Tumor Burden Index as a Prognostic Tool for Cutaneous T-Cell Lymphoma

A New Concept

Monika Hess Schmid, MD; Patricia Bird, MD; Reinhard Dummer, MD; Werner Kempf, MD; Günter Burg, MD

Objectives: To introduce a prognostic tool for cutaneous T-cell lymphoma that takes into account the tumor burden and to compare the prognostic value of this tumor burden index (TBI) with that of other prognostic factors.

Design: Retrospective clinical and statistical study.

Patients: One hundred sixteen patients with cutaneous T-cell lymphoma.

Methods: A TBI was designed that takes into account the types, numbers, and severity of skin lesions with the use of the Cox proportional hazard model.

Results: Models of the TBI were developed to test the relative contributions of patches, plaques, and tumors to the total tumor burden and, hence, survival time. Weighting factors reflecting the severity of each skin lesion were tested and incorporated. The best prognostic correlation was a dichotomized index with the following formula: $TBI = 1 + (\text{patches} \times 2) + (\text{plaques} \times 2) + (\text{tumor} \times 1.3)$, where the patches factor equals 0 if 30% or less of the skin area is involved and 1 if greater than 30% of the skin area is involved and where the plaque or tumor factor equals 1 if plaques or tumors are present. Both the TBI and TNM provided predictive information. Discrimination of survival curves and significance of differences was better for TBI ($P < .001$) than for TNM ($P = .009$). Sex was also statistically related to survival (males had a better prognosis; $P = .04$), whereas neither age at first symptoms ($P = .35$) nor age at time of diagnosis ($P = .36$) was of prognostic value.

Conclusions: The TBI offers a simple prognostic index for the evaluation of cutaneous T-cell lymphoma. It may become a valuable tool for designing therapeutic strategies for patients according to their specific survival expectancies. However, this model is preliminary and has to be validated on a larger number of patients.

Arch Dermatol. 1999;135:1204-1208

Cutaneous T-cell lymphomas (CTCLs) represent the most common form (65%) of all primary cutaneous lymphomas. The clinical course of CTCL can be divided into 2 phases; the first phase involves lesions restricted to the skin, and the second, extracutaneous involvement. The first phase is variable in length and can last years or even decades. However, if extracutaneous involvement occurs in CTCL, this is usually in conjunction with transformation into the blast stage, and the remaining survival time rarely exceeds 1 year. Consequently, the longest period during the course of CTCL is characterized by skin involvement only.

A staging system for CTCL is helpful for monitoring the patient; for this application, a detailed quantitative morphometric system is ideal. Such a skin scoring system was developed, for example, by Vonderheid (E. C. Vonderheid, oral communication, 1996); however, this system is very time-consuming. On the other hand, a staging system is a prerequisite for determining prognosis and optimal therapy for the patient. For these purposes, a more practical semiquantitative system might be sufficient. Several staging systems have been proposed; nodal lymphomas are classified according to the Ann Arbor classification, and CTCLs have been classified in the past into patch, plaque, and tumor stage.

The most commonly used system for cutaneous lymphomas at present is the TNM system as adapted by Bunn and Lambert and Bunn et al (Table 1). It takes into account the body surface area involved (≥10% or <10%), quality of skin manifestations (patch, plaque, tumor[s], or erythroderma), type of lymph node involvement (dermatopathic or neoplastic), and visceral organ involvement. It is a satisfactory classification system for the second phase of CTCL (including extracutaneous involvement), but it lacks sufficient detail with respect to types and number of

From the Department of Dermatology, University Hospital of Zürich, Zürich, Switzerland.
PATIENTS AND METHODS

A total of 116 patients with CTCL (61 male and 55 female) from the European Organization for Research and Treatment of Cancer database (94 cases from January 1, 1975, through December 31, 1993) and the Department of Dermatology, University Hospital of Zürich, Zürich, Switzerland (n = 22), were included in the study. One hundred eleven patients had mycosis fungoides and 5 patients had small to medium pleomorphic T-cell lymphoma.10

Excluded from the study were patients with Sézary syndrome and malignant lymphomas with secondary skin involvement. Mean age was 58 years at diagnosis; the duration of follow-up was 1 to 18 years (median, 4 years). Twenty patients died during the observation period. Because of the special patient data of the European Organization for Research and Treatment of Cancer, there was no specific information on cause of death. Therefore, only overall survival was calculated. The skin lesions (patches, plaques, and tumors) were drawn and colored on anatomic diagrams (body mapping; Figure 1). The maps were morphometrically evaluated by means of the grid system (number of squares containing patches or plaques divided by the total number of squares on body front and back); patch and plaque involvement was expressed as a percentage of skin area. The number of tumors was recorded. These data were used in the empirical derivation of the TBI below. Survival was calculated from the date of diagnosis to the date of death or to the last follow-up. Survival curves were obtained by the method of Kaplan and Meier.11

TBI CALCULATIONS

The goal of this study was to develop a dimensionless index that is easy to calculate and gives an estimate of the tumor burden on the weighted basis of the various types of skin lesions. The general formula of the TBI was defined as follows: TBI = 1 + (patches × x) + (plaques × y) + (tumor × z). Patches, plaques, and tumors were defined as shown in Table 2 and in Figure 2 for the clinical findings. The values x, y, and z are dimensionless weighting factors for the 3 types of skin lesions. In the analog TBI models, the types of lesions are expressed as percentages of the skin surface (patches and plaques, according to the body mapping) or totals (tumors). In the dichotomized TBI models, the types of lesions are assigned values of 1 or 0, depending on whether the affected percentage of skin surface area lay above or below an arbitrary cutoff point, ie, if the cutoff point were set at 30%, and patches covered 43% of skin surface, then the value would be 1. Similarly, in the dichotomized models, the plaque value would be 1 if plaque(s) were present and 0 if absent, and the tumor value would be 1 if tumor(s) were present and 0 if absent.

Sets of TBI values were calculated with various weighting factors, by means of both the analog approach and dichotomized models with various cutoff points (10%, 20%, 30%, etc) using the data from the 116 patients above. Weighting factors and appropriate cutoff points were derived from univariate and multivariate analysis of the survival curves (Cox proportional hazard model) and categorical (grouping) analysis by means of the log-rank test. The TBI data sets were then correlated back to the survival curves to find the model formula with the best fit and highest prognostic value.

ANALYSIS OF OTHER PROGNOSTIC VARIABLES

The patient data set was also analyzed according to T stage of TNM classification, sex, age at appearance of first symptoms, age at time of diagnosis, type of skin lesion, and extracutaneous involvement, to look for significant correlations with survival. Statistical analysis was categorical (log-rank test; for sex, grouped data), univariate, or multivariate (Cox proportional hazard model) and categorical (grouping) analysis by means of the log-rank test. The TBI data sets were then correlated back to the survival curves to find the model formula with the best fit and highest prognostic value.

RESULTS

The median observation time was 4 years (range, 0.3-18.3 years). The median age of the patients at appearance of first symptoms was 50.9 years (range, 6-84 years). Their disease was diagnosed a median of 7.1 years (range, 0.2-45.4 years) after the onset of symptoms. The median survival time was 3.9 years (range, 0.3-18.3 years), with men averaging 1 year longer survival than the women.

Seventy-two patients (62.1%) had patches that involved on average 14% of the body surface. Eighty-eight patients (75.9%) had plaques that involved on average 5% of the body surface. Thirty-three patients (28.4%) had tumors, with an average of 5 tumors each.

At time of diagnosis, 51.0% of the patients (n = 59) were in stage T1, 18.1% (n = 21) in stage T2, 28.4% (n = 33) in stage T3, and 5.1% (n = 6) in stage N1 or N3 (palpable peripheral lymph nodes; lymph node biopsies were not performed on all patients) of the TNM classification.

Survival time was significantly dependent on sex (men had a significantly better prognosis, P = .04; OR, 0.40; 95% CI, 0.16-1.01) and inversely correlated with T stage of TNM (P = .09; Figure 3, A) (T1 vs T2, OR, 0.29; 95% CI, 0.08-1.01; T1 vs T3, OR, 0.22; 95% CI, 0.07-0.63; and T2 vs T3, OR, 0.78; 95% CI, 0.26-2.28). Of the TBI variables, having patches covering more than 30% skin lesions for reliable prognostic evaluation of the first, strictly cutaneous CTCL phase. The correlation between tumor volume or burden (in particular, the spread to mediastinal lymph nodes) and prognosis in lymphoma has been documented in the case of Hodgkin disease.8,9 In this study, this concept was extended and adapted to fulfill the characteristics of CTCL, in particular during the cutaneous phase. Clinical observations show that the transition from patch to plaque to tumor stage in CTCL represents progression of the disease. The question raised herein is whether these stages can be reliably quantified and weighted in such a way that they have prognostic value. The goal was to design a simple, dimensionless index (the tumor burden index [TBI]) that reflects the tumor burden in a reproducible manner and to compare its use with that of other prognostic indicators presently available.
of skin surface was also correlated with a poorer prognosis \((P = .02)\) \((OR, 0.32; 95\% CI, 0.12-0.90)\), but significant cutoff points were not found for plaques or tumors examined individually. The following variables were not significantly related to survival: age at appearance of first symptoms \((P = .35; OR, 1.02; 95\% CI, 0.99-1.05)\), age at time of diagnosis \((P = .36; OR, 1.02; 95\% CI, 0.99-1.05)\), and—surprisingly—extracutaneous involvement \((P = .79; OR, 0.76; 95\% CI, 0.10-5.74)\).

Of the TBI models examined, the one with the best fit to the survival curves and hence the highest prognostic significance \((P < .001)\) was obtained by using the following dichotomized terms: patch value equals 0 if 30% or less, 1 if more than 30% patches; plaque value equals 0 if no plaque, 1 if plaque(s) present; and tumor value equals 0 if no tumor, 1 if tumor(s) present \((Table 3)\). The weighting coefficients with the highest significance were \(x\) (patch), 1.98; \(y\) (plaque), 2.03; and \(z\) (tumor), 1.26. These were rounded for the sake of convenience to \(x, 2; y, 2;\) and \(z, 1.3\), to give the following equation: \(TBI = 1 + (\text{patches} \times 2) + (\text{plaques} \times 2) + (\text{tumor} \times 1.3)\).

With this dichotomized formula, 6 discrete TBI values are possible: 1, 2.3, 3, 4.3, 5, and 6.3. Patients within

---

**Table 1. TNM Classification**

<table>
<thead>
<tr>
<th>Stage T N M</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ib</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ila</td>
<td>1, 2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>IIb</td>
<td>3</td>
<td>0, 1</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>0, 1</td>
<td>0</td>
</tr>
<tr>
<td>IIa</td>
<td>1-4</td>
<td>2, 3</td>
<td>0</td>
</tr>
<tr>
<td>IIb</td>
<td>1-4</td>
<td>0-3</td>
<td>1</td>
</tr>
</tbody>
</table>

* \(T1\) is defined as limited lesions (covering < 10% of the skin surface); \(T2\), generalized lesions (covering \(\geq10\%\) of the skin surface); \(T3\), one or more tumors; \(T4\), generalized erythroderma; \(N0\), no palpable lymph nodes, pathologic examination negative for cutaneous T-cell lymphoma (CTCL); \(N1\), palpable peripheral lymph nodes, pathologic examination negative for CTCL; \(N2\), no palpable peripheral lymph nodes, pathologic examination positive for CTCL; \(N3\), palpable peripheral lymph nodes, pathologic examination positive for CTCL; \(M0\), no involvement of visceral organs; and \(M1\), involvement of visceral organs.

---

**Table 2. Histological Features Corresponding to Clinical Features**

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Histological Features*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch</td>
<td>Visible but not palpable</td>
</tr>
<tr>
<td>Plaque</td>
<td>Palpable</td>
</tr>
<tr>
<td>Tumor</td>
<td>Exophytic or subcutaneous (“nodule”)</td>
</tr>
</tbody>
</table>

* CTCL indicates cutaneous T-cell lymphoma.
these 6 TBI groups had significantly different survival curves. However, as 3 of the TBI groups had low frequencies (2 patients had a TBI of 6.3, 6 had 2.3, and 6 had 5), the groups were pooled into 3 prognostic categories: TBI of 2.3 or less, TBI of 3, and TBI of 4.3 or more. The survival curves of these 3 patient categories were significantly different (Figure 3, B) (P < .001). The calculation of CIs and ORs for these 3 TBI prognostic groups (grouped data) was not possible, as all patients in the prognostic group with a TBI of 2.3 or less survived. However, the calculation of the OR and CIs of the non-grouped TBI values was possible (OR, 2.69; 95% CI, 0.16-4.39).

COMMENT

The skin is one of the organs most frequently affected by extranodal lymphomas. Cutaneous lymphomas are peculiar in many aspects. In contrast to nodal lymphomas, CTCLs are more frequent than cutaneous B-cell lymphomas. They develop in a multistep process, with each step exhibiting distinct clinical, histological, and molecular biological features. Since survival time is so variable during the first (strictly cutaneous) stages of CTCL, many factors, including clinical, histological, and serological variables, have been proposed for the evaluation of prognosis in CTCL. Clinical staging with appropriate staging systems is the most important step in determining the individual therapy approach. Since CTCL is confined exclusively to the skin most of the time, the evaluation of skin lesions is most important. Green et al15 emphasized that the extent of skin involvement at the time of registration and number of sites of clinically enlarged lymph nodes are the most important prognostic variables. Other authors support the described prognostic importance of the T category of the TNM classification.15,14 However, this classification unfortunately does not take the details of cutaneous tumor burden into sufficient consideration.

A reasonable approach for the assessment of prognosis, one that is also common in other neoplasias, is the measurement of the tumor mass by determination of a TBI, taking into consideration the evolution of the tumor burden during tumor (or, in this case, lymphoma) progression. The prognostic importance of the tumor mass is well known in nodular lymphomas,8,9,13,16 and recent reports have also emphasized its importance in cutaneous lymphomas. In our study, discrimination of survival curves was better among TBI categories (P = .001) than among T categories of the TNM classification (P = .009). In addition, this TBI is quick and easy to determine and can be calculated during a clinical examination, since it is based exclusively on the skin manifestations of CTCL and requires no additional time-consuming and expensive investigations, such as radiographs, ultrasound, or blood sample results, as input.

Some additional clinical variables that have been evaluated in the literature for their prognostic significance are age, race, localization or type of skin lesion, and extracutaneous involvement. Weinstock and Horn17 reported that advanced age, black race, previous malignant neoplasm, and presence of Sézary syndrome at the time of diagnosis were each independently associated with poor prognosis.17 In our study, no prognostic significance was found for age at time of first symptoms (P = .35) or age at time of diagnosis (P = .36). Although mycosis fungoides is reportedly more common in men,12,17,19 the ratio of males to females in our study was 1:1. Moreover, females showed a statistically worse prognosis than males (P = .04).

Furthermore, the prognosis seems to depend on the involvement of the lymph nodes, the most common extracutaneous manifestation of CTCL. Patients with en-
larged lymph nodes have a worse prognosis than patients without lymphadenopathy.\textsuperscript{13,18-22} A poor prognosis is also reported in patients with lymph node involvement and a clonal T-cell population in the blood,\textsuperscript{23} and in patients with extracutaneous lymphoma involvement of the visceral organs, mainly liver, spleen, and lung.\textsuperscript{7,21,24} In our study, no prognostic value could be shown for extracutaneous involvement ($P = 0.79$), probably simply because too few patients were in this category ($n = 6$) to be able to show a statistically relevant effect.

The results of our study have to be compared with results from a larger number of patients. It is possible that the lack of prognostic significance for both age and extracutaneous involvement is an artifact of our small data set. These contradictory results emphasize the need for validating the TBI formula by means of similar studies at other medical centers with completely different patients, including more patients with extracutaneous disease. Moreover, only lymphoma-related mortality should be considered, since overall mortality may include coexisting comorbid illnesses (eg, cardiovascular or pulmonary conditions), especially during a long follow-up. Interobserver reliability in assessing patients has not yet been tested, since all patients in this study were assessed by the same person. However, with the use of the body mapping and grid system, reliability should be high. The therapy for each patient during this study was performed independently, as this TBI formula can be only considered a preliminary model and has yet to be validated.

In conclusion, a large number of clinical, histological, immunophenotypical, and serological factors have been proposed in the past as possible prognostic indicators for CTCL. However, only a few have practical applicability in daily clinical work. The concept of the TBI presented herein is a preliminary new approach, providing a simple and time-saving procedure for the prognostic evaluation of CTCL. The TBI was not designed as a replacement of the more detailed analyses necessary for monitoring progression or regression of disease in clinical trials, but it may be a valuable tool for designing appropriate therapeutic strategies for individual patients according to their specific survival expectancies.

Accepted for publication June 14, 1999.

Reprints: Guenter Burg, MD, Department of Dermatology, University Hospital of Zurich, Gloriastrae 31, 8091 Zurich, Switzerland (e-mail: burg@derm.unizh.ch).

REFERENCES