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Annals of Oncology 28: 2517–2525, 2017
doi:10.1093/annonc/mdx352
Published online 24 July 2017

ORIGINAL ARTICLE

Global patterns of care in advanced stage mycosis fungoides/Sezary syndrome: a multicenter retrospective follow-up study from the Cutaneous Lymphoma International Consortium

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Note: This study was presented in part at the 3rd World Congress on Cutaneous Lymphoma, 26–28 October 2016, New York, USA.

Background: Advanced-stage mycosis fungoides (MF)/Sézary syndrome (SS) patients are weighted by an unfavorable prognosis and share an unmet clinical need of effective treatments. International guidelines are available detailing treatment options for the different stages but without recommending treatments in any particular order due to lack of comparative trials. The aims of this second CLIC study were to retrospectively analyze the pattern of care worldwide for advanced-stage MF/SS patients, the distribution of treatments according to geographical areas (USA versus non-USA), and whether the heterogeneity of approaches has potential impact on survival.

Patients and methods: This study included 853 patients from 21 specialist centers (14 European, 4 USA, 1 each Australian, Brazilian, and Japanese).

Results: Heterogeneity of treatment approaches was found, with up to 24 different modalities or combinations used as first-line and 36% of patients receiving four or more treatments. Stage IIB disease was most frequently treated by total-skin-electron-beam radiotherapy, bexarotene and gemcitabine; erythrodermic and SS patients by extracorporeal photochemotherapy, and stage IVA2 by polychemotherapy. Significant differences were found between USA and non-USA centers, with bexarotene, photopheresis and histone deacetylase inhibitors most frequently prescribed for first-line treatment in USA while phototherapy, interferon, chlorambucil and gemcitabine in non-USA centers. These differences did not significantly impact on survival. However, when considering death and therapy change as competing risk events and the impact of first treatment line on both events, both monochemotherapy (SHR = 2.07) and polychemotherapy (SHR = 1.69) showed elevated relative risks.

Conclusion: This large multicenter retrospective study shows that there exist a large treatment heterogeneity in advanced MF/SS and differences between USA and non-USA centers but these were not related to survival, while our data reveal that chemotherapy as first treatment is associated with a higher risk of death and/or change of therapy and thus other therapeutic options should be preferable as first treatment approach.

Key words: mycosis fungoides, CTCL, prognosis, treatment, survival

Introduction

Patients with advanced-stage mycosis fungoides (MF)/Sézary syndrome (SS) are characterized by skin tumours (stage IIB) or erythroderma (stage III); blood (stage IVA1), nodal (stage IVA2) or visceral involvement (stage IVB) may occur [1–5]. The prognosis of advanced-stage disease is poor, with 5-year overall survival (OS) rates from 40% to 70% in tumor-stage or erythroderma, down to 15%–40% for extracutaneous involvement [6–10]. Thus, these patients have an unmet clinical need of effective treatments. However, the rarity of the disease and the lack, until recently, of established criteria for staging and response evaluation [11] impaired the development of prospective clinical trials and no treatments have been shown to improve survival. International guidelines detail treatment options for the different stages without recommending any treatment order due to lack of comparative trials [12–15]. The current therapeutic strategies in leading centers worldwide have been influenced therefore by consensus and institutional preference, geographical regulatory status and availability of treatment modalities. No data are available as to therapy heterogeneity across the world, and what impact (if any) this variability may have on survival.

In 2012, members from the Cutaneous Lymphoma Task Force (CLTF) of the European Organization for Research and Treatment of Cancer (EORTC), the International Society for Cutaneous Lymphoma (ISCL) and the United Cutaneous Lymphoma Consortium (USCLC) established the Cutaneous Lymphoma International Consortium (CLIC), with the aim of developing collaborative researches, producing meaningful prospective studies and improving the understanding of CTCL clinical and biological characteristics. As first collaborative step, retrospective studies were undertaken to test the potential of collecting large clinical data sets. The first CLIC project analyzed prognostic markers on OS in 1394 advanced-stage MF/SS patients [16], identifying as independent unfavorable variables stage IV, age >60 years, large-cell transformation and increased LDH values and combining them in a prognostic index model (low-, intermediate- and high-risk group). As a second step, the participating centers were asked to provide treatment modalities for advanced-stage MF/SS patients. The aims of this second CLIC study, reported in this paper, were to analyze the global pattern of care worldwide, the distribution of treatments according to geographical areas (USA versus non-USA) and whether the heterogeneity of approaches can have potential impact on OS.

Patients and methods

Patient selection

Patients were collected retrospectively from 21 international centers (14 European, 4 USA, 1 Australian, Brazilian, and Japanese). Inclusion criteria were: diagnosis from January 2007 to December 2014, clinical stage IIB or higher [5] (Table 1).

MF diagnosis was confirmed according to ISCL/EORTC criteria [2–5]. All the patients were re-classified according to the new ISCL/EORTC classification [2–5, 17]. All patients had a detailed physical exam for the determination of the extent and severity of skin involvement and imaging study to assess nodal or visceral disease. The pathologic diagnosis was based on the biopsy results reported by institution hospital registries. Nodal/visceral involvement was defined in the presence of pathological confirmation.

Data collected

Data retrieved for each patient were: demographics, TNMB staging at initial diagnosis of advanced-stage disease, treatment modalities up to the 10^{th} treatment line whenever performed, total number of treatment lines, start and end date for each treatment; survival status at last contact; date of death or of last contact for patients alive. Treatment response data were not collected due to the absence of homogeneous response evaluation criteria and difficulties to define retrospectively response according to the recent consensus criteria [11].

Statistical analysis

Continuous variable distributions were compared through the Wilcoxon rank-sum test. The possibility of an association between categorical variables was assessed through the Fisher's exact test. The non-parametric test for trend across ordered groups developed by Cuzick [18] was used to compute the test for trend for the prevalence of use of different treatments in consecutive therapy lines. A logistic regression model was fitted to data with the type of treatment as the outcome and geographical area (USA/non-USA), stage (categorical variables with six levels: IIB, IIIA, IIIB, IVA1, IVA2, IVB), and age at diagnosis as predictors.

Overall survival (OS) was established from diagnosis to death or to the last contact date or to the end of follow-up, whichever occurred first, counting all deaths as events. Life-table survival estimates were derived by the Kaplan–Meier method by age, TNMB stage and geographical site, and compared using the Mantel's stratified log-rank test [19]. A

Table 1. Participating centers and number of patients included

Principal investigator	Center	Patient number	Geographical area
Julia Scarisbrick	University Hospital Birmingham, UK	35	Europe
Pietro Quaglino	University of Turin (Torino), Italy	50	Europe
Maarten Vermeer	Leiden University Medical Centre, The Netherlands	54	Europe
Evangelia Papadavid	Athens University Medical School, Greece	40	Europe
Pablo Oritz-Romero	Hospital 12 de Octubre, Madrid, Spain	23	Europe
Martine Bagot	Hospital St Louis, Paris, France	49	Europe
Rudolf Stadler	Unit Univ Munster, Minden, Germany	11	Europe
Pier Luigi Zinzani	Seragnoli Institute of Haematology, Bologna, Italy	4	Europe
Nicola Pimpinelli	University of Florence, Italy	22	Europe
Octavio Servitje	Hospital Universatari de Bellvitge, Barcelona, Spain	15	Europe
Emilia Hodak	Rabin Medical Center, Israel	30	Europe
Alessandro Pileri	Dermatologic Clinic, University of Bologna, Italy	14	Europe
Teresa Estrach	Hospital Clinico, University of Barcelona	13	Europe
Emilio Berti	University of Milano, Italy	28	Europe
Youn Kim	Stanford University Medical Centre, California, USA	123	USA
Joan Guitart	Northwestern Univesity, Chicago, USA	47	USA
Madeleine Duvic	MD Anderson Cancer Centre, Houston, USA	169	USA
Pierluigi Porcu	Ohio State University, Ohio, USA	6	USA
Miles Prince	Peter MacCallum Cancer Centre East Melbourne	58	Australia
Makato Sugaya	Faculty of Medicine, University of Tokyo, Japan	29	Japan
José Antonio Sanches	University of Sao Paulo Medical School, Brazil	33	Brazil

multivariable Cox proportional-hazards regression model was used to estimate the association between mortality for all causes and the variables above [20]. The proportionality assumption was assessed by examination of Schoenfeld residuals, giving no reason for violation.

In order to investigate the effects of the first treatment line, we estimated the cumulative mortality curves treating the change of therapy class as a competing risk event. Cumulative incidence of both therapy change and death by age, TNMB stage, geographical site and first treatment line were compared using a multivariable competing risk regression model for the sub-distribution hazards fitted to data according to the method of Fine and Gray [21].

Statistical analyses were performed with Stata 13 (StataCorp LP, College Station, TX).

Results

Patient cohort characteristics

Among 853 patients included, 40.4% were from USA centers, with the majority of the remaining from Europe. Median follow-up time was 1.7 years. Less than one-third of patients (29%) were followed for <1 year, whereas 43% and 27% were followed for at least 2 or 3 years, respectively.

There was a male preponderance (male/female: 1.61) with a median age at advanced-stage diagnosis of 64 years (range: 8–90), without differences between USA and non-USA centers. Stage IIB was the most frequent at first diagnosis of advanced-stage disease (35.4%). There was a higher percentage of stage III in non-USA centers, while stage IVB was more frequently in USA ($P < 0.001$) (Table 2).

Treatment lines

The median number of treatment lines was two per patient in both USA and non-USA centers, with a remarkable number of patients receiving multiple treatments (36% 4 or more; 2% between 10 and 24).

Table 3 shows the distribution of treatments in time. The most commonly used first approach was photopheresis either alone (10%) or in combination (8.6%), followed by bexarotene and phototherapy. The most frequently used chemotherapies as first-line treatment were gemcitabine (6.2%) and polychemotherapy (5.3%). Photopheresis was the most frequently used approach also as second-line treatment, while as third line, bexarotene and interferon (IFN) were most widely employed. From the fourth treatment line, histone deacetylase inhibitors (HDACi), polychemotherapy and pegylated doxorubicin were more commonly prescribed. Allogeneic transplantation was not performed in any case as first treatment, but it was most common from the fourth line of treatment (from 4.2% to 6.4% of patients) (test for trend with treatment line: $P < 0.0001$).

In summary, a statistically significant decrease of use with the number of treatment lines was found for photopheresis, bexarotene and phototherapy, while there was an increase with lines of therapy for poly-chemotherapy, TSEBT, HDACi, pegylated doxorubicin, new target therapies and transplantation (supplementary Figures S1 and S2, available at *Annals of Oncology* online).

Treatment approaches according to stages

The most frequently used first-line treatment in stage IIB patients was bexarotene followed by local RT, phototherapy, TSEBT and gemcitabine (supplementary Table S1, available at *Annals of Oncology* online). Methotrexate was the most commonly used first treatment for stage IIIA, while photopheresis (alone or in combination) for stage IIIB. Photopheresis was also the most common first-line treatment in stage IVA1 followed by IFN and

Table 2. Demographics, staging and number of treatment lines

Parameter	All (%)	USA (%)	Non-USA (%)	*P*
Gender				
Male	466 (54.6%)	213 (61.7%)	253 (49.8%)	1.000 (exact Fisher's test)
Female	289 (33.9%)	132 (38.3%)	157 (30.9%)	
Missing	98 (11.5%)		98 (19.3%)	
Total	853	345	508	
Age[a]				
Median	64	63	64	0.7466 (Wilcoxon rank-sum test)
Range	8–90	11–90	8–90	
Clinical stage[b]				
IIB	309	137 (39.7%)	172 (33.9%)	<0.001 (exact Fisher's test)
IIIA	117	31 (9.0%)	86 (16.9%)	
IIIB	73	13 (3.8%)	60 (11.8%)	
IVA1	224	88 (25.5%)	136 (26.8%)	
IVA2	74	40 (11.6%)	34 (6.7%)	
IVB	27	15 (4.4%)	12 (2.4%)	
Missing	29	21 (6.1%)	8 (1.6%)	
Total	853	345	508	
Number of treatment lines				
Median	2	2	2	0.045 (Wilcoxon rank-sum test)
Range	1–24	1–24	1–15	

[a]At diagnosis of advanced phase MF/SS.
[b]According to the revised TNMB classification [x].

chlorambucil, while stage IVA2 was mainly treated by poly-chemotherapy as first approach.

First treatment line distribution according to stage, age and geographical site

Figure 1 summarizes first-line treatments used in USA and non-USA centers, while Table 4 shows the odds ratio (OR) of receiving a given first-line treatment according to disease stage, age and geographical site. Phototherapy, alone or in combination, is used less frequently in USA. Photopheresis and bexarotene are significantly associated with the geographical area, being more frequent in USA while IFN, which does not show a statistically significant association with stage, was more frequently prescribed in non-USA centers. HDACi were used in all stages but, as expected, more frequently in USA (FDA approval), while MTX was used predominantly in stage III, without differences between USA and non-USA centers. Compared with USA centers, non-USA centers treat their patients significantly more frequently with chlorambucil also more frequently adopted in elderly patients. No differences were found in poly-CT or pegylated doxorubicin according to geographical areas.

Survival analyses

Two types of analysis were carried out (Figure 2 and Table 5). In the first, the variables age, TNMB stage and geographical site (USA versus non-USA) were included in a Cox regression model, with death due to any cause as the end point. Age and stage showed prognostic significance while geographical site did not show any association with mortality.

In the second analysis, death and therapy change were considered as competing risk events, and the impact of first treatment line on both events was analyzed with a Fine and Gray regression model. Geographical site and stage did not show any prognostic relevance for either outcome, whereas the only statistical significant association was between age and death. Although overall first-line treatment group was not selected as independent prognostic variable, both mono-chemotherapy (SHR = 2.07, 95% CI 1.14–3.78) and poly-chemotherapy (SHR = 1.69, 95% CI 0.61–4.66) showed elevated relative risks of death.

Discussion

In this second CLIC study, the largest cohort of patients presenting with advanced-stage MF/SS (853 cases) with data on treatment collected retrospectively in 21 international centers was analyzed to evaluate the worldwide usage profile of regionally available treatments and potential impact on survival.

The first finding was that treatment approaches are characterized worldwide by a striking heterogeneity with up to 24 different drugs, modalities or combinations used as first-line treatment. Several explanations can lead to this heterogeneity, mainly represented by the rarity of the disease, which impaired the design of randomized clinical trials and thus the development of homogeneous treatment guidelines, and additionally the limited activity of available drugs [15]. This opened the field for treatment algorithms based on institutional preference, skill and equipment of

Table 3. Distribution of treatments performed in time (percentage of patients treated with that therapy out of the total no. of patients treated in a given treatment line) in the first 10 treatment lines

Therapy	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	*P* for trend
ECP (alone or in combination)	18.6	13.3	6.3	5.8	6.4	4.8	2.8	7.7	9.4	5.3	0.952
Bexarotene	11.3	12.8	10.3	7.4	7.4	5.6	4.2	1.9	6.3	10.5	0.001
Phototherapy (alone or in combination)	9.5	5.9	3.5	3.4	3.5	2.4	2.8	1.9		5.3	0.949
Methotrexate	8.8	5.9	7.0	6.8	4.5	9.6	6.9	9.6	6.3	10.5	0.232
Interferon	7.7	7.7	10.8	8.5	8.4	4.8	5.6	1.9	3.1	5.3	0.616
Local RT	7.3	5.7	7.0	5.1	5.0	8.0	6.9	7.7	6.3	5.3	0.442
Gemcitabine	6.2	5.6	6.8	6.1	4.0	8.8	1.4	1.9			0.378
Polychemotherapy	5.3	9.2	9.8	9.8	10.4	10.4	16.7	13.5	9.4	26.3	<0.0001
TSEBT	4.5	7.9	7.0	5.7	9.4	6.4	6.9	9.6	6.3	5.3	0.028
Chlorambucil	3.6	2.5	2.1	2.7	2.0	1.6		1.9			0.067
HDACi	2.9	5.6	5.4	12.5	5.5	8.8	11.1	1.9	9.4		<0.0001
Other Retinoids	2.7	2.7	1.9	1.0			1.4		3.1		0.029
Pegylated Doxorubicin	1.8	4.7	4.4	3.7	10.9	4.8	5.6	5.8	12.5	5.3	<0.0001
Alemtuzumab	1.3	2.9	3.5	3.4	2.0	2.4	5.6	1.9	3.1	15.8	0.006
Interferon plus Bexarotene or Other Retinoids	0.8	0.5	0.7	0.3							0.020
Other Monochemotherapy	0.7	1.7	2.1	2.0	3.0	3.2	5.6	5.8	6.3		<0.0001
Denileukin Diftitox	0.5	0.3	0.7	0.7	1.0		1.4	3.9	6.3		0.008
Brentuximab vedotin	0.4	0.7	4.0	2.4	3.0	5.6	5.6	1.9			<0.0001
Pralatrexate	0.2	0.8	1.4	2.0	1.0	1.6	1.4	5.8	3.1		<0.0001
Topical Nitrogen Mustard (Mechlorethamine)	0.1	0.2	0.5			1.6		1.9			0.001
Bevacizumab					0.5						–
Lenalidomide				0.7	1.5						–
Mogamulizumab		1.2	0.9	2.4	2.5	2.4	2.8	5.8	3.1		<0.0001
Transplantation		1.0	2.3	6.4	6.4	4.8	4.2	5.8	6.3	5.3	<0.0001
Zanolimumab		0.2	0.2	0.3				1.9			0.003

Other retinoids: etretinate, acitretin. Other monochemotherapy: mainly cyclophosphamide, etoposide. First treatment unknown in 5.6% of patients. ECP combos: ECP plus Interferon, ECP plus Bexarotene, ECP plus Other Retinoids, ECP plus IFN plus Bexarotene, ECP plus Methotrexate, ECP plus Phototherapy. Phototherapy combos: Phototherapy plus IFN, Phototherapy plus Other Retinoids, Phototherapy plus Bexarotene, ECP plus Phototherapy, Phototherapy plus IFN plus Bexarotene, Phototherapy plus Other Retinoids.
ECP, extracorporeal photochemotherapy; RT, radiotherapy; TSEBT, total-skin-electron-beam therapy; HDAC, histone deacetylase inhibitors.

each institute, different regulatory status, availability of treatment modalities, entry to clinical trials and health insurance system. In the future, the identification of new clinical and biological prognostic parameters may help to drive clinical treatment decisions [16, 22]. Disease stage clearly remains an important parameter for treatment decision and TNMB stage was associated with relevant differences in treatment approaches, as expected [12–14]. Stage IIB was most frequently treated by skin-directed approaches (phototherapy or radiotherapy), bexarotene and gemcitabine while photopheresis was most commonly used as first-line treatment in SS or erythrodermic MF (stage III and IVA1) and polychemotherapy in stage IVA2/B. There were trends in drug use during the course of the disease with decreased use of photopheresis alone or in combination, bexarotene and phototherapy alone or in combination and conversely, increased use of chemotherapy, target therapies and transplant. These data support a preferential use of immune-modifiers as first line therapy with subsequent use of chemotherapy, targeted therapies or transplant for patients with relapsed/resistant disease. This strategy of using immune-stimulation is solidly based on pre-clinical data, showing the relevance of cancer immuno-surveillance in down-regulating the evolution of the disease [23], now supported by a number of clinical studies [24] such as the superior outcome of photopheresis when performed as first-line treatment early after diagnosis [25]. The USCLC recommendations [26] highlight that one of the principles for SS treatment is to preserve the immune response, fostering the use of immune-modulatory therapy (particularly as combination therapy) before chemotherapy except in the presence of rapid growth of tumor burden or failure of prior such therapies.

The second focus was that there exist significant differences in treatment approaches between USA and non-USA centers. The therapies more frequently prescribed as first-line treatment independent of disease stage distribution are bexarotene and photopheresis in USA while phototherapy, IFN, chlorambucil and gemcitabine for non-USA centers. The same factors that accounted for treatment heterogeneity can partly explain these geographical differences, mirroring different approaches to patient management along with different drug regulatory approvals (HDACi and denileukin diftitox not available outside the USA) and access to new drugs through clinical trials. The major use of photopheresis in USA and gemcitabine in non-USA centers can

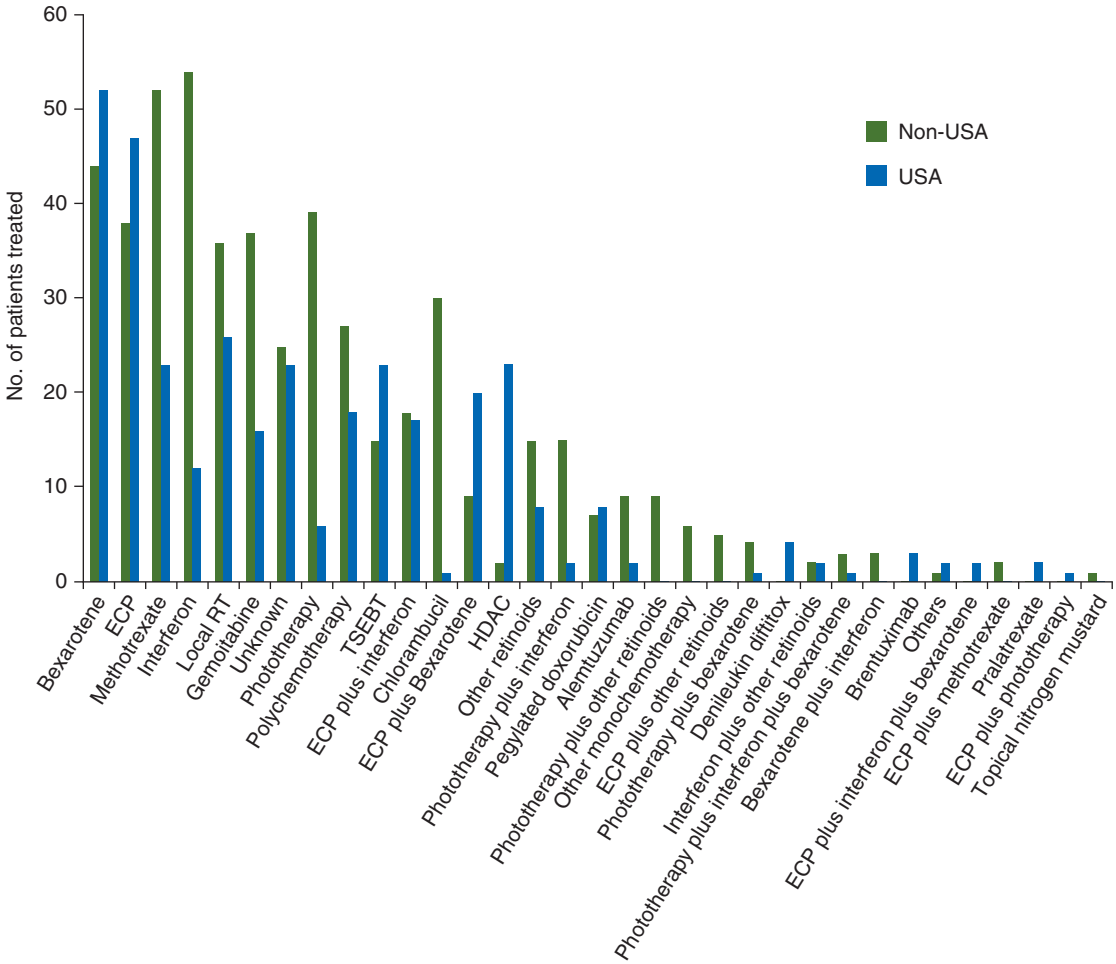

Figure 1. Distribution of first treatment line between USA and non-USA centers.

Table 4. Association (OR: odds ratio) between treatments, stage and age at diagnosis, and geographical region (USA versus non-USA)

OR	Stage (ref: stage IIB)					*P*	USA	*P*	Age	*P*
	IIIA	IIIB	IVA1	IVA2	IVB		(ref: non-USA)			
ECP (alone or in combination)	12.01	25.36	24.79	4.84	13.17	<0.001	2.46	<0.001	1.02	0.026
Bexarotene	0.51	0.45	0.26	0.59	0.59	0.005	1.83	0.013	1.00	0.830
Phototherapy (alone or in combination)	1.11	0.65	0.61	0.98	NA	0.630	0.27	<0.001	0.99	0.135
Methotrexate	3.65	2.45	1.34	1.44	1.42	0.024	0.83	0.506	1.01	0.382
Interferon	0.86	1.11	2.61	2.69	1.16	0.063	0.31	0.001	0.96	<0.001
Local RT	NA	0.19	0.08	0.07	0.18	<0.001	0.82	0.481	1.00	0.771
Gemcitabine	0.89	0.23	0.25	0.46	0.78	0.030	0.55	0.064	1.01	0.504
Polychemotherapy	0.91	1.63	0.78	4.54	2.40	0.009	0.89	0.746	0.98	0.181
TSEBT	NA	NA	0.07	0.35	0.28	0.002	1.74	0.136	1.03	0.018
Chlorambucil	5.08	6.43	17.23	5.11	54.83	0.005	0.04	0.002	1.04	0.029
HDAC inhibitors	1.20	2.84	1.45	2.74	NA	0.481	14.47	<0.001	0.98	0.151
Other Retinoids	1.77	0.80	1.52	0.70	NA	0.852	1.18	0.741	0.98	0.243
Pegylated Doxorubicin	1.35	1.30	0.18	0.50	NA	0.453	1.59	0.389	0.99	0.404
Interferon plus Bexarotene or Other Retinoids	0.76	1.01	2.45	2.31	1.03	0.071	0.36	0.002	0.96	<0.001

ECP, extracorporeal photochemotherapy; RT, radiotherapy; TSEBT, total-skin-electron-beam therapy; HDAC, histone deacetylase inhibitors.

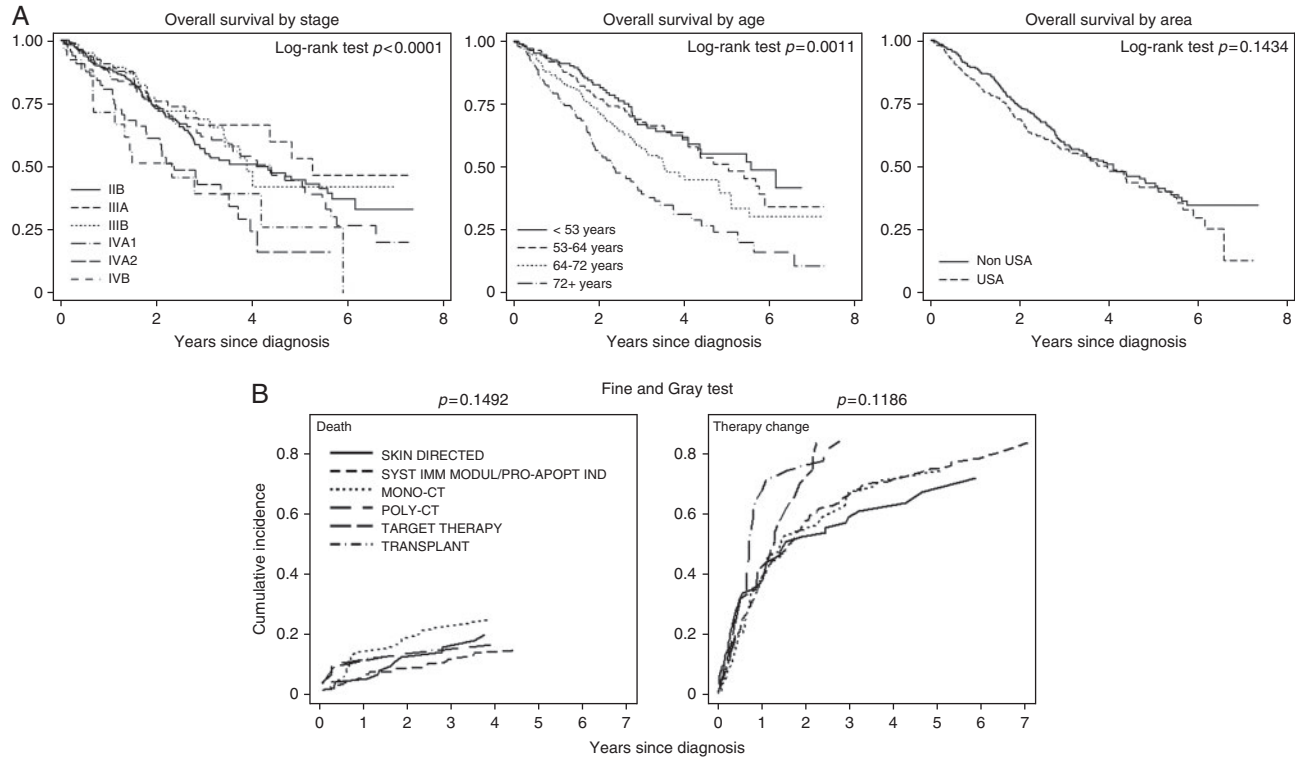

Figure 2. (A) Overall survival estimated with Kaplan Meier curves by age, stage and geographical areas. *P* values for log-rank tests are shown. (B) Cumulative incidence curves for death and change of therapy considered as competing risk events by first treatment line. *P* values for Fine and Gray test are shown. For survival analyses, treatment approaches were grouped into six categories defined after consensus within the participating centers: (1) Skin-directed therapies: phototherapy, local radiotherapy, total-skin electron beam therapy (TSEBT), topical nitrogen mustard; (2) Systemic immune modulators and pro-apoptotic inducers: interferon (IFN), retinoids, bexarotene, extracorporeal photochemotherapy (photopheresis), low-dose methotrexate, lenalidomide, combinations with phototherapy plus retinoids and/or IFN; any combinations of photopheresis plus retinoids and/or IFN; (3) Single agent chemotherapy: chlorambucil, gemcitabine, pegylated doxorubicine, pralatrexate, other mono-chemotherapy; (4) Polychemotherapy: CHOP, CHOP-like, other poly-chemotherapy; (5) Targeted therapies: denileukin diftitox, histone deacetylase inhibitors (HDACi), alemtuzumab, mogamulizumab, zanolimumab, brentuximab vedotin, bevacizumab); (6) Autologous or allogeneic stem-cell or bone marrow transplantation.

be driven by the fact that these treatments were originally trialed in USA and Europe, respectively [27–29]. In USA there were few centers with large volumes while Europe is characterized by many centers each contributing a small number of patients, suggesting a considerable effect of institution 'tradition'. This could explain the preferential use of unexpected drugs such as chlorambucil. The major use of phototherapy outside USA could be related to climate condition with reduced sun exposure in northern Europe countries.

The final observation is that the differences in treatment approaches as first-line therapy between USA and non-USA centers did not lead to a statistically significant impact on survival. Indeed, stage and age were independent OS predictors while the geographical site (USA versus non-USA) was not. The key outcomes of the competing risk event approach (Fine and Gray model) were that patients initially treated with polychemotherapy are those that most frequently change therapy; even if overall first-line treatment group was not selected as independent prognostic variable for mortality of therapy change, both monochemotherapy (SHR = 2.07) and polychemotherapy (SHR = 1.69) showed elevated relative risks of death, showing a negative impact of chemotherapy on disease course when performed as first line therapy. These estimates are adjusted for stage and geographical site but cannot address the potential confounder of tumor bulk or biology which is not adequately reflected by stage. Interpretation of these findings should be taken in the context that no chemotherapy regimen has been shown to improve survival given their modest clinical activity, with responses usually of short duration (6–9 months) [12–14, 30, 31]. Moreover, it has been reported that time-to-next-treatment [15] is significantly shorter for single- or multi-agent chemotherapy (median: 3.9 months) with respect to interferon (8.7 months) and HDACi (4.5 months). The results of the present study suggest that chemotherapy should be reserved only after failure of previous approaches and where other options are exhausted.

The main limitation of this study lies in its retrospective collection of information. Missing data and insufficient information to avoid confounding by indication (estimate the effects of treatments on prognosis not accounting properly for stage and disease status, which in turn are determinant of the treatment and

Table 5. Survival analysis: Cox regression hazard ratios (HR) and 95% CIs, with censoring of observations at the end of follow-up or date of the last contact in which vital status was known; and Fine and Gray subhazard ratios (SHR) and 95% CIs for death and change of therapy class

	Cox regression model			Fine and Gray model					
				Death			Therapy change		
	HR	95% CI	*P*	SHR	95% CI	*P*	SHR	95% CI	*P*
Area									
Non-USA	1		0.322	1		0.25	1		0.561
USA	1.14	0.88–1.47		1.33	0.82–2.16		1.07	0.86–1.33	
Stage									
IIB	1.12	0.82–1.53	0.001	0.91	0.51–1.62	0.871	0.87	0.68–1.13	0.514
IIIA	0.84	0.52–1.35		0.79	0.33–1.86		1.03	0.74–1.41	
IIIB	0.91	0.55–1.51		0.61	0.22–1.68		1.15	0.77–1.70	
IVA1	1			1			1		
IVA2	2.07	1.36–3.17		1.15	0.49–2.70		1.14	0.75–1.74	
IVB	2.15	1.22–3.78		1.29	0.41–3.99		1.41	0.69–2.88	
Age quartiles									
< 53	1		<0.001	1		<0.001	1		0.091
53–64	1.11	0.75–1.65		0.6	0.24–1.49		1.1	0.84–1.43	
64–72	1.74	1.19–2.55		1.54	0.72–3.29		0.92	0.69–1.23	
≥ 72	2.51	1.75–3.61		2.78	1.42–5.48		0.76	0.56–1.02	
First-line treatment									
Skin-directed therapies				1.31	0.68–2.54	0.186	0.97	0.69–1.38	0.379
Mono-chemotherapy				2.07	1.14–3.78		1.00	0.75–1.33	
Systemic immune modulators, pro-apoptotic inducers				1			1		
Poli-chemotherapy				1.69	0.61–4.66		1.49	0.94–2.35	
Target therapies				0.92	0.27–3.12		1.29	0.86–1.93	

prognosis) must be kept in mind to avoid over interpretation. Moreover, the absence of data maintained consistently and differences in response tools and criteria, did not allow us to provide response duration or quality of life information.

In conclusion, this large multicenter retrospective study shows a substantial heterogeneity of treatment approaches in advanced MF/SS between USA and non-USA centers, even if these differences do not influence survival outcome. The sequence of treatments could play a role since we observed that chemotherapy, when used as first treatment, is associated with a higher risk of death and/or change of therapy. This retrospective study highlighted the importance of currently ongoing prospective CLIC studies which will attempt to link treatment data with the prognostic models such as those developed in the first CLIC study [16].

Funding

Drs Martin and Dorothy Spatz Charitable Foundation (no grant numbers apply).

Disclosure

SH: Consultant/advisory for Celgene, Millennium/Takeda, Kiowa, Seattle Genetics, Forty-seven, HUYA, Infinity Pharmaceuticals. SW: consultant/advisory/honoraria: Galderma. JS: honoraria: Therakos, 4SC, Millennium/Takeda. RK: consultant/advisory/honoraria: Therakos, 4SC, Millennium/Takeda. PQ: consultant/advisory/honoraria: Therakos, 4SC, Millennium/Takeda, Actelion. HMP: consultant/advisory/honoraria: Millennium/Takeda, Celgene, Eisai. RW: consultant/advisory: Millennium/Takeda; honoraria: Millennium/Takeda, Actelion. RS: consultant/advisory/honoraria: Millennium/Takeda, 4SC. MV: consultant/advisory: Kiowa, Innate. All remaining authors have declared no conflicts of interest.

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