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CLINICAL REPORT

No Evidence for Increased Skin Cancer Risk in Psoriasis Patients Treated with Broadband or Narrowband UVB Phototherapy: A First Retrospective Study

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Phototherapy of skin diseases such as psoriasis is an effective and safe treatment modality. However, increasing the risk of skin cancer by phototherapy is a serious concern. An increased skin cancer risk occurs after prolonged photochemotherapy (PUVA). In contrast, the role of broadband UVB or narrowband UVB therapy in skin carcinogenesis of humans with psoriasis is less clear. Therefore, we investigated the incidence of skin tumours in a total of 195 psoriasis patients, receiving broadband ($n = 69$) or narrowband ($n = 126$) UVB from 1994 to 2000 with follow-up until 2003. Data were raised from the regional interdisciplinary cancer centre of the University of Tuebingen, Germany and compared with the tumour incidences given for the German population. In this study, with 80% statistical power to detect a 6–7-fold increase in skin cancer with broadband UVB and 83% power to detect a 5–6-fold increase with narrow band UVB at $p = 0.05$, only one patient developed skin cancer – an in situ melanoma. The tumour occurred within the same year that phototherapy was initiated. Thus, the present study does not provide evidence for an increased skin cancer risk for patients treated with either broadband or narrowband UVB phototherapy ***Key words: broadband UVB; narrowband UVB; phototherapy; psoriasis; retrospective study; skin cancer risk; ultraviolet light.***

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Ultraviolet (UV) radiation emitted from either natural or ambient sources is a complete carcinogen and the role of UV radiation in the induction of non-melanoma skin cancer is well established. Different wavelengths of the UV spectrum exert biological effects through distinct mechanisms. UV ranging from 280 to 320 nm (UVB) acts mainly through direct induction of photoproducts in the genome (1, 2). The mutagenic action of wavelengths from 320 to 400 nm (UVA) appears to be mediated mostly through generation of reactive oxygen species (ROS), while UVA in combination with photosensitizers such as 8-methoxypsoralen (photochemotherapy, PUVA) leads to intercalation of the photosensitizer in the DNA double helix, generating a highly mutagenic DNA-distorting photoproduct. In addition to these mutagenic effects, UV radiation has also been shown to exhibit immunosuppressive effects that may contribute to tumour progression (1, 3–5).

In spite of these adverse long-term effects, UV radiation is widely used in the treatment of photosensitive skin diseases such as psoriasis, atopic dermatitis, mycosis fungoides and vitiligo (6–10). Because of the experimentally shown carcinogenic effect of UVA and UVB, controversy exists as regards the increased risk of skin cancer in patients treated with different modalities of phototherapy. The relationship between skin carcinogenesis and PUVA treatment has been investigated extensively (11–14). Although these studies are discussed controversially because of a number of confounding factors, present data appear to support a link between PUVA and an increased risk of developing melanoma as well as non-melanoma skin cancer, which appears to persist after cessation of PUVA (15). Conversely, the role of phototherapy with UVB in the development of skin cancer is less clear. There is a large body of evidence confirming the mutagenic and immunosuppressive effects of UVB radiation in vitro (16–20) and extended UVB exposure seems to be one of the major risk factors in the induction of non-melanoma skin cancer in mice and humans (21–24). However, neither anecdotal reports nor long-term studies brought proof for an increased incidence of skin cancer in patients treated with broadband UVB ranging from 280 to 320 nm (24).

Work by Fischer (25) and Parrish & Jaenicke (26) led to the introduction of light bulbs emitting near-monochromatic radiation at 311 nm. Phototherapy with this wavelength has subsequently been called narrowband or 311-nm phototherapy. This therapeutic modality has been shown to be superior to broadband phototherapy for the treatment of a number of dermatoses including atopic dermatitis, vitiligo and

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psoriasis (6, 7, 10). Following introduction of narrowband phototherapy (311 nm) in the late 1980s, an increasing number of patients have been treated with narrowband UVB instead of broadband UVB. As narrowband UVB has evolved to be the standard phototherapy modality in mild to moderate plaque psoriasis and as it has been employed for more than a decade, in a first retrospective pilot study, we investigated whether patients suffering from psoriasis, treated either with broadband or narrowband UVB phototherapy do exhibit an increased incidence of skin cancer in comparison to incidences given in a cancer registry for the normal population.

MATERIALS AND METHODS

Patients

Patients suffering from psoriasis vulgaris treated in the Department of Dermatology, Tuebingen, Germany, either with narrowband or broadband UVB phototherapy in the years 1994–2000, were included in the study. Patients who received both narrowband and broadband or who received PUVA therapy at any time were excluded. This was done because data for each single wavelength and its role in photocarcinogenesis are scarce and interactions of wavelength were to be excluded. The total number of patients included in the study was 195. The total number of radiations and cumulative doses as well as degree of improvement and reason for termination of treatment were assessed.

Patients' skin types

Retrospective analysis of records did not allow a comprehensive evaluation of patients' skin types according to the Fitzpatrick classification. Two patients were recorded as skin type V; the skin types for the remaining population were not recorded. During treatment patients received genital protection as part of routine treatment. However, patients did not receive face shield protection of exposed sites.

Tumour data in patients

The type of cancer occurring as well as its onset were recorded from the regional interdisciplinary cancer centre of the University of Tuebingen, Germany. In this cancer registry all patients diagnosed with cancer from all departments of the university clinics, Tuebingen, Medical School, Germany are registered, including type, localization and onset of cancer, course of the disease and tumour thickness where applicable.

Control population and statistical analysis

The number of expected skin tumours including malignant melanoma in the German population was drawn from the cancer information service of the Institute for Cancer Research at Heidelberg, where incidences of all tumour types in Germany are collected (27). According to this source, the expected incidence of non-melanoma skin cancers in the German population is 150 cases per 100,000 person-years while the expected number of malignant melanomas is 10 cases per 100,000 person-years. For this study Poisson distribution of skin tumours was assumed and statistical analysis was carried out employing the computer-based statistical program SAS, version 8.2.

RESULTS

In all, 195 patients suffering from psoriasis were treated with UVB radiation between January 1994 and December 2000. Of those 195 patients, 69 were treated with broadband UVB and 126 received narrowband UVB.

Broadband UVB

Of the 69 patients with psoriasis receiving broadband UVB, 49 were male and 20 female (Table I). The mean age was 47.1 years. The mean cumulative dose of broadband UVB was 2.34 J/cm^2. The mean number of treatments was 17.8 sessions and the mean cumulative UVB dose needed for clearance was 4.48 J/cm^2.

Table I. *Summary of clinical and therapeutical parameters in psoriasis patients treated with broadband or narrowband UVB*

	Broad band UVB (n=69)			Narrow band UVB (n=126)		
	Mean	Min	Max	Mean	Min	Max
Age (years)	47.1	14	91	45.5	6	91
Cumulative dose (J/cm^2)	2.34	0.01	30	35.75	0.81	886
Treatments (n)	17.8	6	96	44.2	1	441
No. of treatments until improved	18	4	96	32	5	120
Lesions cleared (J/cm^2)	4.48	0.37	30	38.79	2.03	113
	Total	Male	Female	Total	Male	Female
Treatment efficacy:						
Improvement	52	37	15	108	65	43
No improvement	6	6	0	8	4	4
Unknown	11	6	5	10	8	2
Reason for quitting:						
No progress	5	3	2	8	6	2
Physician changed	53	37	16	60	40	20
All lesions cleared	13	11	2	48	26	22
Unknown	–	–	–	10	5	5

The mean follow-up period was 93.6 months with a minimum of 29 months and a maximum of 112 months. Of the 69 psoriasis patients treated with broadband UVB between 1994 and 2000, none developed skin cancer.

Narrowband UVB

Among the 126 patients radiated with narrowband UVB, 77 were male and 49 female (Table I). The mean age was 45.5 years. The mean cumulative dose was 35.75 J/cm^2. The mean number of treatments was 44 and the mean cumulative dose needed for clearance was 38.79 J/cm^2. The mean follow-up period was 68.4 months with a minimum of 28 and a maximum of 112 months. Of the 126 psoriasis patients treated with narrowband UVB between 1994 and 2000, one. A female patient developed an in situ melanoma of the abdomen within the first year of treatment.

Statistical power

Broadband UVB-irradiated patients were followed for 533 person-years. With our set-up, we have the statistical power of 80% to detect a 6–7-fold increase in the incidence of skin cancer including malignant melanoma at the 5% level of significance ($p = 0.05$).

Narrowband UVB-irradiated patients were followed for 726 person-years. With our set-up, we have statistical power of 83% to detect a 5–6-fold increase in the incidence of skin cancer including malignant melanoma at the 5% level of significance ($p = 0.05$).

DISCUSSION

This retrospective pilot study investigated whether broadband or narrowband UVB phototherapy are associated with an increased risk of skin cancer. Such a risk is established for repeated long-term PUVA therapy, especially in Fitzpatrick skin types I and II (28–32). While broadband UVB phototherapy can induce skin cancer in mice (33), in humans a large retrospective 25-year study of 280 patients treated with coal tar and broadband UVB failed to demonstrate an increased skin cancer risk in this population (34). The role of narrowband UVB in skin carcinogenesis is even more controversial. Some studies in mice demonstrated that animals treated with narrowband UVB developed squamous cell carcinomas earlier than mice treated with broadband, but only if continuously treated with suberythemogenic doses (21). On the other hand, skin from patients treated with narrowband UVB showed less sunburn cell formation than that from patients exposed to broadband UVB (35, 36). Furthermore, narrowband UVB is about 5–10-fold less potent than broadband UVB in inducing erythema, hyperplasia, oedema and Langerhans' cell depletion from the skin (35). Clinical studies investigating the skin cancer risk of UVB 311-nm therapy in human individuals have, thus far, not been published. In this retrospective study, we therefore investigated the incidence of tumours in patients receiving either broadband or narrowband UVB for the treatment of psoriasis. The main endpoint of this study was the development of skin tumours during an observation period of 10 years beginning in 1994. An observation period of 10 years is not sufficient to conclusively determine whether an increased skin cancer risk exists in either broadband or narrowband UVB and follow-up of 726 person-years for narrowband and 533 person-years for broadband are not as long as other mono- and multi-centre studies investigating the carcinogenic effects of PUVA (15, 24, 32). However, in reports from other groups the risk of developing squamous cell carcinoma following PUVA treatment incidences were between 5-fold and 12.8-fold as early as 5 years after wide application of this therapy (15, 24, 32). The data provided by the present study indicate (with statistical power of 80% and 83% and at the 5% level of significance for non-melanoma and melanoma skin cancer) that a similarly gross increase of the skin cancer risk may not be induced by broadband and narrowband UVB phototherapy, respectively.

Data regarding tumours occurring in patients treated with UVB were raised from the regional interdisciplinary cancer centre of the University of Tuebingen, Germany. It is known that the reliability of cancer registration with respect to non-melanoma skin cancer is low. However, reported cases are very reliable with respect to diagnosis, onset of disease and relation to commencement of phototherapy. Furthermore, data raised from a cancer registry are more reliable than those from patients' files or questionnaires.

In the case of the female patient who developed an in situ melanoma, treatment-related photocarcinogenesis can most likely be ruled out because she developed the tumour within the same year that phototherapy was commenced. Skin photocarcinogenesis is dependent on cumulative UV doses. None of the five individuals receiving the highest cumulative doses in both cohorts presented with skin cancer, albeit the median cumulative dose for narrowband UVB exceeds 400 J/cm^2.

In the present study 43% of the patients treated with narrowband UVB stopped treatment due to clearance of all lesions while only 18.8% of patients treated with broadband UVB cleared in the time due. Moreover, 85.7% of patients showed improvement of psoriatic lesions under narrowband UVB compared with 75.3% under broadband UVB. This is in line with other reports indicating a higher efficacy of narrowband UVB in the treatment of psoriasis (36–39).

In conclusion, the present retrospective pilot study does not provide evidence for a more than 5–7-fold increased skin cancer risk in psoriasis patients treated

with either broadband or narrowband UVB phototherapy. However, it is prudent to emphasize that a definitive prospective longitudinal study with prolonged follow-up is required specifically addressing skin cancer risk in relation to both broadband and narrowband UVB phototherapy.

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