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INVESTIGATIVE REPORT

Long-term Follow-up of Cancer Risk in Patients Treated with Short-term Cyclosporine

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Cyclosporine increases the risk of skin and lymphoid tissue malignancies in organ transplant patients. A similar increase has been shown among psoriasis patients, but no data exist on the carcinogenic risk of cyclosporine monotherapy in skin diseases. We conducted a retrospective cohort study of 272 patients, all of whom had received at least one month of cyclosporine treatment. The cancer information on these patients was obtained from the Finnish Cancer Registry. The median follow-up time was 10.9 years and the median treatment time with cyclosporine was 8 months. We did not detect any increase in the risk of skin malignancies or lymphoma. The overall risk of cancer was almost identical to that expected in the general population (standardized incidence ratios (SIR)=1.31, 95% confidence interval (CI)=0.70–2.23). This study shows that short-term cyclosporine treatment is probably not related to subsequent malignancy. Since the CI of the SIR estimate was rather wide, larger studies are needed in the future. *Key words: cyclosporine; cancer risk; follow-up study; inflammatory skin diseases; cohort study*.

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Cyclosporine is an immunosuppressive drug, the effects of which are mediated through the regulation of various T-cell cytokines (1). Previous studies have clearly shown an increased risk of skin and lymphoid tissue malignancies in organ transplant patients receiving cyclosporine as a part of systemic immunosuppressive treatments (2). Some studies have related the use of cyclosporine to increased risk of malignancies (3, 4). Cyclosporine has been used in a wide range of inflammatory skin diseases, e.g. psoriasis, atopic dermatitis and palmoplantar pustulosis (PPP) (5). The treatment dosages of cyclosporine used in these dermatological diseases are usually lower and treatment times shorter than those used in organ transplant patients. Also, in these patients, cyclosporine is not combined with other immunosuppressive treatments, such as oral corticosteroids and azathioprine, which are used widely in organ transplant patients. Despite the widespread use of cyclosporine for skin diseases during the past two decades, there are few reports concerning the carcinogenic risk of cyclosporine. The reports of increased cancer risk include patients with psoriasis (6, 7), who have often also experienced other systemic therapies and phototherapy prior to cyclosporine treatment. These two studies are the only ones that have evaluated relative risk analyses. However, no data exist on malignancies related to cyclosporine monotherapy in skin diseases. We investigated the effect of short-term cyclosporine use on the subsequent development of cancer in various inflammatory skin diseases.

MATERIALS AND METHODS

We analysed a cohort of 272 patients with inflammatory skin diseases who were treated with cyclosporine for at least one month during 1987 to 1998 in the Department of Dermatology, Helsinki University Hospital, Helsinki. The age range was 17–76 years and the median age 38 years. Of these patients, 63 had psoriasis, 96 atopic dermatitis, 73 PPP and 40 chronic hand eczema. The inclusion criteria for the different groups in the study have been described previously (8–11). Cyclosporine treatment was not used for patients with a previous history of cancer. In each disease group the treatment time and dosage of cyclosporine were calculated. The patients in the low-dose group had received cyclosporine at a dose of less than 2 mg/kg, in the medium dose group 2–4 mg/kg, and in the high dose group over 4 mg/kg body weight. For methotrexate, the groups were defined as low for a cumulative dose of less than 1 g and high for a cumulative dose of more than 1 g of methotrexate. We checked whether the patients had received any phototherapy during follow-up.

The possible cancers subsequent to cyclosporine treatment were verified from the Finnish Cancer Registry, where every new cancer is registered. For each patient, the follow-up for cancer started at the point when cyclosporine treatment was commenced and ended at the close of the study (31 December 2003), on emigration or death, whichever came first. The earliest follow-up starting date was 18 May 1987.

Standardized incidence ratios (SIRs) were defined as the ratio of observed to expected numbers of cases. To obtain the expected numbers of cancer, age-, sex- and person-specific Finnish incidence rates were applied to the appropriate person-years under observation. The 95% confidence intervals (95% CI) were calculated assuming a Poisson distribution.

To evaluate the influence of cyclosporine, methotrexate and phototherapy on the subsequent development of cancer, a Cox regression model was used. The covariates used were duration

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of cyclosporine in months, methotrexate dose, cyclosporine dose, phototherapy, gender and age in years. The results were presented as hazard ratio and 95% CI. Statistical analyses were performed using SPSS for Windows version 12.0 (Chicago, Il, USA). A complementary log-log-plot was used to test the validity of proportionality assumption for all covariates used in the Cox model. No deviation from this assumption was noticed.

The study was approved by the ethics review board of Helsinki University Hospital.

RESULTS

The cohort comprised 116 men and 156 women, and the median follow-up time was 10.9 years. The median treatment time with cyclosporine was 8 months. The first and second quartiles for cyclosporine exposure were 3 and 12 months, respectively. Malignancies were diagnosed in 13 patients (4.8%) (Table I). The risk for all cancer sites was not significantly increased (SIR=1.31, 95% CI=0.70–2.23). There was no significant difference between men and women in cancer risk (SIR 1.91 and SIR 0.96, respectively). We did not detect any increase in the risk of skin malignancies or lymphoma. For male patients, the risk of all cancers was significantly increased in the 45–49 years age group (SIR=3.28; 95% CI=1.06–7.64).

The 13 cancer cases found were distributed quite evenly among the different skin disease groups. Three cancers occurred in patients with PPP (4%), 4 in patients with psoriasis (6%), 3 in patients with chronic hand eczema (7.5%) and 3 in patients with atopic dermatitis (3%) (Table I). In SIR analysis comparing different skin disease groups, there were no significant findings in patients with palmoplantar pustulosis, atopic dermatitis or chronic hand eczema, but in the psoriasis group, the SIR for basal cell carcinomas was significantly increased 6.05 (95% CI 1.25–17.69). Of the 13 patients with developed cancers, 11 (85%) had received medium dosage (2–4 mg/kg) cyclosporine treatment. In Cox regression model, the hazard ratio was 1.34 (95% CI=0.37–4.89) when moving from low-dose (under 2 mg/kg) cyclosporine treatment to high-dose (over 4 mg/kg) treatment. The exposure to previous methotrexate was a protective factor for the development of later cancers (hazard ratio 0.29, 95% CI=0.04–1.99). These numbers were not significant, however. Neither did we find a tendency for phototherapy to increase the risk of cancer (hazard ratio 0.98). The relative risk of cancer was increased by 7% per year. Gender was not a significant covariant.

Table I. *Type of skin disease and cancer, and the duration of cyclosporine treatment and dosage in the 13 patients who developed cancer during the follow-up*

Skin disease	Cancer type	CSA duration (months)	CSA dosage
Palmoplantar pustulosis	Breast cancer	5	Low[a]
Palmoplantar pustulosis	MALT-lymphoma	12	Low
Palmoplantar pustulosis	Lung cancer[b]	14	Medium
Psoriasis	Lung cancer[b]	2	Medium
Psoriasis	Cervix cancer	8	Medium
Psoriasis	Prostate cancer	30[c]	Medium
Psoriasis	Carcinoid tumour	155	Medium
Atopic dermatitis	Brain tumour (astrocytoma)	6	Medium
Atopic dermatitis	Prostate cancer	10	Medium
Atopic dermatitis	Prostate cancer	19	Medium
Eczema	Testis cancer	1,5	Medium
Eczema	Mouth cancer	3	Medium
Eczema	Brain tumour (meningioma)	3	Medium

[a]Low, cyclosporine dosage under 2 mg/kg; medium, 2–4 mg/kg body weight.
[b]Patient was a smoker.
[c]Only this patient had received methotrexate treatment.
CSA: cyclosporin A.

DISCUSSION

The cohort in this study comprised 272 patients: 63 with psoriasis and 209 with some other inflammatory skin disease. The median follow-up time was 10.9 years. Our sample size is small, but this is the longest follow-up of patients published to date, including patients other than psoriasis patients, receiving cyclosporine monotherapy, and it thus provides new information on the development of cancer related to cyclosporine treatment in atopic dermatitis, palmoplantar pustulosis and hand eczema. No other study has monitored these patients for a period of years after cyclosporine was stopped.

In Finland all cancers (including basal cell carcinomas) that come to the attention of hospitals, pathology laboratories or medical practitioners have to be reported to the Finnish Cancer Registry. Thus, our cancer registration is virtually complete, covering 99% of all cancers in Finland (13). In addition, the computerized record-linkage procedure based on personal identification number is complete (13, 14). Based on this registry, we did not detect any squamous cell cancers and there is no reason to believe that squamous cell or basal cell carcinomas of our cohort would have been reported less often than those of other populations. With our sample size of 272 patients it is possible to exclude two-fold increase in cancer risk with a power of 90% and two-sided significance level of 0.05 (15).

Squamous cell carcinoma is the most common skin cancer among organ transplant patients. The incidence of skin cancer is clearly increased, starting from 5 years after transplantation (16, 17). The risk for skin cancer is higher among multi-organ transplant patients compared with, for example, kidney-transplant patients, apparently as a reflection of higher doses of immunosuppressive therapy in that group (2). Recently, O'Donovan and co-workers (18) presented a possible contributing

mechanism for the development of skin cancer among organ transplant patients. They found that metabolic end-products of azathioprine, an immunosuppressive drug used in organ transplant patients, may act as an endogenous ultraviolet A (UVA) chromophore, which generates oxidative DNA damage. We did not detect any squamous cell carcinomas in our study, not even in patients exposed to phototherapy. This could be explained by the shorter cyclosporine treatment times used for our patients. Paul et al. (7), who found increased incidence of squamous cell carcinoma, had treated their psoriasis patients for an average of 1.9 years, whereas in our study the mean treatment time was 8 months. In psoriasis patients the SIR for basal cell carcinomas was increased, but the CIs were wide.

Patients with psoriasis and rheumatoid arthritis both carry an increased risk of cancer (19, 20). The increased risk of squamous cell cancer associated with psoralen + UVA (PUVA) treatment, commonly used for psoriasis, has been verified by numerous previous studies (21, 22). In one previous study (6) any use of cyclosporine increased the risk of squamous cell cancer after as much as 200 PUVA treatments. These psoriasis patients were, however, treated with PUVA first. In rheumatoid arthritis, it has been suggested that the use of cyclosporine increases the risk of malignancy development by the same degree as disease-modifying anti-rheumatic drugs (DMARDs) (23). Van den Borne et al. (24) reported no increased risk of malignancies, especially skin malignancies, in cyclosporine-treated patients with rheumatoid arthritis. In their study, the use of DMARDs was more common in the cyclosporine-treated group, favouring the negative impact of cyclosporine on the risk of cancer. This is in line with our finding. In our cohort, 77% of patients had some chronic inflammatory skin disease other than psoriasis.

We noted a significant increase in cancer risk among men aged 45–59 years. There was no hypothesis specifically related to this gender and age stratum, and this may well be a chance finding typical to this kind on analyses with multiple testing.

Bert-Jones et al. (25) has conducted a prospective study of 100 atopic patients and found no squamous cell cancers. The only skin cancer found was one basal cell carcinoma. However, the maximum follow-up time was 48 weeks, which is too short to draw any conclusions of the carcinogenicity of cyclosporine. There are no published case reports of squamous cell cancers in atopic patients treated with cyclosporine.

UV irradiation is of paramount importance for the development of cutaneous carcinoma in the general population as well as in organ transplant patients (26). In the latter patient group, skin cancers are located mainly on sun-exposed areas, such as the scalp, hands and lips. The role of UV radiation is also highlighted in geographical cohort studies, where the highest risk of skin cancer is detected in Australia (27). Older transplantation patients are more prone to develop skin cancer after transplantation as a consequence of cumulative sun exposure before transplantation. Significant UV irradiation prior to immunosuppressive therapy following organ transplantation is a clear risk factor for squamous cell carcinoma (28). In a previous study of cyclosporine-related risk of malignancies, the patients received PUVA or UVB/UVA (47% and 19%, respectively) (7). In our study, half of the patients had any phototherapy treatment, but we found no evidence that phototherapy would have increased the incidence of detected cancers.

To conclude, we did not find a significantly increased risk of cancer in patients who had undergone short-term treatment with cyclosporine. This study showed that short-term cyclosporine is probably not related to subsequent malignancy. The CI of the SIR estimate was rather wide. Larger prospective studies excluding psoriasis patients are therefore needed to confirm this finding.

Conflict of interest: None to declare.

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