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SKIN CARCINOMAS AND TREATMENT WITH PHOTOCHEMOTHERAPY (PUVA)

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Abstract. A 3½-year follow-up study of 198 patients treated with photochemotherapy (PUVA) revealed a total of 18 carcinomas developed in 11 patients. There were 12 basal cell carcinomas and 6 squamous cell carcinomas, localized mainly on non-sun-exposed areas. Furthermore 9 actinic keratoses were diagnosed in 8 patients. All patients with carcinomas had been exposed to at least one of the following possible risk factors: ionizing radiation, methotrexate (MTX), arsenic, topical nitrogen mustard, or had a history of skin carcinoma previous to PUVA therapy. No significant differences in accumulated UVA dose existed between patients with carcinoma or keratosis and patients without tumours. A subgroup of 38 psoriatics previously treated with MTX was compared with a control group of 101 psoriatics treated with MTX—but never with PUVA. The control group was matched for sex, age and presence of the risk factors: ionizing radiation, arsenic and history of carcinoma. The carcinoma incidence in the PUVA–MTX group was 9% and in the control group 11%. The difference was not significant ($p = 0.9$).

Photochemotherapy (PUVA) has been used since 1974 in the treatment of psoriasis as well as of other dermatoses. Its effectiveness in inducing and maintaining clinical remission in psoriatics is well documented and the treatment seems to be free from major short-term side effects (5, 8), but non-therapeutic dosage of tocial and intraperitoneal 8-methoxypsoralen plus prolonged exposure to UVA has been shown to be carcinogenic in animals (1, 4, 7). The main issue of concern regarding the PUVA regimen is therefore its potential carcinogenicity for human skin.

This paper presents a 3½-year follow-up of 198 patients treated with PUVA with specific reference to the development of actinic keratosis, basal cell and squamous cell carcinoma (BCC and SCC).

The results from a subgroup of psoriatics who had been treated with MTX were compared with a control group of psoriatics who had never been exposed to PUVA. The control group was matched for age, sex and presence of the following risk factors: previous skin cancer, previous arsenic therapy, and previous ionizing radiation.

PATIENTS AND METHODS

In the dermatologic department of the Finsen Institute a total of 283 patients with various diagnoses, mainly psoriasis, were treated with PUVA during the period February 1974 until January 1980. Of these 283 patients, 198 had been treated with PUVA for more than 3 months and they were included in the study.

An oral dose of approximately 0.6 mg/kg bodyweight 8-methoxypsoralen was given 2 hours before UVA irradiation. Initial UVA dose was ½–1 J/cm² and was increased gradually. Light sources were Sylvania or Philips fluorescent tubes.

Data concerning sex, age, skin type, dermatologic diagnosis, previous treatment with arsenic, ionizing radiation, MTX, presence of skin cancers prior to PUVA therapy, total UVA dose and development of actinic keratoses or skin cancers after commencement of PUVA were obtained from case records.

The patients were asked to participate in a re-examination. At the follow-up, skin lesions suspected to be malignant or premalignant were biopsied and examined by light microscopy. The re-examination took place from January 1981 until February 1982 and included 134 patients. Eleven patients had died. The study included 76 women and 122 men. Median age was 52.2 years (range 21–92) and the average duration from commencing PUVA treatment to the most recent observation was 43 months.

A total of 38 psoriatics in the series had been treated with MTX. Mean follow-up time for these patients was 48 months. They were matched with a control group consecutively selected from the case records of the department of MTX treated psoriatics and compared with the controls in relation to carcinoma development.

Those patients whose interval between the first and most recent examination exceeded 48 months and who had never received PUVA were classified according to the following parameters: sex, 5-year age group history of ionizing irradiation, previous arsenic therapy and skin carcinomas diagnosed earlier than 48 months before the most recent examination. Skin carcinomas diagnosed after that time were classified as new carcinomas and were

Table I. *Number of carcinomas and keratoses in 198 patients treated with PUVA*

BCC = basal cell carcinoma, SCC = squamous cell carcinoma

Number of carcinomas and keratoses	Number of patients		
12 BCC	7	11	16
6 SCC	5		
9 keratoses	8		

Ratio SCC/ (BCC + SCC) = 1/3.

registered separately and suspended until the control group had been selected. It was possible to classify 262 patients from the MTX files according to these criteria. We attempted to select a control group with absent and present parameters that matched 3 : 1 each of the parameters of the PUVA group; however, the number of patients was not sufficient to complete a table with these proportions. The final number of controls was 101, 63 males and 38 females, to be compared with 23 males and 15 females respectively of the PUVA-MTX group. No significant differences in sex, age or presence of risk factors existed between the groups.

The Mann-Whitney two-sample test was used to compare the observed distributions of quantitative variables between groups. Qualitative distributions were compared by means of the χ^2-test for equal proportions. Yates correction was used when numbers were small.

RESULTS

Incidence of carcinomas and keratoses

At re-examination, 7 lesions in 5 patients were excised. Basal cell carcinoma was diagnosed in one patient. In the remaining specimens the following histology was found: hyperkeratosis, papillomatosis, seborrhoeic keratosis and dermatofibroma. In the case reports a total of 17 carcinomas in 10 patients and 9 actinic keratoses in 8 patients were diagnosed (Table I). The incidence of carcinoma was thus 6% and the incidence of carcinomas and keratoses was 8%.

The histology in 4 patients with SCC was not altogether conclusive; however, these patients were included in the carcinoma group.

Seventy-two per cent of the carcinomas and 44% of the keratoses were located on non-sun-exposed areas.

Risk factors

Table II shows risk factors in the carcinoma group. Of the 3 patients with a history of carcinoma, one had been exposed to ionizing radiation and the other 2 additionally to arsenic and MTX years before the first tumour was diagnosed.

Ionizing radiation as the only risk factor besides a history of carcinoma had been given to 101 patients, of whom 5 (5%) developed carcinomas. No significant differences in the number of tumours existed between the group treated with ionizing radiation–arsenic and the group treated with ionizing radiation only. Table III shows the number of patients exposed to the various risk factors.

Thirty patients had not been exposed to any risk factor, and in these patients no carcinomas were observed. Carcinoma incidence in the remaining 168 patients was 7%. Median age was 54 years in both groups. Median UVA dose was 317 J/cm² in the risk group and 210 J/cm² in the group without

Table II. *Risk factors in the carcinoma group*

BCC = basal cell carcinoma, SCC = squamous cell carcinoma, MTX = methotrexate

Patient	Tumour type	Ionizing radiation	MTX	Arsenic	Topical nitrogen mustard	History of carcinoma
1	BCC	+	+			
2	BCC	+	+	+		+
3	BCC		+	+		
4	BCC	+				+
5	BCC	+	+	+		+
6	BCC	+				
7	BCC-SCC	+	+	+		
8	SCC	+				
9	SCC	+				
10	SCC	+				
11	SCC				+	

Table III. *Presence of risk factors*

Risk factor	Number of patients with risk factors	
	Total	Per cent
Ionizing irradiation	158	80
Methotrexate	41	21
Arsenic	28	14
Topical nitrogen mustard	11	6
History of carcinoma	5	3

risk factors, but the difference was insignificant ($p=0.06$).

Skin type

Information concerning skin type was available for 159 patients. Fifty-four patients had skin types I–II and 105 had skin types III–IV. Carcinoma incidence was 6% in both groups.

Cumulated UVA dose

Median accumulated UVA dose was 288 J/cm^2 (range 18–6550) in the group without tumours and 1058 J/cm^2 (range 54–2498) in the keratosis group. In the carcinoma group the median UVA dose was 526 J/cm^2 (range 98–3052). The UVA dose in the non-tumour group was compared with the UVA dose in the carcinoma group. The difference was not significant ($p=0.06$); neither was the difference between UVA dose in the non-tumour group compared with UVA dose in the keratosis group ($p=0.09$).

Control group

In the control group, carcinomas were diagnosed in 9 patients (9%) within 48 months before the most recent examination at the clinic. BCC were found in 8 patients, SCC in one patient and 2 patients had tumours of Bowenoid type. These 2 patients were not included in the carcinoma group. In the PUVA group 3 patients had BCC and in one both BCC and SCC were diagnosed. The incidence of carcinomas was thus 11% in this group. The differences in carcinoma incidence between the groups were insignificant ($p=0.9$).

DISCUSSION

Ionizing radiation was no doubt a risk factor of importance in this study as 5% of the patients exclusively exposed to this risk factor developed carcinomas. In this material there was no significantly different number of tumours in the group treated with ionizing radiation–arsenic vis-à-vis the group treated with ionizing radiation only.

The carcinoma incidence in this paper was twice the incidence (2%) reported by Stern et al. (6) in 1373 PUVA-treated patients (2.1-year follow-up) and approximately five times the incidence (1%) found by Hönigsmann et al. (2) in 418 PUVA patients (follow-up time not indicated). In the present study more patients had been exposed to the risk factors ionizing radiation and arsenic, and their mean age was greater than in the papers by Stern et al. (6) and Hönigsmann et al. (2). These facts may explain the higher incidence of carcinoma found in this paper.

The findings of Stern et al. (6) and Hönigsmann et al. (2) that squamous cell carcinomas were more frequent than basal cell carcinomas was not confirmed in this study, as SCC constituted only one-third of the carcinomas.

In patients without exposure to any of the risk factors registered in this study, no skin cancers developed. This finding cannot be explained by differences in age or accumulated UVA dose between these two groups, as the differences were insignificant. The carcinoma incidence in the subgroup of MTX-treated PUVA patients did not differ significantly from the carcinoma incidence in the control group. In choosing MTX-treated psoriatics as controls it is reasonable to assume that the PUVA group and control group are compatible as regards severity of psoriasis, as the indication for both PUVA and MTX therapy is recalcitrant psoriasis which has failed to respond to traditional topical treatment. These results may be interpreted such that PUVA treatment does not result in an increased incidence of skin carcinomas in the short term, though the numbers of patients in the groups were small. This is in agreement with the results of Lassus et al. (3) who found that the incidence of skin carcinomas in the PUVA treatment series was lower than that in hospitalized psoriatics treated with regimens other than PUVA and was no higher than the incidence in the age-matched general population in Finland. In Lassus' series, 21% had been treated with arsenic and only 4% had been given ionizing radiation.

In conclusion, we have in this short-term study found a relatively large number of skin carcinomas

in patients treated with PUVA, but the results indicate that the documented tumours resulted from the use of potentially carcinogenic treatments other than PUVA, in particular ionizing radiation. But until long-term prospective studies have proved the safety of PUVA, a carcinogenic potential of this treatment modality cannot be disregarded and a restrictive attitude will still be advisable, especially in patients previously exposed to known carcinogenic agents and in patients with a history of skin tumours.

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