Risk of malignancy in myasthenia gravis patients exposed to azathioprine therapy for a median period of 3 years

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To the Editor: The long-term risk of malignancies in patients treated with immunosuppressive drugs is a concern among patients and physicians. Patients with myasthenia gravis (MG) respond well to azathioprine (Aza) but many require long-term treatment. The therapeutic effect is presumably largely due to reduced proliferation of actively dividing lymphocytes; however, the benefit of suppressing autoreactive lymphocytes may theoretically result in a concomitant reduction of immunosurveillance and thereby increase the risk of cancer.

Many have assessed the malignancy risk in autoimmune diseases such as inflammatory bowel disease (IBD) and rheumatoid arthritis (RA), but these may have their own inherent risk such as colorectal cancer in IBD or lymphoma in RA.[1,2] Few studies have been published related specifically to Aza exposure and cancer risk in MG.[3,4] This report concerns the incidence of cancer in a South African MG cohort specifically assessing the Aza dose and the duration of treatment.

Since 1996 observational data have been collected at 1 - 6-monthly intervals at our MG clinic; data before 1996 were retrieved from hospital records. Only patients followed for at least 12 months were included. Prednisone was not considered an immunosuppressive for this analysis. Follow-up data were included until 31 December 2004; records on those not seen in the last 6 months of data retrieval were updated by scrutinising hospital folders for contact with other units, or telephonic contact with those living outside the hospital referral area. The study was approved by the University of Cape Town Research Ethics Committee (109/2005).

Patients were divided into two categories, those exposed to Aza and those not exposed. The cumulative Aza dose (mg/kg) was calculated for each patient. Exposure time was calculated from time of initiating Aza until the last observation. In those patients who developed cancer, the time at cancer diagnosis was considered the endpoint (T_{ca}). If more than one cancer developed, the first cancer was taken as the endpoint. Among the exposed, the dose and duration of treatment were taken as those at T_{ca}. Incidence rates were calculated by taking the number of cancers in each category divided by the appropriate number of person-years. In the exposed category, the denominator (person-years) was the sum of the total exposure time plus the T_{ca}, where relevant. In the unexposed category the person-years was the sum of follow-up times (from MG diagnosis) or until a cancer developed. The relative risk (RR) was the ratio of the cancer incidence rates (exposed/unexposed). Age-specific incidence rates (ASIRs) per 100 000 population were taken from the latest figures in South Africa specific for the particular cancer, gender and ethnic group of the patient.[5] Normally distributed variables were assessed using the 2-sided t-test. Variables with a skewed distribution were summarised as median and interquartile ranges (IQRs) and assessed using the Kruskal-Wallis test. Qualitative variables were analysed using chi-squared tests or Fisher's exact tests. Incidence rate ratios and continuous variables were analysed using Poisson regression. A p-value ≤ 0.05 was considered statistically significant.

After screening 257 MG data entries, only 191 were analysed; 11 patients were excluded as they were on immunosuppressants other than Aza, 16 had either defaulted or were untraceable, and 39 were seen as once-only consultations. One hundred and forty-four subjects had been exposed to Aza and 47 had not been exposed; the mean ages of the groups were 44.43 and 43.72 years, respectively ($p = 0.81$). The proportion of females (73% Aza-exposed, 64% unexposed) and the number of deaths recorded (11/144 and 5/47, respectively) were similar ($p > 0.3$). Those in the Aza-exposed category were followed up for a significantly longer period; cumulative exposure time was 587.3 person-years compared with the follow-up time in the unexposed group of 196 person-years ($p = 0.004$). The median Aza exposure time was 3.4 years (IQR 1.9 - 5.5).

Eight female patients (4.2%) developed cancers (Table I); 3 (2.1%) among the Aza-exposed subjects and 5 (10.6%) among those unexposed ($p = 0.023$). An individual in both groups developed 2 cancers 2 years apart. Only patient G developed MG 30 years after her mastectomy for breast cancer; because of the long interval between the cancer and MG diagnosis we excluded her from the RR calculation. Although the average ages between the two groups were similar, the Aza-exposed subjects developing cancers were older than those never exposed (mean age at T_{ca} in exposed subjects 60.3 years and in unexposed subjects 41.8 years). Table I shows the cancer types, ages at T_{ca} and the appropriate ASIR for that individual. At first glance it appears that breast cancer predominates but the ASIRs for breast cancer are high. Two patients (A and C) in the

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Table I. MG patients who developed cancer (Ca)

	Exposed to azathioprine			Not exposed to azathioprine				
	A	B	C	D	E	F	G	H
Type of cancer	Breast	Breast	Gastric	Breast	Melanoma	Breast	Breast	Breast
Age at cancer diagnosis (yrs)	52	70	59	41	30	40	40	58
Cumulative dose (mg/kg)*	1 074	1 881	5 097	–	–	–	–	–
Years of exposure	1.6[†]	2.5	5.6	–	–	–	–	–
Follow-up (yrs)	8.5	4.9	8.4	18.7	9.8[‡]	27.8	4.8	10.3
ASIR	110.03	233.16	12.77	77.33	15.13	126.26	77.33	156.89
Death	Yes	No	No	No	No	Unknown[§]	Yes	No
Cause of death	Rectal cancer	No	No	No	No	Unknown[§]	Stroke	No

*Cumulative dose refers to the azathioprine dose (mg/kg) from initiation to diagnosis of cancer.
[†]Developed rectal cancer (ASIR 6.67) 2 years later.
[‡]Developed cancer of the cervix (ASIR 16.14) 2 years later.
[§]Metastatic breast cancer at last contact.

ASIR = age-specific incidence rate per 100 000.[5]

exposed group developed cancers with low ASIRs, but so did patient E in the unexposed group, who developed 2 cancers with low ASIRs.

Although the linear relationship between cumulative Aza dose and duration of treatment was expected, there was no correlation between the development of cancer and either dose or duration of Aza exposure ($p > 0.5$, Fig. 1). Only 22 exposed subjects had been followed up for 7 years or longer.

The incidence rate for exposed patients was 5.1 per 1 000 person-years, and for the unexposed 18.3 per 1 000 person-years. The RR risk for developing cancer when exposed to Aza was 0.28 (95% confidence interval (CI): 0.04 - 1.44, $p = 0.081$). For every 1-year increase in subject age the RR in a patient on Aza increases 1.01-fold (95% CI: 0.97 - 1.05). This was not statistically significant ($p = 0.555$). The cancer incidence in MG with thymoma was 12.5 per 1 000 person-years compared with 8.96 per 1 000 person-years in MG without thymoma; this apparent 40% (95% CI: 3.1 - 1089.5%) increased RR of cancer among those with thymoma was not significant ($p = 0.753$). The
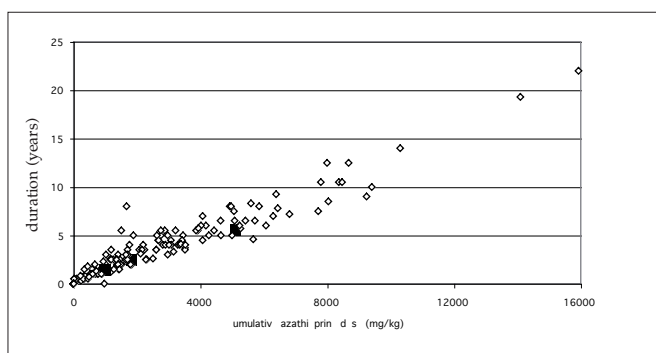
Fig. 1. Duration and dose of azathioprine in exposed subjects with and without cancer. (■ azathioprine (Aza)-exposed patients who developed cancer; ◊ Aza-exposed patients without cancer. Median cumulative Aza dose = 1 979 mg/kg (IQR = 1 138 - 4 040.)

range of the CI illustrates the lack of precision because of the small sample. There were no deaths directly attributed to Aza exposure (data not shown).

This study shows no relationship with either the cumulative dose or the length of treatment in South African patients with MG exposed to Aza for a median period of 3.4 years. There are few publications addressing cancer risk in MG patients on Aza treatment.[3,4,6] None assessed the risk of cumulative Aza doses. Two studies comparable in cohort size (N = 104 and N = 159) and duration of Aza exposure (median 2.4 - 3.4 years), found that 5% of their Aza-exposed patients developed malignancies.[3,4] The authors of both articles did not consider Aza to increase the risk of malignancy significantly compared with age-appropriate controls, nor did they find a predominance of specific cancers. Although breast cancer was prominent in our cohort, there was no difference between the incidence in the exposed and unexposed groups.

Isolated reports of lymphoma in Aza-exposed MG patients have raised concern. One person developed renal lymphoma after 6 years of Aza exposure,[3] 2 developed primary central nervous system lymphoma after 6 and 12 years on Aza[4] and another developed non-Hodgkin's lymphoma of the testes after 8 years.[7] A case of gastric lymphoma was published but the duration of Aza therapy was not reported.[8] There were no cases of lymphoma in this cohort. Analyses of large groups of IBD patients exposed to Aza have not shown an increased incidence of lymphoma.[1,9]

Our results are consistent with those for systemic lupus erythematosus[10] and multiple sclerosis (MS);[11] patients treated with Aza for less than 5 years do not have a significant risk of malignancy. However, the risk appeared to increase in a large cohort of rheumatic patients treated for more than 6 years,[12] and MS patients exposed to Aza for 10 years have a RR of 4.4.[11] Although none of the 22 MG patients in this cohort treated for 7

years or more developed cancers, a larger patient cohort needs longer follow-up for more conclusive results regarding the very long-term risk of cancer in MG patients.

A recent study found that 15% of MG patients developed cancer, regardless of therapy.[8] This is contrary to the experience of others (1.7 - 7.6%)[13] and the findings of the present cohort in which only 4% overall developed cancer. A similar-sized study reported the presence of thymoma with MG to be a risk factor for developing extrathymic malignancies[6] but others[8] found no association. Statistically our results showed that a much larger sample would be needed to yield informative data.

Although our MG patients who developed cancers were generally older, we did not find age to be a confounder for the development of cancer on Aza. The proportion of elderly MG subjects is increasing[14] and cancer incidence generally increases with age.[5] Also, where lymphoma did occur in myasthenics after many years of Aza therapy, the patients were older than 50 years.[4,7,8] Therefore, data are needed on older patients treated with Aza.

Another drawback of our study is the use of retrospective and observational data; patients with more severe disease, requiring higher doses and longer periods of therapy are likely to attend the hospital and report cancers. Despite this the proportion of cancers in the exposed group was lower than in the unexposed group. Previous studies[3,4,8] and this study have comparatively small cohorts but all four independently draw the same overall conclusion.

In summary, this report on cancer risk in Aza-treated MG patients found no increased risk of cancer in patients treated for less than 5 years. The results of long-term exposure in larger cohorts, especially of older patients, is now required.

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