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Malignant Neoplasms Subsequent to Treatment of Inflammatory Bowel Disease With 6-Mercaptopurine

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OBJECTIVE: Most complications of 6-mercaptopurine (6MP) used in the treatment of inflammatory bowel disease (IBD) occur early, whereas neoplasms occur late in the course. Concern persists that the risk is increased when 6MP is used. We report our experience with malignant tumors developing over 27 yr of treating IBD patients with 6MP.

METHODS: A total of 591 patients with IBD treated with 6MP between 1969 and 1997 were followed or traced until present to identify all malignant tumors and blood dyscrasias that had developed to determine the type, distribution, and duration of the IBD, the dose and duration of 6MP therapy, the concurrent *versus* previous use of 6MP, the incidence and probable relationship of 6MP to specific neoplasms, and whether the 6MP had been effective in treatment.

RESULTS: A total of 550 patients (93%) fulfilled the criteria for follow-up; these included 380 with Crohn's disease (CD) and 170 with ulcerative colitis (UC). Twenty-five patients had developed neoplasms (16 of 380 CD and nine of 170 UC) ($p = 0.66$). In half of the cases, the goal of therapy had been achieved with 6MP. In 10 patients, the neoplasm was diagnosed while the patients were taking 6MP (40%) and in 15, many years after the 6MP had been terminated (60%). The incidence of neoplasms (25 of 550) was 2.7/1000 patient-years of follow-up. The most common neoplasms were found in the bowel (eight of 550, 1.6%; five CD, and three UC), and breast (three, 0.5%; two CD, and one UC). Non-Hodgkins lymphomas occurred in two patients with CD; one was cerebral and the other abdominal. One patient with CD developed leukemia. The duration of 6MP therapy ranged from 5 months to 22 yr, with a mean of 5 yr. The dose of 6MP ranged from a quarter of a tablet/day (12.5 mg) to 100 mg/day, with the majority in a range from 50 to 75 mg/day.

CONCLUSION: In no instance could a neoplasm be attributed to the use of 6MP. The incidence of colon cancer is not greater than that with long standing colitis. Suspicion of a relationship between 6MP and leukemia/lymphoma persists, but the incidence is low. This must be weighed against the improved quality of life due to 6MP for patients with IBD.

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INTRODUCTION

Most complications of 6-mercaptopurine (6MP) or azathioprine (AZA) during treatment of Crohn's disease (CD) or ulcerative colitis (UC) occur early after their introduction, seem not to be dose related, are due to an allergic reaction, and are reversible on stopping the drug (1–4). Malignant tumors, however, have sometimes occurred both during and after termination of therapy (1–2, 5). Concern persists among both physicians and patients that the risk of cancer is increased when these immunomodulating drugs are used. We report here our experience with malignant tumors developing over 27 yr of treating IBD patients with 6MP.

To determine how many patients treated with 6MP developed any form of malignancy either during or subsequent to termination of treatment and to observe any increase in incidence of a particular tumor in regard to location, type of other predispositions, and dose and duration of 6MP therapy.

MATERIALS AND METHODS

Records of patients treated with 6MP in one private practice of gastroenterology (B.I.K.) or admitted to the IBD center at Lenox Hill Hospital over a 27-yr period were sought and reviewed by at least two of the authors as of the time of the last office or hospital visit to determine whether the patient had ever developed a malignancy, as well as its type, course, and possible relationship to the drug. Those patients not being followed currently were traced until death or until current status as of 1997 via last addresses, telephone numbers, referring physicians, and subsequent physicians to gather this information. The prevalence and incidence of each malignant neoplasm was determined when feasible for patients with CD and UC not treated with immunomodulators, in search of any possibly statistically significant increase attributable to having taken 6MP.

RESULTS

A total of 591 patients with IBD were treated with 6MP at some time between 1969 and 1997; 550 (93%) were followed until the present and only 41 (7%) could not be traced. Twenty-five had developed a malignant neoplasm or equivalent blood dyscrasia. Four patients with basal cell carcinoma or squamous cell of the skin were excluded from this study, as in no case did it serve to eliminate treatment with 6MP or otherwise alter the prognosis. Data on the type of neoplasm and its relationship to 6MP use are included in Table 1; the data includes the type of IBD, its distribution, the age of onset of IBD and of the neoplasm, duration of disease at the time of diagnosis of the cancer, as well as the effectiveness of the 6MP in treating the IBD as determined by achievement of goals of therapy (6).

The mean duration of IBD at the time of diagnosis of the neoplasm was 20 yr (CD 23, UC 15) with a range of 10–56 years. The mean duration of treatment with 6MP until the diagnosis of the neoplasm was 8 yr (CD 7, UC 9) with a range of 0.5–23 yr. Twenty five patients had developed neoplasms. Sixteen of 380 patients with CD and nine of 170 patients with UC developed neoplasms ($p = 0.66$). In half of the cases the goal of therapy had been achieved with 6MP, and in the other half it had not. In 10 patients the neoplasm was diagnosed while the patients were taking 6MP (40%), and in 15 (60%) many years after the 6MP had been terminated. The prevalence of neoplasms was 25 of 550, or 4.5%. The 550 patients were followed for an average of 17.43 yr each, for a total of 9218 person-years of follow-up subsequent to the use of 6MP. The specific incidence of some malignancies are provided in Table 2 according to person-years of follow-up of the IBD and the duration of 6MP.

The most common neoplasms were found in bowel (eight of 550, 1.6%; five CD, three UC), and breast (three, 0.5%; two CD, one UC). Non-Hodgkins lymphomas occurred in two cases; one was cerebral and the other abdominal. One patient with CD developed leukemia. Table 2 provides the specific incidence of total bowel cancers, blood dyscrasia, and lymphomas. The overall incidence of total neoplasms for this cohort was 2.7/1000 yr of follow-up.

The duration of 6MP therapy ranged from 5 months to 22 years, with a mean of 5 years. The dose of 6MP ranged from a quarter of a tablet per day (12.5 mg) to 100 mg/day, with the majority ranging from 50 to 75 mg/day. The dose was not determined by body weight but was started at 50 mg/day, increased when success had not been achieved and the white blood count and platelet levels permitted, and reduced when the initial dose was not tolerated.

Table 3 provides the outcome of the 25 patients. Nine patients including the one with abdominal lymphoma remain alive and most are well, whereas 16 have died; in all except one, the death was caused by the carcinoma or blood dyscrasia.

DISCUSSION

Twenty years ago, any reluctance to use 6MP or AZA in treatment and for maintenance of remission of IBD could be attributed both to lack of conviction as to efficacy and to fear of the unknown potential toxicity. The efficacy has now been demonstrated and confirmed (6–13). The most common complications of 6MP and AZA include systemic allergies, pancreatitis, and bone marrow depression, all of which are reversible by early detection and by stopping the drug; the remaining area of greatest concern is malignancy. Data presented until now have greatly relieved this concern (1, 2, 13), but the lack of accurate controls from the general population and the IBD population not treated with immunosuppressives has not erased all doubt.

This report of malignant neoplasms or blood dyscrasias found in 25 of 550 patients treated with 6MP, with a 93% follow-up to 1997, provides further evidence of the relative safety of the drug. The overall prevalence of neoplasms in our earlier study had been 3.1% (1), but the mean duration, of follow-up from onset of IBD to the diagnosis of malignancy then had been 5 yr, whereas in the current study the mean follow-up has been extended to 17.4 yr. Furthermore, the mean duration of treatment with 6MP had been 33.6 months (range 1–162 months) and, in the current study, 8 yr (6 months to 23 yr). Therefore, the number of treated patients, the duration of follow-up, and the length of time patients were treated with 6MP have all been increased, permitting a greater vulnerability to cancer in the general IBD population as well as in IBD patients treated with 6MP.

The cancer most logically expected to increase in incidence if provoked by an immunosuppressive drug would arise from the colon (14) and the incidence should be equal in CD and UC (15). We did indeed encounter seven bowel cancers. One of these was a carcinoma of the terminal ileum discovered at ileocolic resection performed for small bowel obstruction, and the other small bowel carcinoma occurred at the site of ileocolic anastamosis after 56 years of CD; both were more likely to have occurred in the natural course of CD than related to 6MP. Of the five carcinomas of the colon (0.9%), three had UC and two had extensive Crohn's ileocolitis; the mean duration of the UC was 23 yr (range 11–29 yr) and the other two suffered with CD for >30 yr. In the one patient with carcinoma of the colon reported in our earlier study, the 58-yr-old man had UC for 38 yr; elective surgery recommended for active disease had been refused before the introduction of 6MP, which was taken only briefly (6). In this patient and one other, low grade dysplasia had been found earlier and, coincidentally, in another two of five cases of colorectal cancer. Dysplasia led to resection in one case only, whereas the lesion was recognized endoscopically in the other four. In the study by Bouhnik *et al*., of 157 patients with CD treated with 6MP or AZA, no bowel cancers were found (12). Connell *et al*. (16) found a significant difference in colorectal and anal carcinomas among 755 patients with IBD who were treated with AZA, com-

Table 1. Malignant Neoplasms in 25 IBD Patients Once Treated With 6MP

Case No.	Type of Cancer	IBD Type	IBD Distribution	Age at Onset of IBD (yr)	Age at Diagnosis of Neoplasm (yr)	Duration of IBD (yr)	Duration of 6MP (yr)	Effectiveness of 6MP	6MP Mean Dose	6MP Stopped Before Neoplasm	Years Off 6MP
1	colorectal rectum	CD	ileocolic	26	50	24	4.5	–	50 (50–100)	+	21
2	colorectal rectum	UC	universal	48	69	21	2	–	75 (50–100)	+	?
3	colorectal cecum	UC	universal	49	58	11	?	–	100	+	?
4	colorectal desc.	UC	universal	9	32	23	2	+	50 (25–75)	–	
5	colorectal rectum	CD	ileocolic	14	43	29	8	–	50 (50–100)	+	23
6	ileum	CD	ileum	24	34	23	<1	–	25 (25–100)	–	
7	ileocolic anastamosis	CD	ileum	13	69	56	5.5	–	50 (1–100)	+	12
8	colocutaneous fistula desc.	CD	colon	20	52	32	8.5	+	50 (25–75)	–	
9	adenocarcinoma primary site undetermined	UC	universal	12	35	22	3	+	50 (50–100)	–	
10	stomach	UC	universal	50	65	15	<1	+	50 (50–100)	+	12
11	Islet cell pancreas	CD	recurrent ileitis	42	53	11	5	+	100 (25–100)	+	?
12	breast	UC	left-sided	21	51	30	3.5	+	100 (2–100)	+	23
13	breast	CD	colon	23	33	10	13	+	50 (50–100)	–	
14	breast	CD	ileum	64	84	20	6	+	50–100	–	
15	ovary	UC	universal	50	63	13	1	–	25 (12–50)	+	?
16	uterine cervix	CD	colon	20	40	20	3.5	–	12 (12–100)	+	?
17	skin (melanoma)	UC	left colon	63	66	3	2.5	–	75 (25–75)	+	1
18	testicle	CD	colon	20	43	23	7	+	25 (20–50)	+	20
19	testicle	CD	ileum	22	33	11	6	–	25 (25–100)	+	6
20	lung	CD	ileum	34	64	30	4	–	25	–	
21	lung	UC	left sided	53	63	10	1.3	–	75 (50–100)	–	
22	lymphoma (abdomen)	CD	ileum	39	50	11	7.5	+	35 (12–50)	–	
23	lymphoma (brain)	CD	ileum	16	52	36	.4	–	100 (50–100)	+	1
24	leukemia	CD	ileocolic	36	65	29	9	+	50 (25–10)	+	0.4
25	Waldenstrom's macroglobulinemia	CD	ileum	35	55	20	2	+	25 (12–50)	+	1

CD = Crohn's disease; IBD = inflammatory bowel disease; 6MP = 6-mercaptopurine; UC = ulcerative colitis.

Table 2. Incidence of Selected and Total Neoplasms (per 1000 Person-yr of Follow-up)

Type	No. of Persons	Incidence
Total bowel	8	0.87/1000
Colorectal	5	0.54/1000
Total lymph and blood dyscrasias	4	0.43/1000
Lymphoma	2	0.22/1000
Leukemia	1	0.11/1000
Total neoplasms	25	2.7/1000

pared with the general population (13 *vs* 2.24); but when the frequency of colorectal cancer among patients with extensive UC for >10 yr who had received AZA treatment was compared to that in similar patients who had not received AZA, there proved to be no significant difference. Although it cannot be concluded that any one case of bowel carcinoma influenced in its development by the extent and duration of the underlying IBD is not accelerated by an immunosuppressive drug, there are no data to support any such increase in incidence.

Other cancers occurring in the current IBD population once treated with 6MP include breast in three patients (1.1% of the female population in this study), lung in two (<1%), testicle in two (<1% of male patients), cervix in one, ovary in one, and islet cell carcinoma of the pancreas in one. None of these seemed to have an incidence greater than that in the general population or in the IBD population not treated with 6MP.

Perhaps the neoplasm of greatest concern is the non-Hodgkins lymphoma, which occurred two times in this experience. One was an extraintestinal abdominal B cell lymphoma in a 39-yr-old man who had ileitis for 11 yr, who already had one ileocolic resection, and who was otherwise in remission on 6MP for 7.5 yr. There is no evidence of recurrent lymphoma 8 yr later after appropriate chemotherapy, but there is clinical and endoscopic evidence of recurrent ileitis. Connell *et al*. (16) also reported a case of non-Hodgkins lymphoma in an 89-yr-old man who had finished two yr of AZA for distal UC three yr earlier. The other lymphoma in our series was a non-Hodgkins cerebral histiocystic lymphoma in a 53-yr-old man with Crohn's disease for 37 yr who had been treated with 6MP for 9 months, had been off the drug for 11 months, and who died of this complication. This case was reported previously (1). A brain lymphoma was also included in the series of CD patients treated with AZA by Bouhnik *et al*. (11); this 37-yr-old woman was successfully treated with radiation and chemotherapy, with no evidence of recurrence 7 yr later. It is difficult not to attribute a cerebral lymphoma to immunosuppressive therapy, as it is a rare tumor, reported mostly in transplant recipients who have also been treated with large doses of immunosuppressive drugs (5) and in other conditions treated with immunosuppressives (17). This reasoning is confounded, however, by reports of an increased incidence of lymphomas in patients with both UC and CD not treated with immunosuppressives (18, 19) and an abrupt rise in the number of recorded cases of primary lymphoma of the central nervous system in nonimmunosuppressive cases limited to the period from 1990 to 1991 (20). Nevertheless, in Kinlen's study of neoplasms after transplant surgery, the incidence of non-Hodgkins lymphoma, including cerebral lymphomas, was markedly increased (observed 42, expected 0.85, relative risk 49.4) (21). Evidently, there must still be other factors to be considered, such as a lesser dose used in treatment of a disease as opposed to transplants, as the number of cases of non-Hodgkins lymphoma observed by Kinlen after immunosuppressive treatment of rheumatoid arthritis was only four (expected 0.31, relative risk 21); no cases of lymphoma developed among 321 patients with CD and UC treated similarly (22). It cannot be concluded that one malignant melanoma be considered to be due to 6MP, when the same tumor has been reported in 11 patients with IBD (nine CD, two UC) not treated with 6MP (23). Nevertheless, this has been reported once before in relation to immunosuppressives (12).

Table 3. Type and Outcome of Neoplasms

	Type of Cancer	Type of IBD	Alive or Dead
1	colorectal (ascending)	CD	L
2	colorectal (rectal)	CD	D
3	colorectal (cecal)	UC	D
4	colorectal (rectal)	UC	D
5	colorectal (rectal)	UC	D
6	terminal ileum	CD	L
7	ileocolic anastamosis	CD	L
8	colocutaneous fistula (left flank)	CD	D
9	metastatic adenoca	UC	D
10	Carcinoma of stomach	UC	D
11	Islet cell Carcinoma of pancreas	CD	D
12	Carcinoma of breast	UC	L
13	Carcinoma of breast	CD	L
14	Carcinoma of breast	CD	D
15	Carcinoma of ovary	UC	L
16	Carcinoma of uterine cervix	CD	D
17	melanoma of skin	UC	D
18	Testicular germ cell tumor	CD	L
19	Testicular seminoma	CD	L
20	Carcinoma of lung adenosquamous	CD	D
21	Carcinoma of lung	UC	D
22	lymphoma, non-Hodgkins B cell	CD	L
23	lymphoma, cerebral	CD	D
24	leukemia	CD	D
25	Waldenstrom's macroglobulinemia	CD	D

CD = Crohn's disease; D = dead; IBD = inflammatory bowel disease; UC = ulcerative colitis.

There were two patients with CD who developed blood dyscrasias. Anemia in one 57-yr-old woman with a 25-yr history of ileitis and 2 yr of treatment with 6MP led to a diagnosis of Waldenstrom's macroglobulinemia. This is a lymphoproliferative disease and probably should be grouped with other lymphomas. Persistent leukopenia in a 64-yr-old woman with a 34-yr history of extensive ileocolitis and 9 yr of treatment with 6MP led to a diagnosis of myelodysplasia terminating as acute myelocytic leukemia.

Leukemias have been reported in patients with IBD not treated with immunomodulators (24–30).

The number of IBD patients who developed cancer, lymphoma, or blood dyscrasia is too small to compare with data from the national population of the United States. There are studies from Sweden on the population of patients with IBD untreated with 6MP or AZA (31, 32). The most common malignancies (breast, lung, and colon) are apparently not more frequent in our 6MP-treated IBD population than in any general population.

No conclusion would be justified in attributing the malignancies or blood dyscrasias to 6MP or AZA with single cases of cancer of the stomach, ovary, uterine cervix or melanoma. However, suspicion without conclusion persists about the two cases of testicular carcinoma, one leukemia and two lymphomas—one of which was a rare brain lymphoma, as described in the transplant literature. Nevertheless, most of these malignancies (including pancreatic, breast, liver, cervix and pancreatic islet cell) have been reported in association with IBD, especially CD, not treated with 6MP or AZA (33). Even the brain lymphoma most likely to be influenced by 6MP/AZA has been reported only twice (1, 12). In our own experience, the effectiveness of 6MP once the drug is stopped diminishes rapidly by more than one-third in 1 yr and by two-thirds in 2 yr (34). Although it cannot be stated that in any one case the 6MP contributed to the development of the malignancy or the blood dyscrasia, the risk must be very small and it must be weighed against a prolonged remission from the destructive results of CD and UC, which too may result in death (35). In fact, the prolongation of life and health in itself increases the time for which cancer has the opportunity to develop (36). To some patients with CD and UC, still more important than any small risk of cancer is the crippling influence on the quality of life caused by their disease, especially when it starts at an early age.

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