Clinical Characteristics and Long-term Outcome of Patients With Generalized Patch and/or Plaque (T2) Mycosis Fungoides

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Objectives: To study the long-term results of treatment of patients with generalized patch and/or plaque mycosis fungoides and to identify clinical characteristics predictive of survival and response to treatment.

Design: A single-center, 35.5-year retrospective cohort analysis.

Setting: Private referral medical center.

Patients: One hundred seventy-six patients with generalized patch and/or plaque (T2) mycosis fungoides.

Main Outcome Measures: Long-term actuarial survival and freedom-from-relapse results as calculated by the Kaplan-Meier method.

Results: The long-term (35.5-year) survival of patients with T2 mycosis fungoides is worse than the expected survival of a race-, age-, and sex-matched control population ($P<.001$). The median survival of the T2 group is 11.7 years. Patients younger than 58 years (median age) at presentation have a more favorable overall and disease-specific survival than the patients who are 58 years or older ($P<.001$ vs $P<.025$). Patient sex or race had no significant effect on overall survival. Patients who presented with palpable clinically significant lymph nodes (stage IIA) had long-term survival results similar to those without lymphadenopathy (stage IB), despite improved freedom-from-relapse outcome for patients with stage IB. Twenty-four percent of patients who progressed to more advanced disease had a lower complete response rate to initial therapy than did other patients (21% vs 65%) ($P<.001$). Patients who received total skin electron beam therapy had a better complete response rate than patients treated with topical mechlorethamine hydrochloride alone; the relapse-free results were superior in patients with a total dose of 30 Gy or higher and in patients who received topical mechlorethamine as adjuvant therapy following total skin electron beam therapy. Despite differences in freedom-from-relapse results among different treatment groups, long-term overall or disease-specific survivals were not significantly different.

Conclusions: A significant proportion (24%) of patients with generalized patch and/or plaque (T2) mycosis fungoides experience disease progression to a more advanced clinical stage, and nearly 20% eventually die of the disease. Younger patients have a more favorable disease-specific long-term outcome than patients who are older. Presence of lymphadenopathy (stage IIA) at diagnosis does not predict worse long-term survival outcome. Clinical features predictive of disease progression include initial lymphadenopathy (stage IIA) and lack of complete response to initial treatment. Despite superior complete response rate to a 30-Gy or higher dose of total skin electron beam therapy, topical mechlorethamine proves to be a cost-effective initial treatment for patients with T2 disease. The concept of an adjuvant therapy after irradiation is appealing, although it may not lead to improved long-term survival.

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M YCOSIS fungoides (MF) is a major subtype of cutaneous T-cell lymphoma characterized by the presence of epidermotropic atypical T cells found on histological examination and a tendency for a long natural history with a premycotic cutaneous appearance that may resemble other common dermatologic disorders.[1-3] The extent and type of skin involvement, the T stage, and presence of lymph node or visceral involvement with MF are important clinical predictors of survival.[4-7]

We have reported that our patients with limited skin involvement (T1) have a long-term survival outcome that does not differ significantly from their age-, sex-, and race-matched control population.[8] We have also demonstrated that patients who received total skin electron beam therapy (TSEBT), a more aggressive initial treat-

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PATIENTS AND METHODS

PATIENT SELECTION AND STAGING

Five hundred eighty-six patients with MF were evaluated and treated in the Stanford Mycosis Fungoides Clinic from 1958 to 1997. For classification and staging, patients underwent a complete physical examination, complete blood cell count with examination of the blood smear for Sézary cells, a general chemistry panel, chest radiography, and skin biopsy. Patients with palpable lymph nodes clinically suggestive of involvement with MF had their lymph nodes evaluated by needle aspiration or lymph node biopsy. When indicated clinically, patients underwent additional staging studies, including bone-marrow biopsy and imaging studies to determine visceral involvement. After initial evaluation, the lesions of all patients were staged according to the TNMB categories (**Table 1**) and overall staging classification system (**Table 2**).[10]

We identified 220 patients seen between 1958 and 1997 whose skin involvement was classified as T stage = 2 (T2) with generalized patch and/or plaque disease (>10% of total skin surface). Of these, 176 patients had their diagnosis established or confirmed and all treatments managed at the Stanford Mycosis Fungoides Clinic. We excluded 44 patients from our study who received their initial primary treatments prior to their evaluation at Stanford Mycosis Fungoides Clinic and/or who received most of their treatments at a site unrelated to Stanford University Medical Center or its affiliated hospitals. Five patients with T2 disease (3 with stage IB and 2 with stage IIA) were lost to follow-up. All 176 patients had the diagnosis of MF confirmed by results of skin biopsy.[1,11]

PRIMARY AND ADJUVANT THERAPIES

Most patients received either topical mechlorethamine (nitrogen mustard) or TSEBT as their initial primary treatment. Topical mechlorethamine was given in an ointment base or dissolved in water. The treatments were initiated at 10 mg/100 mL and the concentration was increased after 2 to 3 months if the clinical response was not satisfactory.[11] The total dose of TSEBT ranged from lower than 20 Gy to 40 Gy; most patients before 1970 received doses lower than 20 Gy, and those after 1970 received doses of 30 Gy or higher.[12] A few patients were treated with psoralen plus UV-A (PUVA), local radiation in conjunction with topical mechlorethamine, or single-agent chemotherapy.

Twenty of the 106 patients who were treated with TSEBT as primary therapy received adjuvant therapy with topical mechlorethamine immediately following their course of TSEBT. Adjuvant topical mechlorethamine was given for 3 to 44 months with a median treatment duration of 15 months. All patients with T2 disease treated with adjuvant topical mechlorethamine therapy had complete response to TSEBT.

RESPONSE TO TREATMENT

Clinical response to treatment was determined primarily by physical examination. Skin biopsy specimens and/or imaging studies were obtained in some patients. *Complete response* has been defined as a complete clinical regression of all MF lesions; *partial response* as any response that is less than complete; and *no response* as no observable clinical response to therapy.

STATISTICAL ANALYSIS

Actuarial survival and FFR curves were calculated from the date of the initial Stanford Mycosis Fungoides Clinic visit and from treatment initiation date, respectively, and were plotted according to the Kaplan-Meier technique.[13] Analysis of differences in actuarial curves was performed by using the Gehan test.[14,15] All *P* values correspond to 2-sided significance tests. Relative risk and 95% confidence interval (CI) were determined using standard methods.[15] The "expected survival" used as the expected outcome of race-, age-, and sex-matched control population for our 176 patients with T2 disease was obtained from US decennial life tables.[16] Disease-specific survival (DSS) is defined as survival calculation where death events are specifically related to MF, such as, progressive disease, fatal infections, and complications related to MF.

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ment than topical mechlorethamine hydrochloride, did not have an improved long-term survival outcome, despite a superior complete response rate.

A substantial proportion of patients with MF present with generalized patch and/or plaque disease (T2) at diagnosis. Many of these patients with T2 disease have had some history of skin manifestation treated as either eczematous dermatitis, psoriasis, or parapsoriasis prior to a more definitive diagnosis of MF.[1-3] Some of these patients present with a distinct poikilodermatous skin appearance, thus alerting the clinician to the possibility of MF. Then there are patients with T2 disease who display a more aggressive clinical course, presenting with indurated cutaneous plaques. Patients with T2 disease may present with palpable lymphadenopathy, although they rarely have frank extracutaneous disease at presentation.

Patients who present with either tumors (T3) or generalized erythroderma (T4) have an overall worse survival outcome than patients with either T1 or T2 disease.[1-3] Our recent review of erythrodermic (T4) patients with MF revealed that patient age at presentation and lymph node and peripheral blood involvement with MF are clinically significant, independent prognostic indicators of survival.[9] Patients with palpable lymph nodes (with or without histological involvement of MF) appeared to have a less favorable outcome than those without palpable nodes; however, the difference was not statistically significant.

The goal of this study was to review the long-term outcome of our patients with generalized patch and/or plaque (T2) disease and to define any clinical predictive factors of survival or disease progression. Also, we wanted to evaluate the impact of the type of initial treatment on freedom from relapse (FFR) and long-term survival.

RESULTS

T2 OVERALL SURVIVAL

Patients with T2 MF have worse overall survival than the expected survival of the race-, age-, and sex-matched con-

Table 1. TNMB Classification for Mycosis Fungoides

T (Skin)
  T1   Limited patch/plaque (<10% of total skin surface)
  T2   Generalized patch/plaque (≥10% of total skin surface)
  T3   Tumors
  T4   Generalized erythroderma
N (Nodes)
  N0   Lymph nodes clinically uninvolved
  N1   Lymph nodes enlarged, histologically uninvolved
            (includes "reactive" and "dermatopathic" nodes)
  N2   Lymph nodes clinically uninvolved,
            histologically involved
  N3   Lymph nodes enlarged and histologically involved
M (Viscera)
  M0   No visceral involvement
  M1   Visceral involvement
B (Blood)
  B0   No circulating atypical (Sézary) cells
            (<5% of total lymphocytes)
  B1   Circulating atypical (Sézary) cells
            (≥5% of total lymphocytes)

Table 2. Clinical Staging System for Mycosis Fungoides

Clinical Stages	TNM Classification*		
	T	N	M
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T1-2	N1	M0
IIB	T3	N0-1	M0
IIIA	T4	N0	M0
IIIB	T4	N1	M0
IVA	T1-4	N2-3	M0
IVB	T1-4	N0-3	M1

The "B" classification does not alter the clinical stage.

Figure 1. *Actuarial survival of 176 patients with T2 disease (1) compared with that of a race-, age-, and sex-matched control population (2) (Gehan[14] P<.001).*

Table 3. Demographic and Clinical Characteristics of Patients With Generalized Patch/Plaque (T2) Mycosis Fungoides

Characteristic	No. (%) of Patients
Age range, y	
20-88	NA*
Mean, 56	NA
Median, 58	NA
Sex	
Male	111 (63)
Female	65 (37)
Race	
White	150 (85)
Black	7 (4)
Asian	4 (2)
Hispanic	15 (9)
Clinical stage at presentation†	
IB	116 (66)
IIA	56 (32)
IVA	4 (2)

NA indicates data not applicable.
†See "Initial Clinical Stage and Long-term Outcome" subsection of the "Results" section for staging explanation.

trol population (*P*<.001) (**Figure 1**). The relative risk of death for patients with T2 disease compared with the general population is 2.3 (95% CI, 1.9-2.8). The median survival of the T2 group is 11.7 years and the calculated survival rates at 5, 10, and 20 years are 73%, 55%, and 27%, respectively. The median follow-up was 8.0 years with a range of 6 months to 35.5 years. Twenty-two patients (13%) have follow-up intervals of greater than 20 years, and 55 patients (31%) have been followed up for 10 to 20 years. Patients with T2 disease have worse overall survival than patients with T1 disease where the median survival has not been attained, but much improved survival compared with patients with T3 or T4 disease, with median survivals of 3.2 and 3.7 years, respectively (data not shown).

PATIENT AGE AT PRESENTATION, RACE, AND SEX

The demographics of our T2 group are summarized in **Table 3**. The patients with T2 disease who were younger than 58 years (median age) had a more favorable long-term outcome than those 58 years or older (*P*<.001), with a median survival of 18.2 and 7.1 years, respectively (data
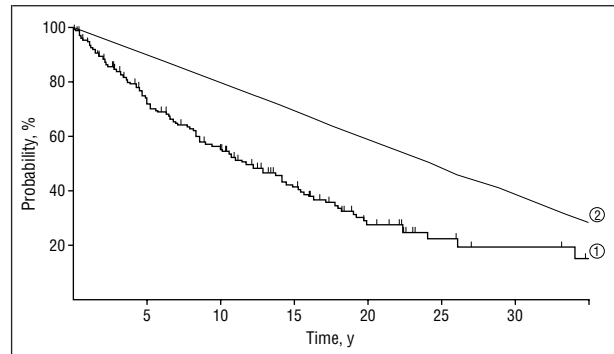
not shown). To correct our results for the expected increase in death rate associated with age, we also compared DSS between the 2 age groups. The DSS outcome is superior for patients younger than 58 years (*P*<.03). Despite the differences in long-term survival results, there were no significant differences in the relapse-free outcome between the 2 age groups.

Women had a slightly better survival than men (*P*<.05); however, there was no significant difference in their DSS outcome (*P* = .33) (data not shown). The racial background of our patients was predominantly white (Table 3). The number of patients in other racial groups was too small to perform any significant statistical analysis.

INITIAL CLINICAL STAGE AND LONG-TERM OUTCOME

Most of our patients with T2 disease had clinical stage IB at presentation. However, 56 patients (32%) had clinically significant palpable lymph nodes (stage IIA), and
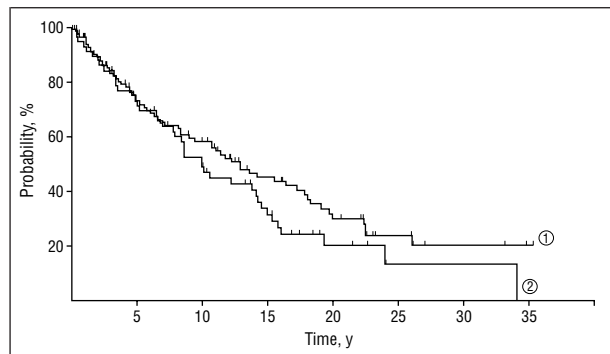
Figure 2. *Actuarial survival of T2 patients who presented with clinical stage IB (1) (n = 116) compared with patients presenting with clinical stage IIA (2) (n = 56) (Gehan[14] P = .38).*

4 patients (2%) presented with frank lymph node involvement with MF (stage IVA) (Table 3). Twenty-three of the 56 patients with stage IIA disease had palpable lymph nodes that were not clinically suggestive of lymphoma, such as reactive or dermatopathic nodes; thus, histopathologic assessment was not obtained. The long-term survival of patients with stage IB disease was not significantly different from those with stage IIA (P = .38) (**Figure 2**). The median survivals of patients with stage IB and IIA disease were 12.8 and 10.0 years, respectively. The DSS calculations suggested a trend toward improved survival for patients with stage IB, but the difference was not statistically significant (P = .08).

DISEASE PROGRESSION AND CAUSES OF DEATH

Overall, 43 (24%) of 176 patients with T2 disease experienced disease progression to a more advanced clinical stage. Of the 116 patients with stage IB, the diseases of 23 patients (20%) progressed to more advanced stages: 5 to IIA (palpable nodes), 16 to IIB (cutaneous tumors), and 2 to stage IVA (frank nodal disease). Nineteen (34%) of the 56 patients with initial stage IIA had their diseases progress to more advanced stages: 13 to IIB, 1 to IIIB (erythroderma with palpable nodes), 4 to IVA, and 1 to stage IVB (visceral disease). Of the 4 patients who presented with lymph node involvement with MF (stage IVA), 1 experienced progression to visceral disease (stage IVB).

Table 4 compares the clinical characteristics of the T2 patients experiencing disease progression (n = 43) with those having no progression (n = 133). The patient age, sex, and racial distribution are similar in each group. More patients with initial stage IIA experienced disease progression than those with stage IB (34% vs 20%; P = .07). The patients who experienced disease progression had a lower complete response rate to initial therapy than did the remainder of patients with T2 disease (21% vs 65%; P<.001).

One hundred ten (62%) of 176 patients with T2 disease died. Thirty-four patients (19%) died of MF; of these, 24 had their conditions progress to a more advanced clinical stage. Seventy-six patients (43%) died of intercurrent causes such as second cancers (n = 13) or cardiopulmonary diseases. The second cancers included breast,

Table 4. Clinical Characteristics of T2 Patients With Progressive Disease Compared With Patients Without Disease Progression

Characteristics	T2 Patients*	
	Without Progression	With Progression
Total No. of patients	**133 (76)**	**43 (24)**
Mean age, y	56.5	56.3
Sex		
Female-male ratio	1:1.6	1:2.1
Race		
White-nonwhite ratio	6:1	5.1:1
Initial clinical stage†		
IB	93 (80)	23 (20)
IIA	37 (66)	19 (34)
IVA	3	1
Primary therapy		
Mechlorethamine hydrochloride	53 (84)	10 (16)
TSEBT‡	78 (73)	29 (27)
Other	2	4
Treatment response		
Complete	87	9
Partial	33	27
None	13	7

*Unless otherwise indicated, data are given as number or number (percentage).
†See "Initial Clinical Stage and Long-term Outcome" subsection of the "Results" section for staging explanation.
‡TSEBT indicates total skin electron beam therapy.

lung, ovarian, and pancreatic carcinomas, malignancies of the liver, and metastatic squamous cell carcinoma from the skin, and 2 patients with hematopoetic malignancies. Twenty patients (12%) are alive without evidence of MF, and 46 patients (26%) are alive with active disease. The longest follow-up of patients who are alive without disease is 33.5 years.

FREEDOM FROM RELAPSE

The FFR calculations reveal that 57% of our patients with T2 disease had a complete response to initial treatment (**Figure 3**, top). The FFR rates at 5, 10, and 20 years were 25.3%, 20.1%, and 17.4%, respectively (95% CIs, 17.9%-32.7%, 12.9%-27.3%, and 10.2%-24.6%). Most patients who relapsed did so within 5 years after achieving complete response. Four patients are relapse free for more than 20 years, and 1 patient is relapse free for more than 33 years since initial therapy.

Despite lack of significant differences in patient long-term survival between stages IB and IIA, patients with stage IB had a superior response rate to initial treatment (complete response rates of 62% vs 48%) and better overall FFR outcome (P<.005) (Figure 3, bottom). The respective 5- and 10-year calculated FFR rates were 35.5% and 30.7% (95% CIs, 25.5%-45.5% and 20.5%-40.9%) for the stage IB group and 9.3% and 3.1% (95% CIs, 1.1%-17.5% and –2.7% to 6.0%) for the stage IIA group. Sixteen patients with stage IB were relapse free at 10 years with initial treatment, compared with only 1 patient in the stage IIA group.
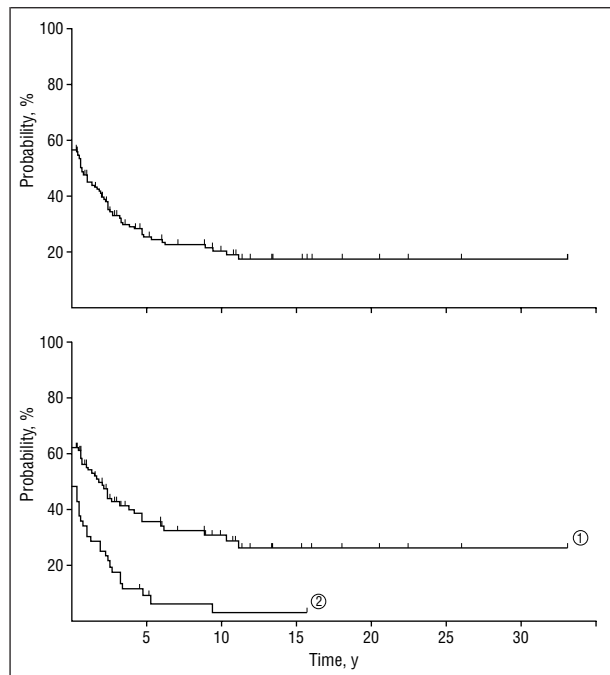
Figure 3. *Top, Freedom-from-relapse analysis of patients with T2 mycosis fungoides (n = 176). Bottom, Freedom-from-relapse outcome of T2 patients who presented with clinical stage IB (1) (n = 116) compared with patients presenting with clinical stage IIA (2) (n = 56) (Gehan[14] P<.005).*

Figure 4. *Freedom-from-relapse outcome of T2 patients treated with topical mechlorethamine hydrochloride (nitrogen mustard) (1) (n = 63) compared with patients treated with total skin electron beam therapy (2) (n = 106) (Gehan[14] P = .73).*

Figure 5. *Freedom-from-relapse outcome of T2 patients treated with topical mechlorethamine hydrochloride (nitrogen mustard) (1) (n = 63) compared with patients treated with 2 different doses of total skin electron beam therapy: lower than 30 Gy (2) (n = 45) and 30 Gy or higher (3) (n = 61) (Gehan[14] P = .11 for 1 vs 2; Gehan[14] P = .08 for 1 vs 3; Gehan[14] P<.001 for 2 vs 3).*

EFFECT OF INITIAL TREATMENT ON FFR AND LONG-TERM SURVIVAL

Most of the patients with T2 disease received either topical mechlorethamine (n = 63) or TSEBT (n = 106) as their initial primary therapy. Twenty of the 106 patients treated with TSEBT were given topical mechlorethamine as adjuvant therapy for a median duration of 15 months immediately following their radiation course. Other patients received PUVA (n = 3), single-agent chemotherapy (n = 1), topical mechlorethamine plus orthovoltage radiation (n = 1), and TSEBT plus total lymphoid irradiation (n = 1).

Treatment responses and outcome were compared between the T2 patients treated with topical mechlorethamine (n = 63) and those treated with TSEBT (n = 106) as clinically significant initial therapy (**Figure 4**). The overall FFR results were similar between the 2 treatment groups (*P* = .73), although the complete response rate was better with TSEBT (62%) than with topical mechlorethamine (49%). The calculated FFR rates at 5, 10, and 15 years are 22.8%, 17.1%, and 17.1% (95% CIs, 14.2%-31.4%, 8.9%-25.3%, and 8.9%-25.3%), respectively, for patients treated with TSEBT, and 30.8%, 26.4%, and 14.1% (95% CIs, 16.4%-45.2%, 11.6%-41.2%, and −1.1% to 29.3%), respectively, for patients treated with topical mechlorethamine. Ten patients treated with TSEBT as initial therapy are relapse free after 10 years of follow-up. The longest FFR follow-up of patients treated with topical mechlorethamine as initial treatment is 16 years; 3 patients are relapse free after 10 years.

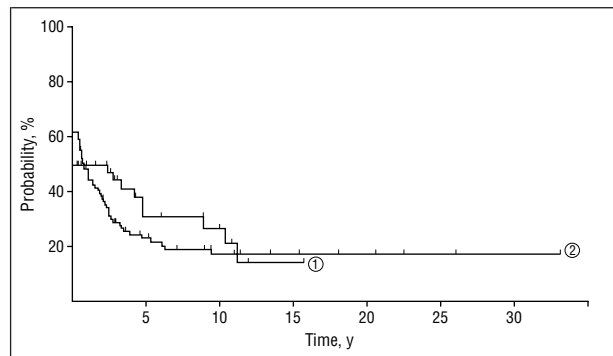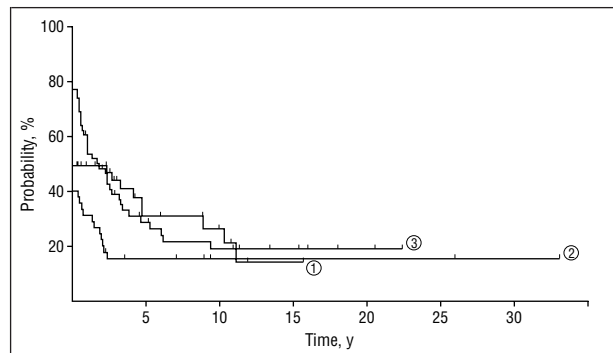The FFR outcome and complete response rates varied among the patients treated with TSEBT, primarily depending on the total dose of radiation with a major break point at 30 Gy. The overall FFR outcome was superior for patients who received an initial dose of 30 Gy or higher (n = 61) compared with those who received a dose lower than 30 Gy (n = 45) (*P*<.001) (**Figure 5**). The complete response rate was 40% for T2 patients who received a total dose lower than 30 Gy and 77% for those who received 30 Gy or higher. The FFR outcome comparison of the group receiving a TSEBT therapy dose of 30 Gy or higher with the group receiving topical mechlorethamine treatment demonstrates that despite a superior complete response rate with a TSEBT dose of 30 Gy or higher (77% vs 49%), there was no statistically significant difference in the overall FFR outcome between the 2 treatment groups (*P* = .078).

There were no significant differences in the long-term overall and disease-specific survivals between patients treated with topical mechlorethamine and those treated with TSEBT (combined doses) as primary therapy (*P* = .47, *P* = .68) (data not shown). The 10-year overall survival rates were 50% and 54%, and DSS rates were 81% and 80% with topical mechlorethamine and TSEBT, respectively. Also, despite superior FFR outcome and complete response rate of the subgroup treated with TSEBT doses of 30 Gy or higher, when compared with patients

treated with either topical mechlorethamine or TSEBT doses lower than 30 Gy, there were no significant differences in their long-term overall survivals ($P = .26$, $P = .19$) and DSS outcomes ($P = .89$, $P = .38$) (data not shown).

Patients who received topical mechlorethamine as adjuvant therapy immediately following their course of TSEBT (n = 20) had a superior complete response rate (100%) with better FFR outcome compared with patients treated with topical mechlorethamine alone ($P < .005$) or TSEBT (all doses) without adjuvant therapy ($P < .001$). The superior FFR results of the group who received adjuvant mechlorethamine therapy were maintained when only the subgroup treated with the 30-Gy or higher dose of TSEBT alone was compared ($P < .005$). The median disease-free interval of patients who received adjuvant mechlorethamine was longer at 2.7 years vs 2.0 years for those who received TSEBT alone at all doses and at 30 Gy or higher doses. Despite the superior FFR results, there was no long-term survival benefit in overall survival or DSS outcomes with adjuvant therapy compared with topical mechlorethamine alone ($P = .31$, $P = .55$) or a TSEBT dose of 30 Gy or higher ($P = .78$, $P = .36$) (data not shown).

Efficacy of TSEBT and topical mechlorethamine was assessed when either treatment was used following the other as initial therapy. Thirteen of the 63 patients who received topical mechlorethamine as initial therapy were subsequently treated with TSEBT doses of 30 Gy or higher. Nine (69%) of these patients had complete response, which is similar to the complete response rate of 77% when TSEBT at doses of 30 Gy or higher was given as initial therapy. Of the 106 patients who were initially treated with TSEBT, 41 were later treated with topical mechlorethamine. Nineteen (46%) of these patients had complete response, which is similar to the 49% complete response rate when topical mechlorethamine was given as initial therapy.

COMMENT

Unlike patients with limited MF (T1, stage IA),[8] patients with generalized patch and/or plaque (T2) disease have worse long-term survival outcome compared with that of their age-, race-, and sex-matched control population. Twenty-four percent of our patients with T2 disease experienced disease progression to a more advanced clinical stage, compared with a 9% disease progression rate in patients with T1 disease. Nearly 20% of the patients with T2 disease died of MF, whereas only 2% of patients with T1 disease died of MF.

Younger patients with T2 disease had a more favorable disease-specific long-term outcome than the patients aged 58 years (median age) or older. Patient age was also an independent prognostic indicator for our patients with erythrodermic (T4) MF.[9] Patient sex or racial background was not a significant prognostic factor of survival for our patients with T2 disease.

In our study, patients with clinical stages IB and IIA had similar long-term survival results. Thus, palpable lymphadenopathy (stage IIA) at presentation did not predict worse survival in our patients with T2 disease. In a review of 152 patients with MF, Sausville et al[6] found palpable lymphadenopathy to be an adverse prognostic feature with univariate analysis, along with cutaneous tumors, generalized erythroderma, blood involvement with Sézary cells, lymph node effacement, eosinophilia, and visceral involvement. However, their multivariate analysis revealed that presence of visceral disease and type of skin involvement were the only important independent prognostic factors.

Several clinical features were studied to determine potential clinical parameters predictive of disease progression (Table 4). A greater proportion of patients with initial stage IIA disease experienced disease progression compared with patients who presented with stage IB disease (34% vs 20%). However, this differential rate of disease progression of stages IB and IIA did not result in a difference in patients' long-term survival outcome. Also, the patients whose disease progressed appeared to have more resistant disease reflected by a much lower complete response rate to initial therapy compared with the remainder of the T2 patients (21% vs 65%). A greater rate of disease progression and a lower complete response rate may explain why our patients with stage IIA had worse FFR outcome than those with stage IB (Figure 3, B). Patient age, sex, or racial background was not a significant predictor of disease progression.

Patients with generalized patch and/or plaque (T2) MF achieved long-term disease-free status; many patients achieved clinical remission for more than 10 years after initial treatment as observed in the FFR curves. Thus, potential "cures" can be achieved with treatment in T2 MF, similar to that observed in our patients with T1 disease.[8] Further follow-up with pertinent biopsy would have to be performed to verify an actual "cured" state.

The type of initial primary therapy did not alter long-term survival when patients received either topical mechlorethamine or TSEBT. The complete response rate was better with TSEBT (combined doses) than with topical mechlorethamine (62% vs 49%), although there were no significant differences in their overall FFR outcomes. The complete response rate was significantly greater in the subgroup treated with TSEBT at 30-Gy or higher doses compared with topical mechlorethamine alone (77% vs 49%); however, there was no long-term survival advantage to the patients treated with TSEBT at doses of 30 Gy or higher.

The patients treated with TSEBT plus adjuvant mechlorethamine therapy were expected to have superior FFR results, since in addition to receiving adjuvant therapy, these patients all had complete response selectively to qualify for adjuvant therapy. The patients who did not have complete response were given other treatments as a second primary or salvage therapy and not as an adjuvant therapy. Despite superior FFR outcomes of the subgroup treated with TSEBT with adjuvant topical mechlorethamine, their long-term survival results were not significantly different from those of the patients treated with topical mechlorethamine or TSEBT (regardless of dose subgroups) alone as initial therapy. Similar to our results, Quiros et al[17] reported that in their series of patients with T2 disease treated with TSEBT with or without adjuvant PUVA therapy, there were no significant dif-

ferences in the overall survival outcome between the 2 treatment groups, despite more favorable FFR survival results with adjuvant PUVA.[17] Thus, use of adjuvant therapy, PUVA, or topical mechlorethamine following completion of TSEBT offers superior FFR outcome, but without any favorable impact on the long-term overall survival.

Since the mid 1970s, TSEBT has been given mostly in doses of 30 Gy or higher at Stanford University Medical Center,[12] which clearly results in higher complete response rate than treatment with topical mechlorethamine. There may be some selection bias for choice of either TSEBT or topical mechlorethamine as initial therapy. Patients with extensive symptomatic T2 disease can benefit from a more reliable and faster response from TSEBT. Some patients who are very old or debilitated with other medical issues may not be able to tolerate the TSEBT regimen. Topical mechlorethamine should be considered as initial therapy in patients with less symptomatic or indolent skin involvement because of patient convenience, lower cost, limited toxicity, and the lack of long-term survival benefit with TSEBT. Other therapeutic alternatives include UV light therapies such as PUVA. The efficacy of topical mechlorethamine and TSEBT was preserved when given as salvage therapy after the other as initial therapy. Thus, TSEBT can be used for salvage therapy on failure or with relapse following initial topical mechlorethamine therapy.

In summary, a significant proportion of patients with generalized patch and/or plaque (T2) MF experience disease progression to a more advanced clinical stage, and eventually die of MF, in contrast to patients with limited patch and/or plaque (T1) disease. Younger patients have a more favorable disease-specific long-term outcome than older patients. The presence of lymphadenopathy (stage IIA) at diagnosis does not predict worse long-term survival outcome. Clinical features predictive of disease progression include initial lymphadenopathy (stage IIA) and lower complete response rate to initial treatment. Despite superior FFR results of certain regimens of TSEBT, topical mechlorethamine proves to be a cost-effective initial treatment for patients with T2 disease. Treatment with TSEBT should be considered in patients who require rapid symptomatic control of skin involvement. The concept of an adjuvant therapy after TSEBT is appealing, though it may not lead to improved long-term survival.

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