CONCISE REPORT

Antimalarials may influence the risk of malignancy in systemic lupus erythematosus

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Background: Recent studies suggest that antimalarials have antineoplastic properties.
Objective: To investigate whether antimalarials decrease the risk of cancer in systemic lupus erythematosus (SLE).
Methods: An observational prospective cohort study was carried out. 235 patients were included in the study at the time of diagnosis (American College of Rheumatology criteria). The end point was the diagnosis of cancer. Kaplan–Meier cancer-free survival curves for patients treated and not treated with antimalarials were compared. A Cox proportional hazards model was fitted, with cancer as the dependent variable. Age at diagnosis, gender, treatment with azathioprine, cyclophosphamide and methotrexate, smoking, Systemic Lupus International Collaborating Clinics (SLICC) Damage Index 6 months after diagnosis, year of diagnosis and treatment with antimalarials were entered as independent variables.
Results: 209 (89%) patients were women. 233 (99%) patients were white. Mean (SD) age at diagnosis was 37 (16) years. Median (range) follow-up was 10 (1–31) years. 156 (66%) patients had ever received antimalarials. 2/156 (1.3%) ever-treated patients compared with 11/79 (13%) never-treated patients had cancer ($p<0.001$). Cumulative cancer-free survival in treated and not treated patients was 0.98 and 0.73, respectively ($p<0.001$). Adjusted hazard ratio for cancer among malaria drug users compared with non-users was 0.15 (95% CI 0.02 to 0.99).
Conclusions: This study launches the hypothesis of a protective action of antimalarials against cancer in patients with SLE. This effect should be confirmed in larger multicentre studies.

Recent studies have shown that patients with systemic lupus erythematosus (SLE) are at increased risk of cancer.[1 2] Not surprisingly, neoplastic diseases are among the leading causes of death in patients with lupus.[3 4]

Antimalarials are among the most frequent medications for lupus. They are usually prescribed to patients with mild–moderate disease, but long-term beneficial effects are being recognised.[4] A new potential therapeutic field has just opened for antimalarials. A recent randomised clinical trial has shown that chloroquine could be useful as adjuvant therapy in patients with glioblastoma.[5] Our aim is thus to investigate the potential effects of malaria drug treatment on the development of cancer among patients with SLE.

METHODS

Study design and patients

All patients with lupus attending the Internal Medicine Department, Hospital de Cruces, University of the Basque Country, Bizkaia, Spain, have been included in an ongoing prospective, observational study. All patients fulfilled the updated American College of Rheumatology criteria for the classification of SLE[6] and were included in the cohort at the time of lupus diagnosis (T_0). This was defined as the point when four American College of Rheumatology criteria were first met and was also the starting point of the follow-up time. For the purposes of this study, patients who were children (ie, <14 years) at the time of SLE diagnosis were excluded (n = 5).

Variables studied

Detailed information on the characteristics of our cohort and database have been published.[4] Briefly, patients are assessed every 3 months, unless more (active patients) or less frequent visits (long-standing inactive patients) are required. Clinical and immunological variables are incorporated into the database at T_0, and then on every subsequent visit. The Systemic Lupus International Collaborating Clinics (SLICC) Damage Index (SDI) has been used to quantify the presence of irreversible organ damage.[7] For the purposes of this study, we considered that a given patient was exposed to antimalarials if treated for any period lasting at least 6 months.

End point

The end point of this study is the development of a neoplasm. The diagnosis required radiological and/or histological confirmation, either before or after death. Premalignant lesions were not included as end points.

Statistical analysis

Patients were divided into those ever treated and never treated with antimalarials. The χ^2 test was used to compare the frequencies of cancer in both groups. Kaplan–Meier cancer-free survival curves were created and compared by means of the log rank test. A Cox proportional hazards model was fitted, with cancer as the dependent variable. Apart from antimalarials, age at diagnosis, gender, treatment with azathioprine, cyclophosphamide and methotrexate, smoking, SDI 6 months after diagnosis (divided into three categories: 0, 1 and >1) and year of diagnosis (divided into three groups: 1975–85, 1986–95 and 1996–2005) were entered as independent variables, given their potential influence in the development of neoplasms. Treatment variables were only counted if patients received the drug prior to the time of diagnosis of cancer. The proportionality of the risk of cancer over the time was confirmed using Schoenfeld residuals.

RESULTS

General characteristics of the cohort

A total of 235 patients were studied. Of them, 209 (89%) were women. Only 2 (0.9%) patients were black. Mean (SD) age at T_0 was 37 (16) years. Median (range) follow-up time was 10 (1–31) years. A total of 156 (66%) patients were ever treated

Abbreviations: SDI, Systemic Lupus International Collaborating Clinics (SLICC) Damage Index; SLE, systemic lupus erythematosus

Table 1 Distribution of potential risk factors for cancer among patients treated and not treated with malaria drugs

	Malaria drugs		
	Yes (n = 156)	No (n = 79)	p Value
Mean (SD) age at diagnosis (years)	34 (14)	42 (17)	0.001
Males	14 (9)	12 (15)	0.22
AZA	52 (33)	20 (25)	0.26
CPM	37 (24)	24 (34)	0.12
MTX	27 (17)	3 (4)	0.006
Smoking	63 (40)	24 (30)	0.17
SDI			
0	129/156 (82)	45/79 (56)	
1	23/156 (15)	20/79 (25)	<0.001
>1	4/156 (3)	14/79 (17)	
Year of diagnosis			
1975–1985	19/34 (56)	15/34 (44)	
1986–1995	63/110 (57)	47/110 (43)	0.001
1996–2005	74/91 (81)	17/91 (19)	

AZA, azathioprine; CPM, cyclophosphamide; MTX, methotrexate; SDI, Systemic Lupus International Collaborating Clinics (SLICC) Damage Index, 6 months after diagnosis.
Values are n (%) unless otherwise indicated.

with antimalarials. Median time on antimalarials was 53 (6–238) months.

Comparison between patients receiving and not receiving antimalarials

Patient ever receiving antimalarials were younger, more likely to receive methotrexate and less likely to have severe damage at 6 months than never-treated patients. Likewise, patients diagnosed with SLE during the years 1996–2005 were given antimalarials more frequently. For the remaining variables included in the Cox model, differences between groups were not statistically significant (table 1).

Cancer

The total observational time of the cohort from T_0 was 2620 patient-years. During this period, 13 patients had cancer, resulting in an incidence of 4.9 cases per 1000 patient-years (95% CI 2.6 to 8.5 cases per 1000 patient-years). The specific neoplasms observed were: basal cell carcinoma (n = 3), glioblastoma (n = 2), hepatocarcinoma (n = 1), renal cell carcinoma (n = 1), endometrial carcinoma (n = 1), carcinoma of the cervix (n = 1), breast cancer (n = 1), sarcoma (n = 1), urothelial carcinoma (n = 1) and Hodgkin's lymphoma (n = 1). Median (range) follow-up from T_0 to the time of the diagnosis of cancer was 3 (1–24) years. Seven patients died as a consequence of cancer.

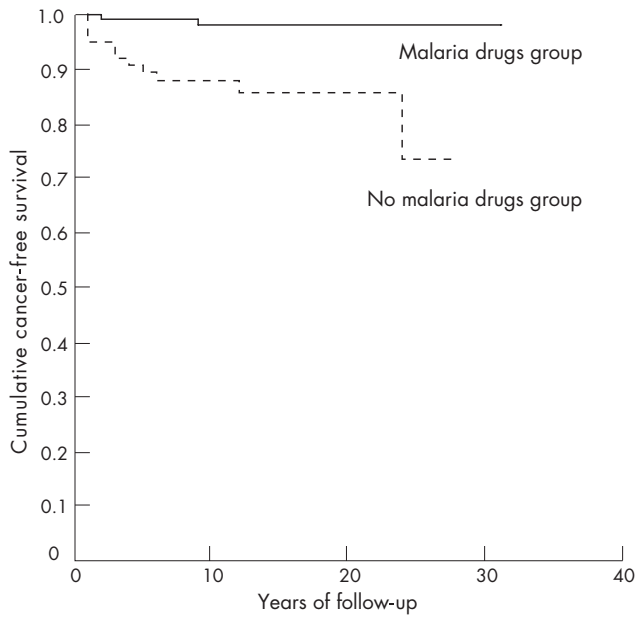

Figure 1 Kaplan–Meier cancer-free survival curves.

Among patients treated with antimalarials, 2/156 (1.3%) patients had cancer compared with 11/79 (13%, p<0.001) not-treated patients. The cumulative cancer-free survival was 0.98 and 0.73, respectively (p<0.001; fig 1). The unadjusted hazard ratio for cancer in ever users of antimalarials compared with never users was 0.10 (95% CI 0.02 to 0.45). The adjusted hazard ratio of patients treated with antimalarials was 0.15 (95% CI 0.02 to 0.99). Apart from antimalarials, only age at diagnosis and male gender showed an independent association with cancer (table 2).

DISCUSSION

A recent international collaborative project, recruiting 9547 patients from 23 centres in North America, Europe and Korea, has found an increased risk of malignancy in patients with SLE, particularly non-Hodgkin's lymphoma, lung and hepatobiliary carcinoma.[2] The incidences of neoplasms found by Bernatski *et al*[2] and ourselves were remarkably similar (5.6 and 4.9 cases per 1000 patient-years, respectively), although no case of non-Hodgkin's lymphoma was seen among our patients.

The causes for the increased susceptibility of patients with lupus to cancer are a matter of debate. The use of immunosuppressive drugs has been frequently advocated, however this point has not been confirmed by most studies.[1 8 9] Likewise, the link between cyclophosphamide and urological malignancies has not been established in lupus, maybe owing to the lower toxic potential of intravenous schedules.[1]

antimalarials are widely used in SLE. They are usually prescribed for mild–moderate manifestations. However, they have important long-term effects in lupus. A recent study has shown that treatment with antimalarials reduces the accrual of damage in patients with SLE.[10] Data from two different observational cohorts suggest that treatment with antimalarials reduces long-term mortality in patients with lupus.[4 11] Such a reduced mortality has been primarily attributed to the prevention

Table 2 Cox proportional hazards model with cancer as the dependent variable

	OR (95% CI)	p Value
Age at diagnosis	1.06 (1.01 to 1.11)	0.018
Male	7.14 (1.61 to 33.3)	0.009
Malaria drugs	0.15 (0.02 to 0.99)	0.049
AZA	0.68 (0.13 to 3.37)	0.632
CPM	2.47 (0.61 to 10.05)	0.205
MTX	1.76 (0.17 to 18.23)	0.634
Smoking	2.12 (0.52 to 8.63)	0.294
SDI		
0	Reference	
1	0.37 (0.06 to 2.36)	0.294
>1	1.29 (0.27 to 6.10)	0.748
Year of diagnosis		
1975–1985	Reference	
1986–1995	5.20 (0.42 to 64.74)	0.2
1996–2005	7.934 (0.46 to 138.16)	0.155

AZA, azathioprine; CPM, cyclophosphamide; MTX, methotrexate; SDI, Systemic Lupus International Collaborating Clinics (SLICC) Damage Index, 6 months after diagnosis.

of cardiovascular events. However, some influence on the other causes of death cannot be discarded. Sultan *et al*[8] included antimalarials in their analysis of risk factors for cancer in SLE and did not find any association, however the temporal relationship with exposure was not taken into account.

Some recent data point to a potential influence of antimalarials in malignancy. antimalarials are weak bases with a well-known tropism for lysosomes.[12] In addition, they are strong DNA-intercalating agents that prevent mutations in cells with a high mitotic rate.[5] Chloroquine has shown an inhibitory action on telomerase, which is centrally involved in the unlimited replication of tumorous cells.[5] Chloroquine also increases the synthesis of Tp53, a short-lived protein which protects DNA against genotoxic stimuli.[13] Although an increase in Tp53 levels usually occurs in response to DNA damage, there is evidence for the lack of mutagenicity of antimalaria agents in mammalian cells.[14] Moreover, chloroquine improves cellular mechanisms of DNA repair after damage caused by alkylating therapy.[15]

These protective properties against DNA damage have potential implications in patients with cancer. In a recent randomised clinical trial, Sotelo *et al*[5] have shown that the addition of chloroquine to conventional treatment with surgery, radiotherapy and chemotherapy improved survival in patients with glioblastoma multiforme. The presumed mechanism of action was preventing the mutagenicity of tumorous cells.

Although the potential utility of antimalarials as coadjuvant agents in cancer treatment does not imply any preventive action on the development of neoplasms, this possibility is suggested by our results. We found an inverse relationship between the use of antimalarials and the development of cancer that persisted after adjustment for the variables potentially associated with malignancy.

This study has some limitations. First, patients ever treated with antimalarials were, on average, younger and had a lower frequency of severe damage at diagnosis. However, patients with severe damage were few (18 patients, 7.6% of the cohort). Only age, gender and antimalarials showed an independent association with cancer (table 2).

Second, some patients included in the antimalarials group spent part of the time at risk without actually receiving these drugs. The intermittency in the treatment with antimalarials would have tended to dilute their effect, thus a significant association with a lower frequency of cancer is unlikely to be explained by this fact. In addition, antimalarials accumulate in tissues such as the liver and skin, persisting for several years after withdrawing the drug,[12] although the clinical implications of this are not known.

Third, carcinogenesis is an extremely complex process in which different factors take part. We found a great variety of neoplasms with different underlying biology in our population. Nevertheless, antimalarials could exert some favourable action against some of the yet unidentified predisposing factors in patients with SLE. This working hypothesis should be confirmed in larger and more ethnically diverse cohorts. If that were the case, this additional beneficial action of antimalarials would reinforce the recommendation of universal use of hydroxychloroquine in all patients with SLE.[4]

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