Mycosis Fungoides

Disease Evolution and Prognosis of 309 Dutch Patients

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Objectives: To determine the disease course of Dutch patients with mycosis fungoides and to define factors related to disease progression and survival.

Design: A multicenter, 13-year, retrospective cohort analysis.

Setting: Eight dermatology departments collaborating in the Dutch Cutaneous Lymphoma Group.

Patients: Three hundred nine patients with mycosis fungoides registered between October 1985 and May 1997, including 89 patients with limited patches or plaques (stage Ia), 135 with generalized patches or plaques (stage Ib), 46 with skin tumors (stage Ic), 18 with enlarged but uninvolved lymph nodes (stage II), 18 with lymph node involvement (stage III), and 3 with visceral involvement (stage IV).

Main Outcome Measures: Response to initial treatment, sustained complete remission, actuarial disease progression, and overall and disease-specific survival per clinical stage.

Results: The median follow-up was 62 months (range, 1-113 months). For the entire group, the actuarial overall and disease-specific survival was 80% and 89% at 5 years, and 57% and 75% at 10 years, respectively. The actuarial 5-year disease-specific survival of patients with stage Ia, Ib, and Ic disease was 100%, 96%, and 80%, respectively, and only 40% for patients with stage III disease. Using multivariate analysis, the presence of extracutaneous disease, the type and extent of skin involvement, the response to initial treatment, and the presence of follicular mucinosis were independently associated with higher disease progression and mortality rates. The calculated risks of disease progression at 5 and 10 years gradually increased from 4% to 10% for those with stage Ia disease, from 21% to 39% for those with stage Ib disease, and from 32% to 60% for those with stage Ic disease; for those with stage III disease, the risk remained at 70% at 5 and 10 years. The overall risk of disease progression at 5 and 10 years was 24% and 38%, respectively, for the total study group.

Conclusion: At least within the first 10 years after diagnosis, disease progression and mycosis fungoides-related mortality occur in only a subset of patients generally presenting with advanced disease.

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PATIENTS AND METHODS

Between October 1985 and May 1997, 345 patients with MF were included in the registry of the Dutch Cutaneous Lymphoma Group, and follow-up data had been collected yearly. For the present study, only patients with clinical and histological features consistent with MF, and who underwent a follow-up period of at least 12 months after histological confirmation of the diagnosis, unless death due to MF occurred earlier, were selected. Thirty-six patients were excluded because of insufficient clinical information or follow-up. The final study group comprised 309 patients. In each patient, the diagnosis had been made by an expert panel of dermatologists and pathologists at 1 of the quarterly meetings of the Dutch Cutaneous Lymphoma Group. The histological criteria for the diagnosis of early MF are essentially the same as those described by Nickeloff,1 and require the presence of hyperchromatic, slightly to markedly atypical lymphoid cells in the epidermis, either as single, often haloes, cells, or in a linear configuration at the dermo-epidermal junction. Patients with patches or plaques clinically suspected but histologically not diagnostic of MF, are included as a separate category in the Dutch registry and were not included in the present study, unless at a later point a definite diagnosis of MF was made. The time of the first diagnostic biopsy was taken as the time of diagnosis. The study group did not include patients with Sézary syndrome, pagetoid reticulosis, or other CTCL, recognized as distinct entities in the European Organization for Research and Treatment of Cancer classification for primary cutaneous lymphomas.20 However, to allow comparison with other published series, patients with MF-associated follicular mucinosis, included as a distinct variant of MF in the European Organization for Research and Treatment of Cancer classification, were included. Association with follicular mucinosis was included as one of the variables in univariate and multivariate analyses of survival and disease progression.

The stage of the disease was determined based on the type and extent of skin involvement and the presence of lymph node, visceral, or blood involvement according to a modification of the Fuks classification scheme,4,18 which can easily be translated into the TNM system5 (Table 1). Staging evaluation consisted of obtaining a complete medical history and a complete blood cell count and performing a physical examination, serum chemistry studies, and a skin biopsy. In the presence of lymphadenopathy, a lymph node biopsy and thoracic and abdominal computed tomographic scans were performed, and a chest x-ray film was obtained. Lymph node involvement was assessed throughout the study (1985-1997) with the same criteria, described previously.20 When indicated clinically, additional staging studies to determine visceral involvement were performed. The following variables were recorded: age; sex; clinical stage at the time of diagnosis; duration of skin lesions before diagnosis; type of initial therapy; whether there was complete remission after initial therapy; disease course after initial therapy; the date of disease progression, if applicable; and the date of last contact and cause of death, if applicable. In addition, the presence of follicular mucinosis in the first diagnostic biopsy specimen and the presence of lymphomatoid papulosis or B-cell neoplasms prior to, concurrent with, or following the development of MF were recorded. Complete remission on initial treatment was defined as complete disappearance of all skin lesions. In most cases, histological confirmation of complete remission was not obtained. No distinction was made between partial or no responses on initial therapy. For clinical course, distinction was made between sustained complete remission, defined as the total disappearance of all (extra) cutaneous lesions after initial therapy without subsequent relapse (without maintenance treatment); continued disease, disease without progression to a higher clinical stage; and disease progression, the development of skin tumors in patients with a previous patch or plaque (stage Ia-Ib), the development of histologically documented nodal involvement (stage III) in patients with previous skin-limited disease, the development of visceral involvement in patients with prior skin and/or lymph node involvement, and death due to MF.

As indicators of survival, disease-specific survival, including only death related to MF as the event, and overall survival, including death due to any cause as the event, were investigated. Actuarial survival and disease progression curves were calculated from the date of diagnosis to the date of death or last contact and the date of disease progression, respectively, using the Kaplan-Meier technique.21 Patients lost to follow-up were considered to be censored at the time of last contact. Differences between survival and disease progression rates were analyzed using the log-rank test. Comparative analysis of groups of numerical variables was performed using 2-tailed t tests. P <.05 was considered significant. Relative risks and 95% confidence intervals were determined using standard methods. Univariate analysis of possible prognostic factors was performed using the log-rank test and Cox proportional hazards regression analysis. Multivariate analysis was performed by entering significant univariate variables for survival and disease progression in Cox proportional hazards regression analysis19 to establish their independence as prognostic factors. All analyses were performed using Statistical Product and Services Solutions software (SPSS Inc, Chicago, Ill).

RESULTS

CLINICAL CHARACTERISTICS AT PRESENTATION

Of the 309 patients included in this study, 72.5% had either stage Ia or Ib MF at the time of diagnosis, whereas
14.9% presented with 1 or more skin tumors in addition to patches and plaques, but no evidence of extracutaneous disease. Of the 309 patients, 270 (87.4%) had only skin lesions at the time of diagnosis; 18 (5.8%), enlarged but histologically uninvolved lymph nodes; and 21 (6.8%), nodal and/or visceral involvement (Table 2).

Considering the entire group of patients, the age at diagnosis varied between 14 and 92 years (median, 61 years). Only 2 patients (0.6%) were younger than 20 years at the time of diagnosis. Patients presenting with stage Ic MF were significantly older than patients with stage Ia MF (67.5 vs 58.0 years; P < .001). There was a male predominance, with a male-female ratio of 196:113, which is consistent with that of other large series.2,3,13 The duration of skin lesions before a definite diagnosis could be made varied between 1 month and more than 50 years (median, 48 months) and was significantly shorter in the 21 patients presenting with extracutaneous disease (median, 24 months) compared with patients with only skin lesions at presentation (median, 48 months) (P = .006).

Of the 309 patients with MF, 32 (10.4%) had associated follicular mucinosis at the time of diagnosis.

### Table 1. Clinical Stage of 309 Patients With MF at the Time of Diagnosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patches and Plaques Covering the Skin Surface</th>
<th>Skin Tumor</th>
<th>Erythroderma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10% (a)</td>
<td>≥10% (b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MF confined to the skin (I)</td>
<td>89</td>
<td>139</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>MF with dermatopathic lymphadenopathy (II)</td>
<td>0</td>
<td>9</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>MF with lymph node involvement (III)</td>
<td>1</td>
<td>7</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>MF with visceral involvement (IV)</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>90</strong></td>
<td><strong>151</strong></td>
<td><strong>64</strong></td>
<td><strong>4</strong></td>
</tr>
</tbody>
</table>

* The clinical stage is given according to the modified Fuks classification.4 Translation into the TNM classification18 is as follows; Ia, T1 N0 M0; Ib, T2 N0 M0; Ic, T3 N0 M0; Id, T4 N0 M0; Ia through IId, T1 through T4 N1 M0; IIIa through IIId, T1 through T4 N3 M0; and IVa through IVd, T1 through T4 N0 through N3 M1. MF indicates mycosis fungoides.

### Table 2. Patient Characteristics and Disease Outcome per Clinical Stage

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stage</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients†</td>
<td></td>
<td>309 (100)</td>
</tr>
<tr>
<td>Age at diagnosis, median (range), y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male-female ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of skin lesions before diagnosis, median (range), mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission on initial therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of follow-up, median (range), mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of disease progression, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-specific survival, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival, %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Data are given as number (percentage) of patients within each column unless otherwise indicated. Percentages may not total 100 because of rounding. The clinical stages are explained in Table 1. CR indicates complete remission; MF, mycosis fungoides; and ellipses, data not applicable.

† The row total was used to obtain the percentages.
group included 28 patients with stage I, 3 with stage II, and 1 with stage IV MF. The combination of MF—stage Ia in 2 and Ib in 6 patients—and lymphomatoid papulosis was noticed in 8 (2.6%) of the 309 patients. Associated B-cell lymphoproliferations were documented in 5 patients with stage Ia or Ib MF, including 4 with B-cell chronic lymphocytic leukemia and 1 with nodal follicular lymphoma.

**TREATMENT AND FOLLOW-UP**

The initial therapies at the different stages of MF are listed in Table 3, and reflect the approach used in the treatment of MF in the Netherlands. The treatment modality most commonly used for stage Ia or Ib disease was psoralen–UV-A therapy (140 [62.5%] of 224 cases); less frequently used modalities included topical corticosteroids, UV-B therapy, topical mechloretamine hydrochloride, and, in case of extensive skin lesions, total skin electron beam irradiation. Patients with stage Ic disease were treated similarly, often with additional local radiotherapy for persistent tumors (Table 3). Systemic polychemotherapy consisting of cyclophosphamide, vincristine sulfate, doxorubicin, and prednisone was mainly given to patients presenting with nodal (stage III) or visceral (stage IV) involvement, often in combination with or followed by skin-directed therapies.

Initial treatment resulted in clinical complete remissions in 98 (31.7%) of 309 patients. However, in most patients, these complete remissions were short-lived. Sustained complete remissions on initial treatment were observed in only 33 (10.7%) of the 309 patients, among whom 26 had stage Ia or Ib disease. The disease-free survival in these 33 patients varied between 10 and 163 months (median, 68 months). In 199 (64.4%) of the 309 patients, there was continued disease without progression, typically having a fluctuating course, while in the remaining 77 (24.9%), disease progression, including death due to MF, occurred.

The median follow-up was 62 months (range, 1-313 months). During that period, 92 of the 309 patients died, including 47 of MF. The disease-specific survival at 5 and 10 years for the whole group of 309 patients was 89% and 75%, respectively; the 5- and 10-year overall survival was 80% and 57%, respectively. The survival rates according to clinical stage are presented in Table 2, Figure 1, and Figure 2. Consistent with prior reports, patients with MF and lymphomatoid papulosis had an excellent prognosis. None of these patients showed disease progression after a median follow-up of 158 months (range, 23-244 months).

**PROGNOSTIC VARIABLES**

Univariate analysis of variables possibly influencing disease-specific survival in the entire group of 309 patients showed that the following factors were statistically significant: stage at diagnosis (P < .001), including the presence of extracutaneous disease (P < .001) and the type and extent of skin involvement (P < .001); no complete remission on initial treatment (P < .001); associated follicular mucinosis (P = .005); and older age (P = .01). Sex (P = .69) and duration of skin lesions before diagnosis (P = .34) were not significantly related to survival, when the total group was considered.

Univariate analysis of the prognostic variables per clinical stage showed that only complete remission on initial treatment within the group of patients with stage Ib MF was significantly related to survival (P = .04) (Figure 3). Multivariate analysis revealed that—in order of predictive value—presence of extracutaneous disease, type and extent of skin involvement, no complete response to initial treatment, and presence of follicular mucinosis were independently associated with MF-related mortality. The relative risks for MF-related mortality are presented in Table 4.

Regarding clinical stage, patients with stage Ia and stage Ib MF had a significantly better survival than patients with stage Ic MF (P < .001). However, no significant difference in survival was found between patients with stage Ia and stage Ib disease (P = .11). Notably, not only patients with histologically documented lymph node involvement (stage III) but also patients with enlarged, but histologically uninvolved, lymph nodes (stage II) had...
a significantly lower survival compared with patients with stage I MF (P < .001 and P = .02, respectively).

**DISEASE PROGRESSION**

One of the goals of this study was to assess the risk of disease progression, including death due to MF, for patients with different stages of MF. The calculated risks of disease progression at 5 and 10 years gradually increased from 4% to 10% for those with stage Ia disease, from 21% to 39% for those with stage Ib disease, and from 32% to 60% for those with stage Ic disease; for those with stage III disease, the risk remained at 70% at 5 and 10 years (Table 2). Table 5 shows the actual frequency of disease progression in the group of 309 patients after a median follow-up of 62 months. It also shows that the higher the clinical stage at diagnosis, the shorter the duration until disease progression.

Multivariate analysis revealed that—as for disease-specific survival—the presence of extracutaneous disease, the type and extent of skin involvement, the response to initial treatment, and the presence of follicular mucinosis were independently associated with disease progression.

**COMMENT**

In the present study, the main clinical characteristics, disease evolution, and survival of 309 Dutch patients with MF, included in the Dutch registry for cutaneous lymphomas between October 1985 and May 1997, were evaluated. In addition, prognostic variables and the risk of disease progression for those with different stages of MF were analyzed. The median age at diagnosis of 61 years and the male-female ratio of 196:113 were similar to those given in the few other large series studied. At the time of first presentation, 93.2% of the patients with MF had only skin lesions, including 5.8% with concurrent en-
larged but histologically uninvolved lymph nodes, whereas only 6.8% presented with concurrent nodal or visceral involvement.

In the Netherlands, patients with MF are treated traditionally with skin-directed therapies, including topical corticosteroids, psoralen–UV-A therapy, UV-B therapy, or topical mechlorethamine hydrochloride, and additional radiotherapy in case of concurrent skin tumors, whereas multiantiport chemotherapy is generally only used in patients with extracutaneous localizations. Initial treatment according to this classic approach resulted in a complete remission in almost one third of the patients (98 of the 309 patients). As expected, in most patients, this complete remission was short-lived. However, in 33 (34%) of the 98 patients achieving complete remission on initial treatment, and not receiving any type of maintenance treatment, there was no subsequent relapse. Eighteen of these 33 patients, including 9 with stage Ia, 5 with stage Ib, 3 with stage Ic, and 1 with stage IIb MF, have been in complete remission for more than 5 years, and, since most relapses occur within 5 years after achieving complete remission, 10,13 may be considered as potential cures. The present retrospective study does not allow a representative comparison of the effects of the different treatment modalities, since treatment selection may have been affected by disease severity. It is, therefore, not surprising that we did not find a relation between the results of initial treatment and the type of treatment given (data not shown). The complete response of only 10 (55.6%) of the 18 patients to total skin electron beam irradiation at initial therapy may be explained by the fact that 4 of 18 patients had stage III disease, and 8 of the 14 remaining patients had MF-associated follicular mucinosis, a combination known to be rather refractory to total skin electron beam irradiation. 25

The disease-related and overall survival for the whole group of 309 patients was 89% and 80% at 5 years, and 75% and 57% at 10 years, respectively. For the survival rates for the different stages of MF, the overall and disease-specific survival rates at 5 and 10 years for patients with stage Ia and Ib MF (Table 2) were similar to those reported in previous studies. 1,5,13,14 In this study, we did find a difference in survival between those with stage Ia and those with stage Ib MF, but this did not reach statistical significance. The fact that disease progression was much more frequent in patients with stage Ib MF than in those with stage Ia MF suggests that with longer follow-up, the difference in survival might become statistically significant.

Our study did not include patients with large-plaque parapsoriasis, characterized by the presence of patches or slightly infiltrated plaques but with histological changes not diagnostic of MF. While we consider such lesions as a potential precursor of MF, other groups 26 have expressed the view that large-plaque parapsoriasis, and even small-plaque parapsoriasis, should be considered as MF, and not as precursors of MF. However, in view of the excellent prognosis of patients with stage Ia MF—similar to that of a race-, age-, and sex-matched control population 10—and the low tendency to progress, it is questionable which patient with small-plaque parapsoriasis will benefit from being marked as a patient with CTCL. Because of this ongoing controversy and the inconsistent use of the terms large-plaque parapsoriasis and small-plaque parapsoriasis, it is perhaps better to abandon these terms. The only question that really matters is the following: is it MF or is it not MF?

Tumor stage MF is often associated with a poor prognosis. However, this and other studies 11,12,14 clearly indicate that patients with skin tumors without concurrent extracutaneous disease (stage Ic) still have a disease-related 5-year survival of approximately 70% to 80%. Whether patients with enlarged, but histologically uninvolved, lymph nodes (stage II) have a more unfavorable prognosis compared with patients without clinically enlarged lymph nodes is a matter of controversy. 11,13 In the present study, patients with stage II disease had a significantly lower survival rate than patients with stage I MF (P < .001). Previous studies 27 suggested that T-cell receptor gene rearrangement analysis is a more accurate and objective method of diagnosing early lymph node involvement in patients with MF than routine histological features. However, in prior studies, 28 which included lymph nodes of 7 of the 18 patients with stage II MF included in this study, no clonal T-cell populations were found in any of the dermatopathic, but noninvolved, lymph nodes. There is, therefore, no evidence that the lymph nodes of these patients with stage II MF were actually involved, which leaves the more unfavorable prognosis of this group unexplained.

Table 5. Actual Disease Progression in 309 Patients With MF After a Median Follow-up of 62 Months*

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>Skin Tumors</th>
<th>Lymph Node Involvement</th>
<th>Visceral Involvement</th>
<th>Death Due to MF</th>
<th>Duration Until Disease Progression, mo‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia (n = 89)</td>
<td>3 (3)</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Ib (n = 135)</td>
<td>28 (21)</td>
<td>19 (14)</td>
<td>5 (4)</td>
<td>13 (10)</td>
<td>33 (24)</td>
</tr>
<tr>
<td>Ic (n = 46)</td>
<td>0</td>
<td>11 (24)</td>
<td>7 (15)</td>
<td>15 (33)</td>
<td>18 (39)</td>
</tr>
<tr>
<td>II (n = 18)</td>
<td>3 (17)</td>
<td>5 (28)</td>
<td>2 (11)</td>
<td>4 (22)</td>
<td>9 (50)</td>
</tr>
<tr>
<td>III (n = 18)</td>
<td>2 (11)</td>
<td>0</td>
<td>3 (17)</td>
<td>11 (61)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>IV (n = 3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (67)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Total (N = 309)</td>
<td>36 (12)</td>
<td>37 (12)</td>
<td>18 (6)</td>
<td>47 (15)</td>
<td>77 (25)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients unless otherwise indicated. The clinical stages are explained in the footnote to Table 1. MF indicates mycosis fungoides.
†Total number (percentage) of patients showing disease progression.
‡Data are given as the median (range).
In the literature, the following prognostic variables have been described: stage of disease, race, response to initial treatment, and malignant neoplasm. In the present study, stage at diagnosis (ie, the presence of extracutaneous disease and the type of skin involvement), complete remission after initial treatment, and the presence of follicular mucinosis proved independently predictive of disease-specific survival and disease progression.

In the group of 32 patients with MF-associated follicular mucinosis, disease progression occurred more often and disease-specific survival rates were significantly lower than in the 277 patients without follicular mucinosis. In the 32 patients with follicular mucinosis, disease progression was estimated to occur in 99% within 10 years after diagnosis vs 32% in the 277 patients without follicular mucinosis. The disease-related survival at 5 and 10 years was 81% and 36%, and the overall survival 75% and 21%, respectively. A more detailed clinical and histological analysis of a group of 40 patients with MF-associated follicular mucinosis will be published separately.

Older patients had significantly lower disease-specific survival rates and higher disease progression rates. However, older age was associated with more advanced stages of MF, and it appeared not to be an independent prognostic factor.

Mycosis fungoides is generally depicted as a malignant disease that slowly evolves through patch, plaque, and tumor stages, and ultimately may develop into an extracutaneous and generally fatal disease. Because of the increased accessibility of medical literature through Internet services, we are confronted more frequently with patients with newly diagnosed MF who have come to believe that this sequence of events invariably takes place. On the other hand, clinical experience suggests that many patients with MF, in particular those with stage Ia and perhaps also many with stage Ib disease, may have stable disease for decades, and that only a proportion of patients with MF progresses and will develop extracutaneous disease. Consistently, the results of this and other recent studies indicate that the risk of disease progression within the first 10 years after diagnosis is about 5% to 10% for patients with stage Ia and between 17% and 39% for patients with stage Ib disease. In patients with more advanced stages of MF, the risk of disease progression was higher and the duration until progression shorter (Tables 2 and 5). These results confirm the clinical impression that, at least within the first 10 years after diagnosis, disease progression occurs in only a few patients. Further studies are warranted to elucidate the risk factors associated with disease progression within these early stages of MF.

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REFERENCES


