ORIGINAL ARTICLE

Survival and Prognostic Factors in Patients with Aggressive Cutaneous T-cell Lymphomas

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Aggressive primary cutaneous T-cell lymphomas include advanced-stage mycosis fungoides (stage ≥ IIB mycosis fungoides), Sézary syndrome, gamma/delta cutaneous lymphoma, nasal type lymphoma, aggressive epidermotropic CD8+ T-cell lymphoma and some cutaneous lymphomas not otherwise specified. To evaluate their long-term prognosis, we conducted a retrospective cohort study of 85 patients diagnosed between 2005 and 2020 with advanced-stage mycosis fungoides (*n* = 48), Sézary syndrome (*n* = 28) or aggressive non-mycosis fungoides/Sézary syndrome subtypes (*n* = 9). The median survival times in these 3 groups were 118.7, 45.7 and 11.2 months, respectively, and the 5-year survival rates were 55.3%, 27.8% and 33.3%, respectively. Multivariate analyses in patients with mycosis fungoides/Sézary syndrome identified age ≥ 70 years, Eastern Cooperative Oncology Group Performance Status ≥ 2, and the high-risk group according to the Cutaneous Lymphoma International Consortium prognostic model, as adverse prognostic factors. Seven patients in this mycosis fungoides/Sézary syndrome group were in complete long-term remission after treatment with bexarotene, including 4 patients living without any treatment for 16–101 months.

Key words: aggressive cutaneous T-cell lymphoma; mycosis fungoides; Sézary syndrome; prognosis; survival.

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SIGNIFICANCE

There is limited recent data on the prognosis of aggressive cutaneous T-cell lymphomas. This study of French patients found 5-year survival rates of 55% or less in all subgroups. An older age, a low performance status and a high-risk group according to the Cutaneous Lymphoma International Consortium prognostic index were associated with lower survival in patients with advanced stage mycosis fungoides/Sézary syndrome. Bexarotene can provide long-term complete remission in a small subgroup of patients with advanced stage mycosis fungoides/Sézary syndrome.

Primary cutaneous lymphomas (PCL) are a rare group of extranodal non-Hodgkin lymphomas (NHL) characterized by clonal expansion of neoplastic T lymphocytes in the skin, without evidence of extracutaneous disease at the time of diagnosis (1). The skin is the second-most-frequent extranodal location, after the gastrointestinal tract, accounting for 18% of extranodal NHL (2, 3). PCLs were classified based on phenotypic and molecular features by the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) in 2005 as primary cutaneous T-cell lymphomas (PCTCL) and primary cutaneous B-cell lymphomas, representing, respectively, 80% and 20% of PCLs (1).

Within PCTCL, mycosis fungoides (MF) is the most common subtype, with a relative frequency of 70%, and Sézary syndrome (SS) is a less frequent erythrodermic variant with leukaemic involvement. The 2007 revised staging system according to the International Society for Cutaneous Lymphomas (ISCL)/EORTC organizes disease presentation in skin (T), lymph nodes (N), viscera (M), and blood (B). Patients with advanced-stage (IIB to IVB) MF/SS are those with at least one of the following clinical features: tumour lesions, erythroderma, histological lymph node involvement and/or visceral disease (4).

Early-stage (IA to IIA) MF, CD30+ anaplastic large-cell cutaneous lymphoma, lymphomatoid papulosis, primary cutaneous CD4+ small/medium T-cell lymphoma and primary cutaneous acral CD8+ T-cell lymphoma are considered indolent entities, with 5-year survival rates ranging between 75% and 100% (1).

Advanced-stage MF, SS, primary γ/δ T-cell lymphoma (γδCL), adult T-cell leukaemia/lymphoma, extranodal NK/T-cell lymphoma, nasal type (NTCL), primary CD8+ aggressive epidermotropic cytotoxic T-cell lymphomas (AECTCL) and primary cutaneous peripheral T-cell lymphomas not otherwise specified (PCTCL-NOS) are recognized as more aggressive PCTCL (APCTCL) entities, with 5-year survival rates less than 52% (1, 5, 6) For advanced-stage MF and SS, survival has been reported according to stage, with 5-year overall survival (OS) rates of 62.2% in stage IIB, 59.7% in stage IIIA, 54% in stage IIIB, 52.5% in stage IVA1, 34% in stage IVA2 and 23.3% in stage IVB (5). In addition to stage, other potential prognostic markers have been identified in MF/

SS, including advanced age, male sex, folliculotropism, large-cell transformation (LCT) and increased serum lactate dehydrogenase (LDH). However, apart from clinical staging, none of them have been strongly validated (7).

A Cutaneous Lymphoma International Prognostic index (CLIPi) was developed by Benton et al. in 2013 for early- and late-stage MF/SS (8). More recently, in 2015, another index, the Cutaneous Lymphoma International Consortium prognostic model (CLIC index) was proposed by Scarisbrick et al. (6), based on a retrospective study of 1,275 advanced-stage patients.

There have been only a few recent reports on prognosis of APCTCL, and to our knowledge no studies have been performed in France (9–12). The aims of this study were to evaluate the long-term survival of patients with APCTCL, and to identify prognostic factors in patients with advanced-stage MF and SS, in a French referral centre, over a 15-year period. The findings were also compared with the proposed CLIPi and CLIC prognosis indexes.

MATERIALS AND METHODS

Study population

This was a retrospective cohort study including a series of 85 patients with advanced-stage MF, SS, γ/δCL, NTCL, AECTCL or PCTCL-NOS. Patients were diagnosed and followed between January 2005 and March 2020 in the Oncodermatology Department of Reims University Hospital, a referral centre for cutaneous lymphomas in Champagne-Ardenne, France.

To identify eligible patients, the national register of the French Study Group of Cutaneous Lymphomas (GFELC) was used. The GFELC registers all new PCTCL cases referred by 39 centres in France, including Reims University Hospital. Records from the Reims University Hospital cutaneous lymphoma multidisciplinary meetings, from January 2005 to March 2020 were also used.

Accurate diagnosis of APCTCL was made according to the 2008 WHO classification of haematopoietic and lymphoid tumours and its 2016 update, and after correlating the clinical, histological, immunophenotypical and molecular findings (13). All diagnoses were confirmed by histological examination and validated by the GFELC. Patients with doubtful diagnoses and those who presented with a secondary cutaneous involvement from a systemic lymphoma were excluded.

Data collection

The following data at the time of diagnosis of advanced-stage MF/SS or other APCTCL were recorded in all cases: age; sex; type of lymphoma; stage according to the ISCL/EORTC classifications for MF/SS and non-MF/SS APCTCL (4, 14) In patients with MF and SS, the following additional data were recorded at the same time: whether the diagnosis of advanced-stage MF/SS was preceded by an early phase; Eastern Cooperative Oncology Group Performance Status (ECOG-PS); LCT and serum LDH level. LCT was defined as >25% overall or microscopic nodules of atypical lymphocytes being 4× greater than normal size (15). Elevated serum LDH was defined as greater than 214 units per litre, the upper limit of the normal range in the referral centre. We also recorded treatments, date and status at last follow-up for each patient. Missing data were recorded as "not done" or "not recorded".

In the MF/SS group, we were able to evaluate the CLIPi and the CLIC index with these data, as shown in **Table I** (6, 8). Patients were assigned to low-, intermediate- or high-risk groups and the prognostic significance of these indexes was analysed.

Table I. Cutaneous Lymphoma International Prognostic index (CLIPi) and Cutaneous Lymphoma International Consortium prognostic model (CLIC index)

CLIPi
Male sex
Age >60 years
B1/B2 vs B0
N2/N3 vs N0/N1
M1 vs M0
Interpretation: 0–1 (low risk)/2 (intermediate risk)/3–5 (high risk). Adapted from Benton et al., 2013 (9)
CLIC index
Age >60 years
Elevated LDH
Large-cell transformation
Stage IV
Interpretation: 0–1 (low risk)/2 (intermediate risk)/3–4 (high risk). Adapted from Scarisbrick et al., 2015 (7)

This retrospective study based on medical records was authorized, in accordance with French law, by the French national data-protection authority (CNIL, Commission nationale de l'informatique et des libertés), allowing the computerized management of the medical database at Reims University Hospital. The participants were informed of the possibility of their data being used for biomedical research purposes and had the right to refuse such use.

Statistical analysis

Quantitative variables were reported as mean ± standard deviations or as median [range] and qualitative data as number and percentage. OS was calculated from the date of diagnosis of advanced-stage MF, SS or other APCTCL to the date of death or censoring. The survival curves were computed using the Kaplan–Meier method. In the MF/SS group, variables associated with OS were identified by univariate analyses using the Log-rank test and by multivariate analyses using a Cox proportional hazards regression model (factors significant at the 0.10 level in univariate analyses were included in a stepwise regression multivariate analysis with entry and removal limits set at 0.10). A p-value < 0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC, USA).

RESULTS

Patient characteristics

The distribution of the cases and demographic characteristics according to specific diagnosis are shown in **Table II**.

Table II. Characteristics of patients with aggressive primary cutaneous T-cell lymphomas ($n = 85$)

Classification	Cases *n*	Frequency %	Sex M:F (ratio)	Age at diagnosis, years Median (range)
Mycosis fungoides	48	56.4	33:15 (2.2)	63.8 (28–89)
Sézary syndrome	28	32.9	18:10 (1.8)	72.5 (53–93)
AECTCL	3	3.5	1:3 (0.3)	54.6 (45–60)
PCTCL-NOS	3	3.5	2:1 (2.0)	69 (49–90)
Extranodal NK/T-cell lymphoma, nasal type	2	2.3	2:0 (NA)	61.5 (54–69)
Primary γ/δ T-cell lymphoma	1	1.2	0:1 (NA)	68 (68)

AECTCL: primary CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma; PCTCL-NOS: primary cutaneous peripheral T-cell lymphoma not otherwise specified; F: female; M: male; NK: natural killer; NA: non-applicable.

The study cohort comprised 85 patients, 56 males (65.9%) and 29 females (34.1%), corresponding to a sex ratio of 2. Mean age at diagnosis was 67 years (range 28–93 years). Seventy-six patients had advanced-stage MF/SS (89.4%), including 48 patients with advanced-stage MF and 28 patients with SS, and 9 patients had other APCTCL subtypes (10.6%).

Characteristics of patients with MF/SS are summarized in **Tables** II and **III**. Among the 76 patients with MF/SS, 51 patients were men and 25 were women (sex ratio 2). Age ranged from 28 to 93 years (median 63.8 years). Stage at diagnosis was IIB in 29 patients (38.1%), III in 20 patients (26.3%) and IV in 27 patients (35.6%). Only 3 patients had visceral involvement (stage IVB) at presentation. Forty-five patients (59.2%) were first diagnosed with advanced-stage MF/SS, while 31 patients (40.8%) had a previous early-stage phase. ECOG-PS was 0 in 41 (53.9%) patients, 1 in 21 (27.6%), 2 in 11 (14.5%) and 3 in 3 patients (3.9%). Thirty-six patients (47.3%) were diagnosed with LCT. Serum LDH level was available at diagnosis for only 59 patients (77.6%) and was elevated in 40 cases (67.8%). Serum LDH level being part of the CLIC criteria, the CLIC index could only be calculated for 59 patients.

Table III. Overall survival according to different prognostic factors in patients with advanced-stage mycosis fungoides and Sézary syndrome (univariate analysis)

Characteristics	*n* (%)	Survival Median (range)	5-year OS (%)	*p*-value
Age				0.0004
<70 years	38 (50)	NA (4.2–NA)	67	
≥70 years	38 (50)	31.2 (1.4–168)	19	
Sex				0.80
Male	51 (67.1)	–	–	
Female	25 (32.9)	–	–	
Stage				0.09
IIB	29 (38.1)	118.7 (36.5–168.0)	59.1	
III	20 (26.3)	45.7 (1.4–179.6)	34.9	
IV	27 (35.6)	31.2 (3.0–149.1)	35.3	
III/IV (vs IIB)	47 (61.8)	–	–	0.04
ECOG-PS				0.0001
2	62 (81.6)	90.3 (1.4–179.6)	54.9	
≥2	14 (18.4)	8.8 (1.5–42.6)	0	
Previous early-stage phase				0.13
Yes	45 (59.2)	–	–	
No	31 (40.8)	–	–	
LDH[a]				0.67
Normal	19 (32.2)	–	–	
Elevated	40 (67.8)	–	–	
LCT				0.27
Yes	36 (47.4)	–	–	
No	40 (52.6)	–	–	
CLIPi				0.14
1	23 (30.3)	NA (4.2–60.2)	63.8	
2	25 (32.9)	47.0 (1.5–168.0)	40.2	
3	28 (36.8)	45.7 (1.4–179.6)	30.0	
CLIC index				0.009
1	15 (25.4)	NA (5.5–127.8)	60.4	
2	25 (42.4)	58.3 (1.5–179.5)	49.9	
3	19 (32.2)	10.5 (1.4–118.7)	23.2	
3 (vs 1–2)	–	–	–	0.0025

[a]Data missing for 17 patients.
OS: overall survival; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; LDH: lactate dehydrogenase; LCT: large cell transformation in skin; CLIPi: Cutaneous Lymphoma International Prognostic index; CLIC index: Cutaneous Lymphoma International Consortium prognosis index; HR: hazard ratio.

Demographic characteristics and distribution according to diagnosis of patients with non-MF/SS APCTCL are shown in Table II. Among these 9 patients, 5 had only cutaneous lesions at diagnosis while 4 patients had extracutaneous involvement (nodal: 1 case; visceral: 4 cases).

Follow-up data and outcome

The mean follow-up duration from diagnosis was 7 years (range 1–176 months). OS curves according to diagnosis are shown in **Fig. 1**A. In patients with advanced-stage MF, the median survival time was 118.7 months (95% CI 42.9–168.0) and the 5-year OS was 55.3%. In patients with SS, the median survival time was 45.7 months (95% CI 13.7–51.1) and the 5-year OS was 27.8%. In patients with non-MF/SS APCTCL, the median survival time was 11.2 months (95% CI 3.0–77.6) and the 5-year OS was 33.3%.

Long-term complete remissions

At the end of the study, a subgroup of 9 patients among the MF/SS group (11.8%) were in complete, long-term (≥18 months) remission (CLLR). This CLLR was achieved in 6 stage IIB, 2 stage III and 1 stage IV patients. Seven of these patients had been treated with bexarotene, most of them being stage IIB (4 patients). The 2 other patients were treated with interferon and pegylated liposomal doxorubicin associated with radiotherapy, respectively. Among the 7 patients in CLLR after bexarotene treatment (corresponding to 14.8% of the MF/SS patients treated with bexarotene), 3 patients were still taking maintenance bexarotene at the end of the study. The treatment was interrupted in 2 patients, who presented grade 3 adverse effects after 2 and 60 months, without any relapse 24 months and 101 months after discontinuation, respectively. In the 2 other patients, bexarotene was stopped for a persisting complete response (CR) after 10 and 19 months of treatment, without any relapse 16 months and 53 months after treatment was discontinued, respectively.

Prognosis factors in the MF/SS group

In univariate analysis, age ≥70 years ($p=0.0004$), ECOG-PS ≥ 2 ($p<0.0001$), stage III/IV vs IIB ($p=0.04$) and the high-risk group (vs low- and intermediate-risk groups) according to the CLIC index ($p=0.0025$) were identified as adverse prognostic factors of OS in patients with MF/SS. Sex, a previous early-stage phase, elevated serum LDH, LCT and CLIPi had no significant prognostic value.

In multivariate analysis, age ≥ 70 years the ECOG-PS ≥2 remained statistically significant, independent adverse prognostic factors of OS. When the CLIC index (including age, LCT, serum LDH level and stage) was introduced in the model, including the 59 cases with all

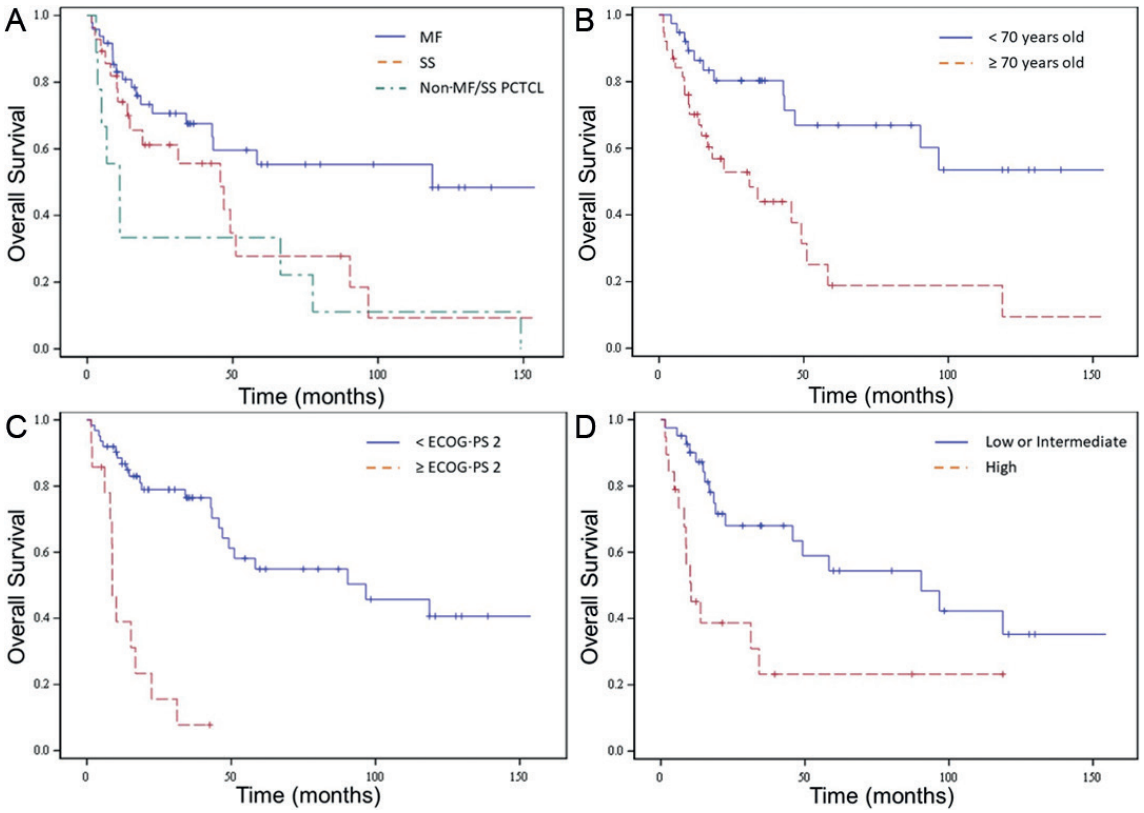

Fig. 1. Overall survival (OS) in patients with (A) advanced-stage mycosis fungoides (MF), Sézary syndrome (SS) and non-MF/SS aggressive primary cutaneous T-cell lymphomas (PCTCL). OS in patients with advanced-stage MF and SS according to (B) age, and (C) Eastern Cooperative Oncology Group Performance Status (ECOG-PS). (D) OS in patients with advanced-stage MF and SS according to Cutaneous Lymphoma International Consortium prognosis index for low- or intermediate- vs high-risk groups.

data available, the ECOG-PS and the CLIC index were independent prognostic factors of OS. Survival curves in the MF/SS group according to age, ECOG-PS and CLIC index are shown in Fig. 1B–D, respectively.

The median survival and 5-year OS rates according to prognostic factors identified in univariate and multivariate analyses are shown in Table III.

DISCUSSION

Although several studies evaluating the prognosis of PCTCL have been published over the last few decades (1, 6, 8, 16–18), more recent ones and those focusing on APCTCL are rare. The current study confirms that, although clinically and histologically heterogeneous, APCTCL share a poor prognosis, with a 5-year OS of 55% or less whatever the lymphoma subtype. Non-MF/SS APCTCL and SS had the worst prognosis, with a 5-year OS approximately 30%, while patients with advanced-stage (≥ IIB) MF had a 55% 5-year OS.

This study found that age ≥70 years and ECOG-PS ≥2 were adverse prognostic factors of OS in patients with advanced-stage MF/SS. Age is a well-known prognostic factor for advanced-stage MF/SS, as reported in many studies described in a 2014 literature review by Scarisbrick et al. (7). In contrast, this is the first time to our knowledge that the ECOG-PS has been validated as a strong prognostic factor in patients with advanced-stage MF/SS.

In addition, the current study confirms the prognostic value of the CLIC index. This is consistent with Nikolaou's study, which found that, in patients with late-stage MF/SS, intermediate- and high-risk CLIC groups had an increased risk of death compared with the low-risk group (19). To our knowledge, the current study is the second to evaluate the prognostic value of the CLIC index in patients with advanced-stage MF/SS. In contrast, as reported in 2 previous studies, the CLIPi did not provide any further information in the current study in this group of patients with advanced-stage MF/SS (19, 20).

Interestingly, the current study identified a subgroup of 7 patients, most of them with a stage IIB MF, who achieved a CLLR after bexarotene treatment. This small subgroup represented 15% of all patients treated with bexarotene in our series. According to Duvic et al. (21), CR occurred in 2% (1 of 56) of patients treated with bexarotene at the recommended dose of 300 mg/m^2/day and in 13% (5 of 38) of those treated at a higher dose with a median duration of response of 42.7 weeks. In a prospective study evaluating 70 patients treated with oral bexarotene, Talpur et al. (22) reported 4 patients

who achieved a CR > 3 years in duration, as they received a maintenance dose. Bexarotene seems to have the potential to produce CLLR in a subgroup of patients, but there are no long-term studies to determine the optimal duration of treatment in good or complete responders. In the current study, the treatment was interrupted in 4 patients because of adverse events and/or a CLLR, without any relapse after a treatment-free follow-up time of 16–101 months. To our knowledge, this is the first report of sustained CRs after interruption of bexarotene in patients with advanced MF/SS.

The main limitations of the current study are its retrospective design and the small number of patients. Patients with non-MF/SS APCTCL were very few in number, preventing us from providing comprehensive data on these rare subtypes. However, their inclusion in the APCTCL group may provide useful information for clinicians, highlighting their very low relative frequency and poor prognosis.

In conclusion, this study of 85 patients diagnosed with APCTCL over a 15-year period in a French referral centre showed a 5-year survival rate of 55% or less in any lymphoma subtype, confirming their poor prognosis. However, in some cases of advanced-stage MF treated with bexarotene, a long-lasting complete response was achieved. In the group of MF/SS, ECOG-PS ≥2, age ≥70 years and an elevated CLIC index were identified as independent adverse prognostic factors of OS. This study seems therefore to validate the accurate prognostic value of the CLIC index in the subgroup of patients with advanced-stage MF and SS.

The authors have no conflicts of interest to declare.

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