokal and Lessmann, '60
1	1.36 g (total)	Leukemia	7.5-8.5 months	None	Normal	Hill JM and Loeb E, personal communication, cited in Sokal and Lessman, '60
1	75 mg/d	Leukemia	4-5 months, 6 months to term	None	Normal	Hill JM and Loeb E, personal communication, cited in Sokal and Lessman, '60
1	175 mg/d	Leukemia	3.5 months to term	None	Normal	Sandberg AA, personal communication, cited in Sokal and Lessman, '60
1	2.5 mg/kg/d	Leukemia	14 th week to term	Death 2 weeks postdelivery	Normal	Loyd, '61
1	3.5 mg/kg/d	Leukemia	7 th month to term	None	Normal	Loyd, '61
1	100 mg/d	Leukemia	6 th -8 th months	Death 1 week postdelivery	Normal	Schumacher, '57
1	No data	Leukemia	6 th months to term	Premature delivery; death 5 months postdelivery	Normal	Neu, '62
1	70 mg/m ²	Leukemia	23 weeks for 10 days	Premature delivery	Normal	Morishita et al., '94
1	No data	Leukemia	3 rd week to term	None reported	Stillborn, abruptio placentae, polydactyly	Mulvihill et al., '87
1	60 mg/m ²	Leukemia	23.5-27.5 weeks	PROM	Transient severe bone marrow hypoplasia	Okun et al., '79
4	100 mg/d	Leukemia	Entire pregnancy	Spontaneous abortion (2)—one fetus with major malformations	Set of twins born—one normal, the other had minor anomalies: microcephaly, hypertelorism, and probable phocomelia	Sosa Muñoz et al., '83
1	25-75 mg/d	Leukemia	1 st month, 4 th month to delivery	None	Normal	Wegelius, '75; Moe et al., '79
1	75 mg/d	Leukemia	22.5 weeks to term	Death 6 months postdelivery	Normal	Awidi et al., '83
1	60 mg/m ²	Leukemia	3 rd trimester	None reported	Normal; chromosomal gaps and rings	Schleuning and Clemm, '87
1	No data	Leukemia	Up to 2 weeks before delivery	None reported	Normal, slight leukopenia	Khurshid and Saleem, '78

Table 4 continues on next page

TABLE 4. Pregnancy outcomes for women treated with 6-mp during pregnancy* (continued)

Number of Infants	Dose of 6-MP	Reason for treatment	Length of treatment during pregnancy	Maternal complications	Infant outcome	Reference
2	350 mg/d	Leukemia	28 weeks to term	None	Neonatal sepsis; normal twins	Turchi and Villasis, '88
1	100 mg/d	Leukemia	1-6 weeks	None reported	Normal; polycythemia, hyperbilirubinemia	Dara et al., '81
1	100 mg/d	Leukemia	33 rd week for only 3 days	Premature delivery	Normal, cushingoid	Doney et al., '79
1	25-100 mg/d	Leukemia	16 weeks to term	Preeclampsia; death 3 weeks postdelivery	Normal	Coopland et al., '69
1	150 mg/d	Leukemia	3 days in 5 th month	Death 6 days postdelivery	Spontaneous abortion	O'Leary and Bepko, '63
1	150-300 mg/d	Leukemia	8 th -9 th months	Death 1 month postdelivery	Normal	Stewart, '64
1	50-200 mg/d	Leukemia	0-4 months, 5-6 months	Premature delivery	Death 19 hours after birth	Smith et al., '58
1	50 mg/d every other day	Leukemia	Entire pregnancy	None reported	Asymptomatic cardiac murmur of unknown type	Li and Jaffe, '74
1	50 mg/d	Leukemia	26.5-27.5, 29-31 weeks	None	Normal	Krueger et al., '76
1	No data	Leukemia	2-3 months	Death 2 months post abortion	Spontaneous abortion at 3 months	Hoover and Schumacher, '66
1	150-200 mg/d	Leukemia	8 months to term	Death 3 days postdelivery	Normal	Rigby et al., '64
1	No data	Leukemia	3 rd trimester	None	Normal	Blatt et al., '80
1	No data	Leukemia	2 nd -3 rd trimester	None	Normal	Reynoso et al., '87
1	No data	Non-Hodgkin lymphoma	1 st trimester	None reported	Spontaneous abortion	Zemlickis et al., '92
1	25 mg/d	SLE	Entire pregnancy	None	Normal	Shearman et al., '63
2	No data	IBD	1-3 weeks (1) 1-4 weeks (1)	None	Normal	Present et al., '89

*IBD, inflammatory bowel disease; IUGR, intrauterine growth retardation; PROM, premature rupture of membranes; SLE, systemic lupus erythematosus.

cause DNA synthesis in oögenesis is restricted to embryonic and fetal life. Mutation of germ cell precursors could also occur during embryogenesis (and therefore be associated with treatment of the mother during pregnancy), but any constitutional chromosomal abnormalities or new dominant diseases produced would occur in her grandchildren, not in her children.

Both AZA and 6-MP have been found to be mutagenic in various mammalian *in vitro* and *in vivo* assays (Voogd, '89; Mosesso and Palitti, '93; Bishop et al., '97). Dominant lethal effects, which usually result from chromosomal or genic mutations, were observed when male mice were injected *i.p.* with the equivalent of 5–602 times the maximum human therapeutic dose of 6-MP (Ray et al., '73; Generoso et al., '75a, b; Schencking and Frohberg, '75; Sykora, '81). Similar effects were observed after protracted oral administration of 6-MP at doses that were 5–10 times the maximum human dose in one study (Sykora, '81), but not in another (Ray et al., '73). Damage occurred in the early stages of spermatogenesis, mainly affecting the late differentiating spermatogonia and early spermatocytes (Generoso et al., '75b; Schencking and Frohberg, '75). Similarly, the dominant-lethal test was positive when AZA was administered orally to male mice at 5–20 times the maximum human therapeutic dose (Clark, '75; Racine and Schmid, '84). Both AZA and 6-MP have also been found to increase the frequencies of chromosome aberrations, micronuclei, and sister chromatid exchange in rodent bone marrow cells (Holden et al., '73; Maier and Schmid, '76; van Went, '79; Matter et al., '82; Sono et al., '82; Cozzi et al., '83).

Preconception Exposures to 6-MP in humans

The largest experience with respect to the mutagenic effects of 6-MP in humans is with men and women who were given the drug for treatment of malignant disease before conception. Congenital anomalies did not appear to be unusually frequent in two series of 11 and 49 children whose parents had previously received 6-MP as part of their treatment for leukemia (Pajor et al., '91; Green et al., '97). Similarly, only 1/38 (2.6%) liveborn infants of women who had been successfully treated with 6-MP and other medications for trophoblastic tumors before pregnancy was reported to have congenital anomalies (Walden and Bagshawe, '79). This affected infant had spina bifida and hydrocephalus. Spontaneous abortions occurred in 13% of the pregnancies in this series; this is about the expected frequency. In addition, published case reports include 21 normal infants (Hinkes and Plotkin, '73; Bacon and Kernahan, '75; Wegelius, '75; Barkhan and Evans, '76; Kroner and Tschumi, '77; Moe et al., '79; Blatt et al., '80; Gasser, '80; Sanz and Rafecas, '82; Evenson et al., '84), two children with minor anomalies (Moe et al., '79; Blatt et al., '80), and one child with multiple congenital anomalies (Evenson et al., '84) born to men or women who were treated with 6-MP before conception.

In a retrospective cohort study of pregnancies fathered by men with IBD, the incidence of adverse out-

comes was significantly higher when the fathers were treated with 6-MP within 3 months of conception than when they were not (OR = 19.6, 95% confidence interval 3.1–122) (Rajapakse et al., '00). There were two spontaneous abortions and two infants born with congenital anomalies in 13 pregnancies fathered by men in the 6-MP-treated group. The congenital anomalies observed were a missing thumb in one child and acrania, digital malformations, and limb anomalies in a fetus that was therapeutically aborted. Two spontaneous abortions and no congenital anomalies were observed among 90 pregnancies fathered by men with IBD who were not treated with 6-MP. The difference between the groups is largely attributable to lower than expected frequencies of spontaneous abortions and congenital anomalies in the pregnancies fathered by men who were not treated with 6-MP. No significant difference in the frequency of adverse pregnancy outcomes was observed between a third group of fathers with IBD who conceived at least 3 months after stopping 6-MP treatment and the fathers with IBD who were not treated.

Wilms tumor was reported in one 4-year-old boy whose father took 6-MP for IBD at the time of conception (Present et al., '89).

Preconception exposures to AZA in Humans

Very few studies have investigated the pregnancy outcomes for spouses of men treated with AZA before conception. Golby ('70) found 38 normal pregnancies and two spontaneous abortions among the spouses of 40 male renal transplant recipients who conceived while receiving long-term immunosuppressive therapy with AZA. In two other studies, congenital anomalies were found in nine (3.3%) of 273 and two (4.8%) of 42 infants of male renal and cardiac transplant recipients, respectively (Ahlsvede et al., '94; Wagoner et al., '94). Most of the men were treated with AZA in addition to other immunosuppressants before conception. No recurrent pattern of anomalies was apparent in either of these studies. The rates of miscarriage and other adverse outcomes in pregnancies fathered by renal transplant recipients were similar to those of the general population (Ahlsvede et al., '94). One case report describes an infant with lumbar myelomeningocele born to a male renal transplant recipient who was treated with AZA (125 mg/d) and prednisone (15 mg/d) (Tallent et al., '70).

Increased frequencies of acquired chromosomal breaks and rearrangements have been observed in the lymphocytes of renal transplant recipients receiving AZA therapy and, transiently, in the infants of women who were given such treatment during pregnancy (Gevers et al. '71; Leb et al., '71; Sharon et al., '74; Price et al., '76; Henahan, '83). The clinical significance, if any, of these observations is unknown.

One child with two separate *de novo* constitutional chromosomal anomalies has been reported whose mother was treated before and during pregnancy with AZA and prednisone (Ostrer et al., '84). Another re-

ported child whose father was treated with AZA for Crohn disease for 4 years before conception had a de novo deletion of chromosome 11p13 and aniridia and psychomotor delay consistent with the WAGR syndrome (Ben-Neriah and Ackerman, '01). These observations raise the possibility that parental AZA treatment during gametogenesis may predispose to constitutional cytogenetic abnormalities in subsequently conceived children. If this does occur, it must be infrequent because most children born to men or women treated with AZA appear to be normal (EDTA, '80; Penn et al., '80; Pirson et al., '85).

The number of reported children conceived by men or women treated with AZA or 6-MP is too small to draw conclusions regarding the possible mutagenic effects of these drugs.

SUMMARY

Maternal AZA or 6-MP treatment during pregnancy is clearly teratogenic in animals at doses similar to or greater than those used in humans, but information on the teratogenicity of these medications in human pregnancy is limited. Most available information is from single cases or clinical series of organ transplant recipients or women undergoing treatment for cancer. Less information is available on the use of AZA or 6-MP for treatment of other diseases in pregnant women. Without the benefit of well-controlled studies, it is difficult to determine if the risk of birth defects is higher among infants whose mothers are treated with AZA or 6-MP during pregnancy than in the general population. Given the animal and mechanistic data, however, one must assume that some risk exists with chemotherapeutic doses of 6-MP early in pregnancy. The available human data, although limited, suggest that this risk is not great.

In addition, prenatal exposure to these drugs may cause bone marrow suppression in neonates. It is likely that women treated with AZA or 6-MP for malignancies have a higher risk of adverse pregnancy outcomes than women treated for other diseases because of the higher doses used to treat cancer. The evidence from clinical series suggests that the risk of congenital anomalies among infants of transplant recipients who are treated with AZA throughout pregnancy is minimal to small. One might expect a greater risk on the basis of the animal studies, but the poor bioavailability of AZA and 6-MP after oral administration may produce levels that are too low to have a substantial teratogenic effect.

Both AZA and 6-MP are often used in conjunction with other medications. The teratogenic risks associated with polydrug therapy that includes AZA or 6-MP may be greater than the risks associated with maternal monotherapy with either drug.

Genetic variations may influence the teratogenicity of AZA or 6-MP. Women with polymorphic variants that reduce the activity of TPMT may experience potentially toxic drug levels when treated with conven-

tional doses of AZA or 6-MP. The occurrence of higher circulating concentrations of drug in women with such genetic variants seems likely to increase their risk of an adverse pregnancy outcome, but this has not been studied.

It is important to remember that many of the women treated with cytotoxic immunosuppressants such as AZA and 6-MP have serious illnesses. Poor pregnancy outcomes are common among women with chronic illnesses, such as cancer and rheumatic diseases. Nevertheless, these medications may permit a woman to become pregnant who otherwise would be too ill to do so. These chronic diseases may pose very serious risks to both the mother and fetus during pregnancy. In many cases, the risk associated with effective treatment using AZA or 6-MP may be smaller than the risk that accompanies an untreated pregnancy in a seriously ill woman.

Because AZA and 6-MP inhibit the synthesis of nucleic acids, it is possible that treatment with these drugs interfere with DNA replication in the germ cells. Although cytogenetic abnormalities and congenital anomalies have been described in a few of the offspring of patients treated with AZA or 6-MP before conception, too little information is available to draw any firm conclusions regarding the germ-cell mutagenicity of these drugs. Large populations are required to detect even a small increase in germ cell mutation (Byrne, '99). The limited available data suggest that the risk of birth defects associated with preconceptional treatment with these drugs is likely to be increased only slightly, if at all.

COUNSELING THE PREGNANT PATIENT

Women of reproductive age who must be treated with AZA or 6-MP should be advised about the potential teratogenic and mutagenic risks of these drugs in humans. In addition to the factors mentioned above, a woman's risk of giving birth to an infant with congenital anomalies will depend on her state of health, other potentially adverse exposures, previous and current pregnancy history, and family history. In general, an individual's risk should be presented with reference to the background risk of congenital anomalies that attends every pregnancy; but because of her illness, the "background" risk for a woman who requires treatment with AZA or 6-MP will probably be higher than the 3–5% that is usually quoted for the general population. Women who must be treated during the first trimester of pregnancy with AZA or 6-MP will have a higher risk of teratogenic effects than women treated in the 2nd or 3rd trimesters.

Pregnancies in women who require AZA or 6-MP treatment require careful management and coordinated perinatal and medical care. Detailed fetal ultrasound examination can be used to screen for many serious fetal malformations and to monitor fetal growth and well-being (Framarino di Malatesta et al., '93; Davison, '95).

Although potentially teratogenic, drugs such as AZA and 6-MP enable some chronically ill women to have healthy children. The risks and benefits of treatment must be carefully balanced by the patient in consultation with her doctor and partner. More research is needed to develop alternative therapeutic agents that can be used safely during pregnancy.

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