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Combination of High Risk Factors as an Accurate Guide to Prognosis in Malignant Melanoma

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Abstract—*Prognostic factors were determined retrospectively in* 102 *surgically treated patients with melanoma stage I and II. A combination of high-risk factors is described which consists of five tumour-dependent and three immunological criteria. Relapses occurred only in melanoma patients with one or more of these high-risk factors. All patients without high-risk factor were free of disease up to* 54 months *after removal of the primary melanoma. If this trend could be confirmed in the future, it would be possible by this method to identify patients with a good prognosis. For these cases, any adjuvant therapy would be unneccessary.*

INTRODUCTION

MALIGNANT melanoma follows an often unpredictable course [1–4]. In spite of many clinicopathologic studies of prognostic factors in cutaneous malignant melanoma [5–10] and of prognostic indicators of the patient [11, 12], a prediction for an individual seems to be impossible. The numerous immunological parameters cannot provide a definite prognosis either. On the basis of many data of a BCG immunotherapy adjuvant trial in melanoma, we tried to find a combination of high risk factors which would give us an aid to assess prognosis.

MATERIALS AND METHODS

In a five-year period between January 1975 and January 1980, 102 patients with histologically proven cutaneous malignant melanoma (clinical stage I and II) were included in this study. In all cases, wide surgical excision was performed first. All 102 tumours were classified according to the histopathological criteria of Clark [13], Breslow [8] and McGovern [14]. Because of technical reasons, a detailed immunological work-up was done in 54 melanoma patients only four to six weeks after the surgical removal of the primary melanoma.

The following immunological tests were carried out:

(1) Intradermal test with tuberculin (PPD).

(2) Skin test with DNCB (2–4 dinitrochlorbenzene), according to the method of Bleumink *et al.* [15].

(3) Lymphocyte transformation (LTT) by PHA (normal range of stimulation index 43.2 ± 10.6), PPD and DNCB.

(4) Leukocyte migration inhibition by PPD and DNCB, according to the method of Söborg and Bendixen [16].

(5) Peripheral lymphocyte number.

(6) Quantification of T-lymphocytes, by spontaneous rosette formation with sheep red blood cells [17].

(7) Quantification of B-lymphocytes by rosette formation with mouse erythrocytes, according to the method of Dobozy *et al.* [18].

(8) Immunoglobulins IgG, IgA and IgM determinations by single radial immunodiffusion on commercial Tri-Partigen plates (Behring–Werke AG, Marburg, FRG).

(9) Whole complement level by immune hemolysis, according to Stelzner and Stein [19].

The data were computerized and statistically evaluated (H-test of Kruskal–Wallis). The clinical course of all patients was followed at monthly intervals by clinical and X-ray examinations.

RESULTS

Tumour-dependent, i.e., histological risk factors

The histological examination of the melanomas leads to the detection of high-risk factors, as shown by Breslow [8], Clark [13] and McGovern [14]. We used five risk factors which have definite prognostic relevance and are

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easily reproducible and objective. Poor prognosis follows when one or more of the following criteria are present:

(1) Maximal tumour thickness greater than 3 mm.

(2) Level V according to Clark [13].

(3) High mitotic activity [> 1/high power (× 400) field].

(4) Any metastasis, near and/or distant.

(5) Incomplete removal of primary melanoma by the first surgical treatment.

We compared the recurrence rate of melanoma in all 102 patients with and without high risk factors. The clinical course of the patients with histological high-risk factors (Fig. 1) is significantly worse than that of those without.

Immunological risk factors

The following immunological tests have been found to be of prognostic relevance in our statistical analysis (Table 1).

(1) Negative tuberculin (PPD) skin reaction.

(2) Negative immune response to DNCB in skin test.

(3) PHA stimulation index smaller than 32 in the lymphocyte transformation test.

The recurrence rates of melanoma in 54 patients with and without immunological high-risk factors do not show any significant difference (Fig. 2).

Table 1. *Influence of immunological parameters on recurrence of malignant melanoma*

Immunological Parameters	n	Recurrence %
Skin tests: PPD positive	19	29.6
PPD negative	27	42.1
DNCB positive	14	21.8 P < 0.05
DNCB negative	29	45.3
PHA—Index normal	18	28.1 P < 0.05
PHA—Index reduced	46	71.8

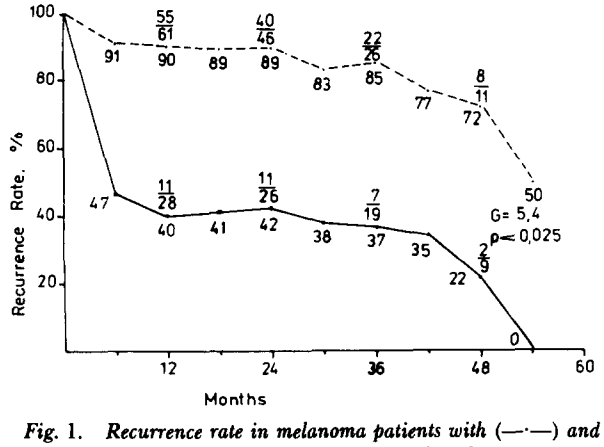

Fig. 1. *Recurrence rate in melanoma patients with (—·—) and without (––·––) tumour-dependent high-risk factors.*

Combination of histological and immunological risk factors

Figures 1 and 2 demonstrate that the tumour-dependent and immunological criteria alone are useless for the assessment of the prognosis in an individual case. Therefore, we combined the tumour-dependent and immunological high-risk factors. An optimal prognostic prediction resulted: relapses occurred only in the patients with one or more of the high risk factors in this combination. Melanoma patients without any of these high-risk factors remain free of disease up to 54 months after removal of the primary melanoma (Fig. 3). There is only a borderline statistical difference 48 months after diagnosis, due to the relatively small numbers of patients.

DISCUSSION

The classification of the melanoma patients according to single high-risk factors is without prognostic value for an individual case and has therefore no therapeutic consequences. Multifactorial analysis of high-risk factors in melanoma by other authors did not allow a

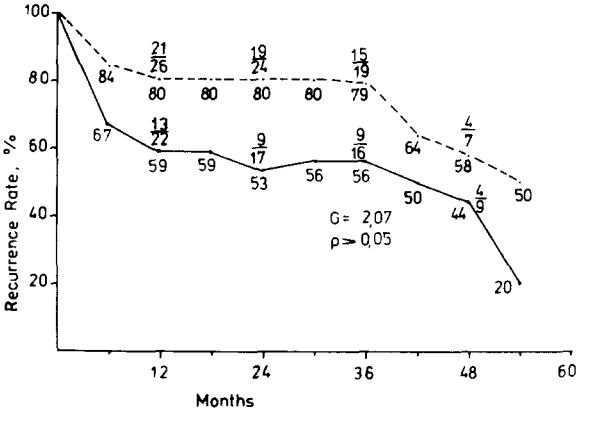

Fig. 2. *Recurrence rate in melanoma patients with (—·—) and without (––·––) immunological high-risk factors.*

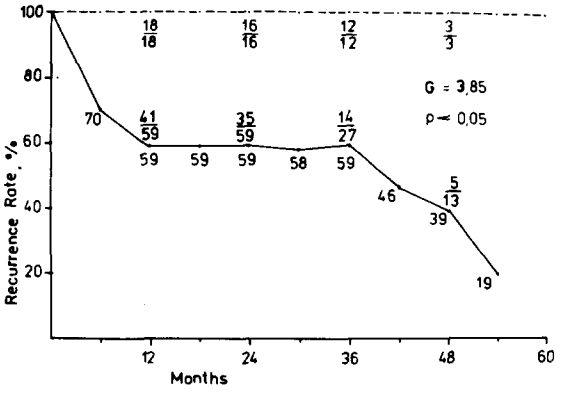

Fig. 3. *Recurrence rate in melanoma patients with (– · –) and without (––·––) a combination of high-risk factors.*

valid prediction of the clinical course either. Barclay *et al.* [7] and Cochran [20] reported that a valid prediction for at least 5 years can be given in 90% of the cases of cutaneous malignant melanoma by the use of a prognostic index based on selected pathological and clinical factors. Another prognostic index was defined by Schmoeckel and Braun-Falco [9] as the product of tumour thickness and mitotic rate. The percentage of false negative and false positive results is 14%. But even with both indices, it is not possible to give an exact prediction for each individual case. It would be important to have some unequivocal parameters which would make it possible to identify patients with a good prognosis and who therefore do not need an adjuvant therapy.

In this paper a combination of tumour-dependent and/or immunological high-risk factors is described. Relapses are found only in melanoma patients with one or more of the high-risk factors. Patients without these high-risk factors were free of disease for 54 months after removal of the primary melanoma. If this trend could be confirmed in the future, it would be possible by this method to separate a subgroup with a good prognosis from high-risk patients. The latter group would then be ideal candidates for an adjuvant chemo- and/or immunotherapy.

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