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Treatment of early-stage mycosis fungoides: results from the PROspective Cutaneous Lymphoma International Study (PROCLIPI study)

Running title: Treatment of early-stage Mycosis fungoides

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What's already known about this topic?

Early-stage Mycosis Fungoides is characterised by a good prognosis. The first-line treatment approach is typically stage-based and usually skin-directed therapy

What does this study add?

This multi-center prospective international study reports that real life treatment decisions are not limited to a stage-based approach but also influenced by the presence of plaques and folliculotropic MF disease. Approximately half the patients with early-stage disease experienced a moderate or severe impact on their quality of life at diagnosis. This study suggests that treatment guidelines in patients with early stage disease should incorporate high-risk features and quality of life evaluation.

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Abstract

Background: The PROspective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) Study is a prospective analysis of an international database and here we examine front-line treatments and quality-of-life in patients with newly diagnosed Mycosis Fungoides (MF).

Objectives: a) differences in first-line approach according to the TNMB staging; b) parameters related to a first-line systemic approach; c) response rates and quality of life (QoL) measures.

Patients and Methods: 395 newly diagnosed patients with early-stage MF (IA-IIA) were recruited from 41 centers in 17 countries between 1/1/2015-31/12/2018 following central clinicopathological review.

Results: First-line therapy was skin directed therapy (SDT) (81.6%) whilst a smaller percentage (44 cases;11.1%) received systemic therapy. Expectant observation was 7.3%. In univariate analysis, the use of systemic therapy was significantly associated with higher clinical stage (IA: 6%; IB: 14%; IIA:20%; IA-IB vs IIA: $p<0.0001$), presence of plaques (T1a+T2a: 5%; T1b+T2b: 17%; $p<0.001$), higher mSWAT (>10: 15%; <=10: 7%; $p=0.01$) and folliculotropic MF (FMF) (24% vs 12%; $p=0.001$). Multivariate analysis demonstrated significant associations with the presence of plaques (T1b/T2b vs T1a/T2a: OR: 3.07) and FMF (OR: 2.82). The overall response rate (ORR) to first-line SDT was 73% whilst the ORR to first-line systemic treatments was lower (57%) ($p=0.027$). Health related QoL improved significantly in both patients with responsive and stable disease.

Conclusions: Disease characteristics such as presence of plaques and FMF influence physician treatment choices and that SDT was superior to systemic therapy even in patients with such disease characteristics. Consequently, future treatment guidelines for early-stage MF need to address these issues.

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INTRODUCTION

Mycosis fungoides (MF) is characterized by long-standing, scaly, patch lesions preferentially involving the buttocks and body areas infrequently exposed to sunlight (''bathing trunk'') and slow evolution over years from patches to plaques (early-stage) and in some patient to tumors or erythroderma (advanced-stage).[1,2]

Early-stage MF has a good prognosis (median survival >15 years, 5-year survival >80%)[3-5] compared to advanced-stage disease which has a median survival of 4-5 years and a predicted 5-year survival of approximately 50%[3-7]. A recent meta-analysis reported a 5-year survival of 85.8% for stage IB, 62.2% for IIB, 59.7% for IIA, 54% for IIB, 52.5% for IVA1, 34% for IVA2 and 23.3% for stage IVB[8]. Moreover, even in early-stage disease, morbidity can be considerable with pain, pruritus, disfigurement and poor quality of life (QoL)[9-12]. Progression to advanced stages (IIB-IVB) occurs in 20-25% of patients with early-stage disease and is associated with increased mortality[3-5, 13].

International treatment guidelines do not recommend any particular order of treatment and there is a lack of specific data to confirm the appropriateness of current guidelines[14-19]. Furthermore, cross study comparisons have been difficult because of the lack of well-established response criteria which have only been developed relatively recently[20].

The PROspective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) database opened in January 2015 to prospectively collect data on international patients with MF and to investigate the disease course and its prognostic factors. The current analysis focuses on the treatments used for early-stage MF. The objectives are to analyze the differences in first-line treatment approach and in particular to compare the patient characteristics according to first-line therapy choice - systemic versus observation versus SDT; the overall response rate (ORR) according to different treatments and stages; the health-related quality of life (HRQoL).

MATERIALS AND METHODS

Study Design & Patients

The PROCLIPI study database has been previously described[21]. The study was reviewed and approved by local ethics committees/institutional review boards prior to recruitment. Written consent for participation, analysis of data and use of tissue or blood samples for

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translational research was obtained at study entry. Data cut-off point for this interim analysis was December 2018.

All patients included in the PROCLIPI database that had a diagnosis of "early-stage MF" (stage IA, IB, IIA) based on a central clinicopathological review process to confirm diagnosis and stage were included in the present study[21]. For each patient clinical, hematological, pathological and treatment data were collected at the time of diagnosis and updated annually or earlier in the event of stage progression or death. HRQoL was captured using the Skindex-29 test as already reported[9]. Response to treatment was evaluated according to standard consensus guidelines[20] The ORR was defined as the proportion of patients with a Complete Response (CR)(100% clearance of skin lesions) and Partial Response (PR) defined as 50% - 99% clearance of skin disease based on the modified Severity Weighted Assessment Tool (mSWAT) score without new tumors in patients with T1,T2, T4 only skin disease, lasting for at least four weeks.

Treatment approaches

Treatment approaches were grouped into two categories after consensus across the participating centers as previously reported[6]: (1) Skin-directed therapies (SDT): topical corticosteroids, phototherapy (UVA, broad-band UVB, narrow-band-UVB, NB-UVB), local radiotherapy, total-skin electron beam therapy (TSEBT), topical nitrogen mustard, topical carmustine;

(2) Biological response modifiers: interferon (IFN), retinoids, bexarotene, extracorporeal photochemotherapy (ECP), low-dose methotrexate.

Topical corticosteroids were considered as a treatment only if performed as single therapy, whilst not recorded when in association with other treatments since they were prescribed in the majority of patients.

Statistical Analysis

The chi-square test was used to assess the associations categorical variables. Non-parametric continuous variables are presented with their medians and ranges. The Wilcoxon matched pairs signed rank test and the Kruskal-Wallis tests were used to analyse differences in the distributions of continuous variables.

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Logistic regression analysis was carried out to investigate predictors of first-line systemic approach. The end-point was first-line systemic approach with respect to SDT and expectant policy. Multivariate analysis included as variables: geographical site (Europe vs outside Europe), gender, age at diagnosis, TNMB stage (stratified as IA-IB vs IIA), T-class (only patches versus plaques: T1a/T2a vs T1b/T2b), FMF, mSWAT. Age and mSWAT were included as continuous variables.

Analyses were performed using STATA SEv15 (StataCorp LP, College Station, Texas, USA).

RESULTS

Patient characteristics

A total of 395 patients were included, recruited from 41 centers in 17 countries (UK, Germany, France, Netherland, Belgium, Spain, Italy, Greece, Finland, Hungary, Switzerland, Austria, Israel, Argentina, Brazil, USA and Australia). European centers accounted for 88% of the patients. The median age at first diagnosis was 57 years (range: 5-97). (Supplementary Table 2).

Stage distribution showed 50% IA and 42% IB whilst stage IIA was represented in 8% of patients. At diagnosis, 49% of patients had only patches (29% T1a and 20% T2a) whilst 51% showed also plaques (24% T1b and 27% T2b). Folliculotropic MF (FMF) was diagnosed in 18% of cases. The majority (79%) had plaque disease (T1b=24, T2b=32), whilst a minority only patches (T1a=7; T2a=8). B1 as B-class[22] was found in 30 patients (7.6%): 14 had stage IA, 14 IB and 2 IIA.

The median mSWAT was 10 (range:0.3-120). The mSWAT increased paralleling the T-classification: median values were 4 (range: 0.3-9) for T1a, 6.5 (0.5-24) for T1b, 18 (10-71.5) for T2a up to 34 (12.4-120) for T2b (Kruskal-Wallis test $p<0.001$). mSWAT values were lower for stage IA (median: 4, range: 0.3-24) whilst similar for stage IB (26; 10-112) and IIA (30; 1.8-120) (Kruskal-Wallis test: IA vs IB-IIA $p<0.0001$)

The median follow-up is 1.3 years (range: 1 month – 4.7 years).

First-line and subsequent treatment lines

The first-line therapy was SDT in the large majority of patients (n=322; 81.5%), whilst 11.1% (n=44) received a systemic treatment (Table1 and Supplementary Figure1). An expectant policy was initially adopted for 7.3% (n=29); the majority of these patients had stage IA (n=16) or IB

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(n=10); only 3 stage IIA patients received expectant policy respectively for 3, 4 and 5.5 months after completing diagnostic and staging procedures. 13/29 patients (45%) who initially had expectant policy received a subsequent treatment after a median of 7.5 months (range: 3- 34).

The most frequently used SDTs were topical steroids (39.2%) and phototherapy (36.9%; 18.5%=PUVA and 18.4%= UVB,). Topical steroids were more frequently used in stage IA (48%vs32% in IB;chi-square:9.643, p=0.002), whilst phototherapy in IB (47%vs29%;chi-square:12.693,p<0.0001). Steroids were more frequently used than phototherapy in T1a (55%) compared with other T-scores (T1b:39%; T2a:34%; T2b:37%) (chi-square:11.061,p<0.0001) (Supplementary Figure2). Patients with patches only (T1a/T2a) were more likely to receive UVB (22%) than PUVA (13%) whilst patients with plaques were statistically more frequently treated with PUVA (25%vs15% UVB;chi-square:5.098,p=0.024). No patients received TSEBT as first-line therapy.

Forty-four patients (11.1%) received systemic therapy as first-line treatment: retinoids (19 patients), IFN-2alpha (n=4), methotrexate (n=4), ECP (n=1); the remaining 16 patients received a combination of phototherapy with oral retinoids and/or interferon. The utilization of systemic treatment increased with the number of treatment lines (Figure1). A systemic treatment was adopted as second-line treatment in 24% of patients, as 3rd line in 35% and as 4th line in 38% of patients (1stvs2nd line; chi-square: 11.188; p<0.001).

Parameters associated with a first systemic approach

The factors significantly associated with a first-line systemic therapy in univariate analysis were clinical stage (IA: 6%; IB: 14%; IIA: 20%; IA vs IB: chi- square: 4.465;p=0.035; IA-IB vs IIA: chi-square:15.398;p<0.0001); T-classification (T1a+T2a:5%;T1b+T2b: 17%; chi-square:13.159;p<0.001); FMF (24%vs12% in classic MF; chi-square=10.779;p=0.001); higher mSWAT (7% when mSWAT<=10 and 15% with higher values) (chi-square:6.222;p=0.013) (Figure2).

No differences were found according to age, gender, duration of MF lesions before diagnosis, B-class, geographical site (17% outside Europevs10% Europe) and low versus high volume centers (less or more than 10 patients; 12.5%vs11.1%).

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Parameters associated with a statistically significant increased use of systemic therapy as first-line in multivariate analysis were: presence of plaques (OR:3.07, 95%CI=1.35-6.98) and FMF (OR:2.82, 95% CI=1-5.77) (Table 2). Overall stage (IA–IB–IIA) was not an independent predictor of systemic therapy as first-line therapy.

Response rate

CR was achieved in 26% and PR in 41% of patients, accounting for a 67% ORR. Moreover, 31% (n=123) of patients achieved stable disease and only 6 had disease progression during their first-line treatment (Table 3). The ORR decreased with increasing T-class, from 74% for T1a to 61% for T2b (T1avsT2b: chi-square:4.260,p=0.039). Higher mSWAT values and FMF were associated with a trend towards lower ORR without statistical significance. Patients with Stage IIA disease had a significantly lower ORR (39%) compared to IA (73%) and IB (66%) (chi-square:12.788,p<0.001); the Stage IIA patients (n=33) did have a high tumour burden with 19 having stage T2b disease and 22 having an mSWAT greater than 10.

The ORR to first-line therapy was 73% for SDT and 57% for systemic treatments (chi-square:4.915,p=0.027) (Table 3). Indeed, the ORR of systemic treatments was similar or even lower than SDT in patients even with those with adverse prognostic factors such as higher stage, presence of plaques, FMF and higher mSWAT.

Among SDTs, phototherapy was associated with slightly higher ORR (UVB 77%, PUVA 83%) compared to topical steroids (70%). Lower ORR for topical steroids were particularly relevant for stage IIA (ORR: 29%) (chi-square:5.375,p=0.020vsIA-IB) and T2b patients (ORR: 52%) (chi-square:4.581,p=0.032 with vs other T-classes).

First-line treatment is ongoing in 39% of patients. In the remaining, reasons for stopping were complete remission (21%), completion of the treatment schedule (17%), inadequate or no response (11%), worsening disease and/or stage progression (2%), toxicity (3%) or other reason (7%).

Stage progression and treatment

Stage progression occurred in 39 patients (18-stage IA, 14=IB and 7=IIA), 22 of whom progressed to an advanced-stage (13 stage IIB, 5 stage III, 4 stage IVA1). Thirty-one progressed

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patients had plaques (T1b/T2b) (chi-square:13.881;p<0.001) (OR 4.19; 95% CI=1.8-9.3), 9/39 FMF (23%) and 24/39 >10 mSWAT (61%). B1 at initial diagnosis was found in 3 progressed patients, 2 of whom progressed to stage IIIB and one to stage IVA1. The median time to stage progression from diagnosis was 13 months (1-41 months). (Supplementary Figure 3).

First-line treatment was SDT in 29 and systemic therapies in 7 patients (3 had a wait and see policy): 22/39 (56%) progressed did not respond to first-line treatment (chi-square:11.072;p=0.001)(OR 3.012; 95%CI= 1.5-5.9).

HRQoL

Skindex-29 data were available at diagnosis in 121 patients. A second evaluation was retrieved in 56 of them after a median of 13 months (range: 1-43). The selection of patients for HRQoL tended to be on the basis of the participating centre rather than the particular patient characteristics.

The first-line treatment in these latter patients was expectant policy (n=10), SDT (n=43) and systemic therapy (n=3) achieving 9 CR, 20 PR, 25 SD and 2 PD.

At baseline the median global Skindex-29 score was 23.95 (95%CI=18.3- 30.2); 18 patients (32%) had values exceeding 32 (moderate impairment)[23] and 11 (20%) exceeding 44 (severe).

A statistically significant reduction in the median global Skindex-29 score was found between the first and the second evaluation (19.41, 95% CI: 14.29-27.62) (p=0.006). The reduction was confirmed for the subscales symptoms (p=0.003) and emotions (p=0.008) but not for functioning (p=0.926) (Figure 3). The reduction in the global Skindex-29 occurred not only in responding (Wilcoxon paired signed ranked test p=0.05) but also in SD patients (p= 0.024).

DISCUSSION

This study reports treatment data on 395 patients with confirmed early-stage MF prospectively enrolled into the PROCLIPI database. This is the largest prospective series of patients with early-stage MF reported in terms of treatment data and outcomes.

The first major conclusion is that the first therapy was SDT in most patients (81.5%), although a minority received systemic therapy as their first therapy (usually retinoids or IFN +/- phototherapy). Although we recognize that a physician's decision to choose a therapy may be

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influenced by external factors other than direct disease-related factors (i.e.regulatory status and health insurance reimbursement), we have focused our analyses on the clinical parameters related to 'real-life' decision-making. (data collection didn't include a 'reason' to choose one therapy over another). Features associated with selecting systemic treatment first-line were clinical stage (20% of stage IIA patients), presence of plaques (17% of patients with plaques T1b/T2b), FMF (24%), and higher mSWAT (15% in patients with values>10). By multivariate analysis, T-classification and FMF remained independent factors. Among SDTs, stage and T-score both modifiedthe treatment decision. Topical steroids were more frequently used for patch-stage disease and limited cutaneous involvement (stage IA and T1a), whilst phototherapy was selected for limited plaque-disease (T1b) or extended skin involvement (T2). PUVA was preferred in plaque disease (22%vs15% UVB) whilst UVB was used mainly for patch MF (22%vs13% PUVA). This real-life scenario reflects European and US guidelines[14,15, 17,19,24] which recommend NB-UVB for patch MF and PUVA for plaque disease, given the UVA potential to penetrate deeper into the dermis than UVB. Moreover, NCCN [19], ESMO[15] and USCLC [24] guidelines consider NB-UVB indicated for patients with patch/flat plaque while PUVA for thick plaques or FMF. Plaque stage patients treated by UVB may have had a preponderance of thin/flat plaques. Moreover, the use of UVB could also be due to the lack of availability of PUVA in some centers.

The second main observation was that the ORR to first-line therapy was relatively high (67%) but the CR rate was low (26%). However, maximum responses may not have been achieved given that a substantial proportion (39%) of patients are still receiving therapy.Moreover, patients with stage IIA, T2b score and, to a lesser extent, FMF and high mSWAT (which are also the patient group more commonly receiving front-line systemic treatment), showed lower ORR, similar to responses in advanced-stage MF[6,27]. Notably, these specific features which have the potential to result in a different clinical course are not captured by the classic TNMB staging system (in which the presence of patches vs. plaques does not modify the overall stage). Of interest, skin plaques (T1b/T2b) also appear to predict a high risk to progression to advanced-stage disease.

Another important observation is that the ORR for systemic therapies (57%) was significantly lower than SDTs (73%). Moreover, a lower ORR to SDTwas also observed in patients with adverse prognostic factors such as higher stage, FMF and higher T scores which was the

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subgroup most likely to receive a first line systemic; for example, the ORR in T2b was 65% with SDTs and 52% with systemic therapies. It is important to recognize that some of these patients may have received SDT prior to their diagnosis of MF as early-stage MF is often misdiagnosed as eczema or psoriasis and there can be a substantial delay in confirming a diagnosis of MF. This has been demonstrated in previous PROCLIPI reports[21] and also confirmed in the present analysis at a median of 32months. Nonetheless, given that the ORR of systemic treatments was similar or even lower than SDT (even in those with adverse prognostic factors), our data suggests that it is generally preferable to initiate therapy with SDT in most cases. We acknowledge that the inferior ORR with systemic therapy is likely to be due to the pre-selection of early-stage patients with more aggressive disease characteristics not captured by TNMB and this emphasizes the need for more effective treatments and better clinical markers beyond TNMB to predict the variation in clinical outcomes. For example, the treatment strategy for MF patients with high-risk features could be improved through the development of combination strategies or new drugs such as brentuximab vedotin and mogamulizumab earlier in the treatment of MF[28,29].

FMF is generally poorly responsive to first-line SDTs and may run a more aggressive course[30-32]. Recent studies from Hodak et al.[33] and the Dutch group[34] showed that FMF present with 2 distinct patterns, the early (follicle-based patch/flat plaques) and the advanced (follicle-based infiltrated plaques and/or tumors). The good prognosis of early-stage FMF implies that these patients should benefit from SDT [32-35]. In our study, 18% of early stage MF had FMF and these patients were more likely to receive systemic first-line therapies. It is conceivable that some of these FMF cases had infiltrated rather than thin plaques, thus representing advanced stage FMF[33-35].

We have shown that the majority of early-stage MF patients have persistent skin lesions after their first-line treatment (CR 26%) which could potentially impact on their QoL. Our results indicate that half of the patients with early-stage disease (52%) suffer from a moderate to severe QoL reduction, in agreement with our recent report from the PROCLIPI database[9]. The reduction of Skindex-29 and thus the improvement in HRQoL, demonstrate the positive impact of treatment even if a minority of patients had only 2 time-points available for analysis. Finally, the finding of improved Skindex-29 scores in SD patients is in concordance with previous data showing that improved HRQoL scores were observed in patients despite the lack of an objective

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response[36]. This supports the need to incorporate HRQoL as part of standard patient evaluation and response criteria becoming a 5th compartment (TNMBQ). Consequently, we may find that patients with SD patients who have an improved HRQoL could be objectively identified as obtaining a clinical benefit despite failing to achieve a formal response.

In conclusion, this PROCLIPI study reports that real-life treatment decisions by clinicians for early-stage MF are not only based on stage, but also take into account presence of plaques, FMF disease and mSWAT; treatment outcomes such as ORR and progression to higher stages are adversely affected by these factors. Our study also highlights that the early use of systemic therapy does not achieve better outcomes than SDT and the importance of incorporating QoL into assessments of treatment activity. Potential limitations are short follow-up time (median: 1.3 years), the low number of patients with HRQoL data available and the relatively lower number of patients included in centers outside Europe thus limiting the capacity to extend the conclusions to geographical areas. The ongoing enrollment in PROCLIPI will allow subsequent analyses to involve a larger patient cohort with longer follow-up. Overall, this study strongly supports that the current "early-stage" grouping is too simplistic and next-generation management guidelines need to be developed incorporating predictive high-risk features to drive treatment decisions.

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Figure legends

Figure 1. Percentages of patients treated according to a different approach (expectant policy, SDT, systemic) across the therapy lines. Numbers at the top of each bar represent absolute number of patients treated by the respective therapeutical approach.

Figure 2. Clinico-pathologic characteristics associated with first systemic approach. Bars represents percentage values of patients treated with a first systemic approach according to the different clinic-pathologic characteristics. Numbers at the top of each bar represent absolute

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numbers of patients. P values of parameters with a statistically significant difference are reported at the top of the graph.

Figure 3. HRQoL Global Skindex before and after treatment

Supplementary figure legends

Supplementary figure 1: Summary of first-line therapies. Numbers represent absolute number of patients treated by each therapy

Supplementary figure 2. Topical steroids and phototherapy according to stage and T score

Supplementary figure 3. Disease-stage progression curve (included only patients who developed a disease progression)

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Table 1. Summary of first treatment approaches in the patient cohort.

	Drug / treatment	No. patients	%
EXPECTANT POLICY	"wait and see"	29	7.3%
SDT	Topical steroids	155	39.2%
	UVB	73	18.4%
	PUVA	75	18.5%
	Topical nitrogen mustard	5	1.3%
	Topical BiCNU	2	0.5%
	Local RT	12	3%
	Total SDT	322	81.5%
SYSTEMIC	Phototherapy + IFN and/or retinoids	16	4%
	ECP	1	0.3%
	Oral retinoids	15	3.8%
	Oral bexarotene	4	1%
	MTX	4	1%
	IFN	4	1%
	Total systemic	44	11.1%

SDT= Skin Directed Therapies

UVB= Phototherapy with Ultraviolet B rays

PUVA= Phototherapy with Psoralens plus Ultraviolet A rays

BiCNU= bis-chloroethylnitrosourea, carmustine

RT= Radiotherapy

ECP= Extracorporeal Photochemotherapy

MTX= Methotrexate

IFN= Interferon

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Table 2. Multivariate analysis of parameters associated with first systemic approach.

Variable	Coefficient	Standard error	p	O.R	95% CI low	95% CI high
Geographical	0.7711	0.4636	0.0962	2.1622	0.8715	5.3643
Age	-0.0011	0.0103	0.9146	0.9989	0.9790	1.0192
Gender	-0.0219	0.3543	0.9508	0.9784	0.4886	1.9593
mSWAT	0.1683	0.4283	0.6943	1.1833	0.5111	2.7395
TNM stage	0.4363	0.3003	0.1463	1.5470	0.8587	2.7871
Plaques	1.1221	0.4186	0.0074	3.0712	1.3521	6.9761
FMF	1.0391	0.3641	0.0043	2.8268	1.3846	5.7709

OR odds ratio

CI Confidence Interval

FMF: Folliculotropic mycosis fungoides

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Table 3. Response to selected SDTs according to the main clinico-pathologic predictors.

FIRST LINE	ORR					
	SDT+expectant+ systemic	SDT	Systemic	Topical corticosteroids	UVB	PUVA
Total	266/ 395 (67%)	235/322 (73%)	25/44 (57%)	106/155 (68%)	54/73 (74%)	62/75 (83%)
IA	145/198 (73%)	131/168 (78%)	11/14 (79%)	71/95 (75%)	26/34 (76%)	21/23 (91%)
IB	108/164 (66%)	94/131 (72%)	11/23 (48%)	33/53 (62%)	25/34 (74%)	36/43 (84%)
IIA	13/33 (39%)	10/23 (43%)	3/7 (43%)	2/7 (29%)	3/5 (60%)	5/9 (56%)
T1a	84/113 (74%)	78/100 (78%)	4/5 (80%)	47/62 (76%)	16/21 (76%)	7/7 (100%)
T2a	53/80 (66%)	51/67 (76%)	1/5 (20%)	18/27 (67%)	17/22 (78%)	16/18 (89%)
T1b	64/96 (66%)	55/76 (72%)	8/11 (73%)	26/37 (70%)	11/15 (73%)	13/16 (81%)
T2b	65/106 (61%)	51/79 (65%)	12/23 (52%)	15/29 (52%)	10/15 (67%)	26/34 (76%)
T1a+T2a	137/193 (71%)	129/167 (77%)	5/10 (50%)	66/89 (74%)	33/43 (77%)	23/25 (92%)
T1b+T2b	129/202 (64%)	106/155 (68%)	20/34 (59%)	41/66 (62%)	21/30 (70%)	39/50 (78%)
mSWAT>10	125/197 (63%)	107/155 (69%)	15/30 (50%)	31/54 (57%)	29/41 (71%)	46/57 (81%)
mSWAT <=10	141/198 (71%)	128/167 (77%)	10/14 (71%)	75/101 (74%)	25/32 (78%)	16/18 (89%)
FMF	43/71 (60%)	32/49 (65%)	9/18 (50%)	16/21 (76%)	2/5 (40)	11/17 (65%)
Not FMF	223/324 (69%)	203/273 (74%)	16/26 (62%)	90/134 (69%)	52/68 (76%)	51/58 (88%)

ORR: overall response rate

SDT: Skin-directed therapies

FMF: Folliculotropic Mycosis Fungoides

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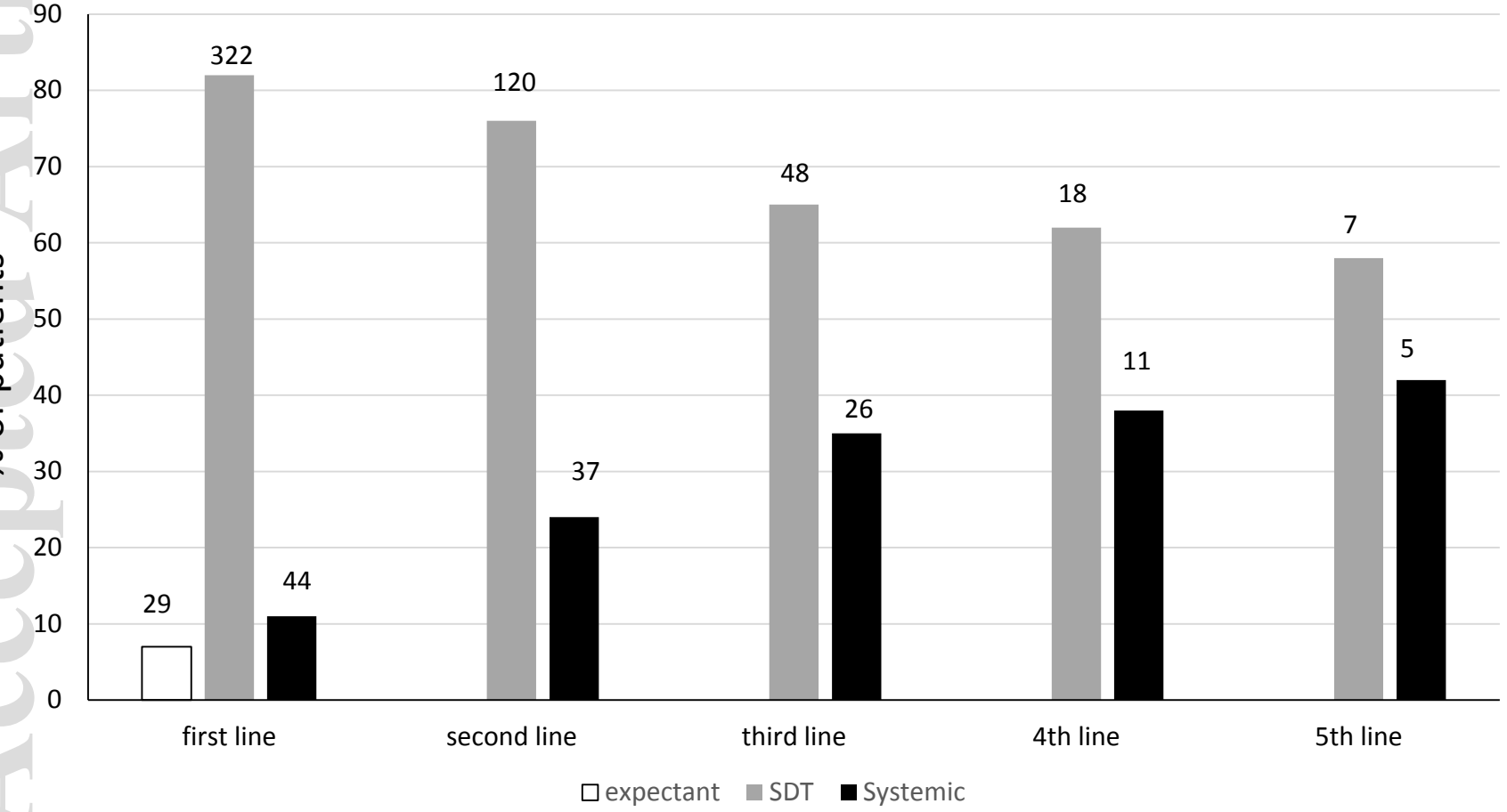

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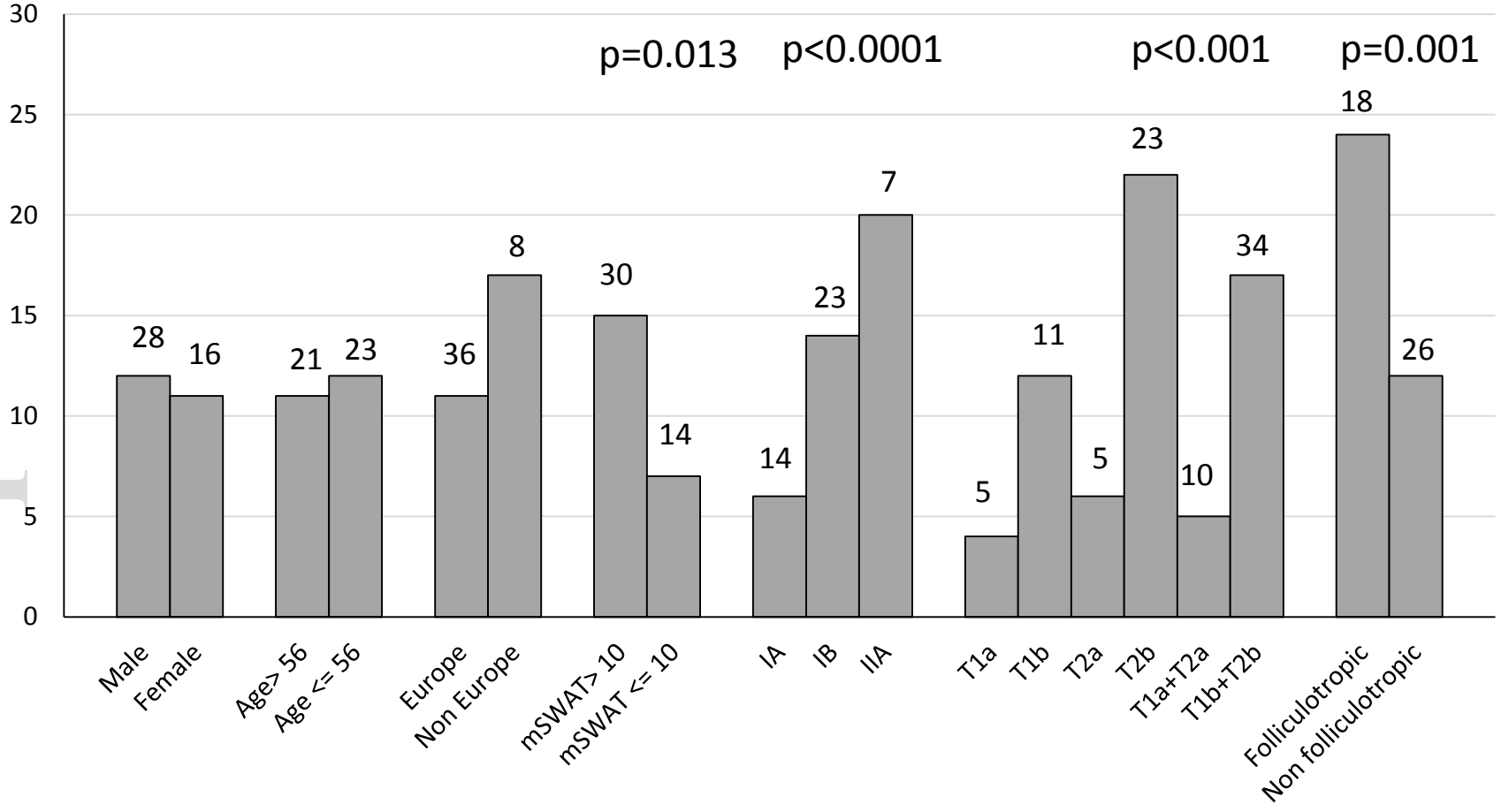

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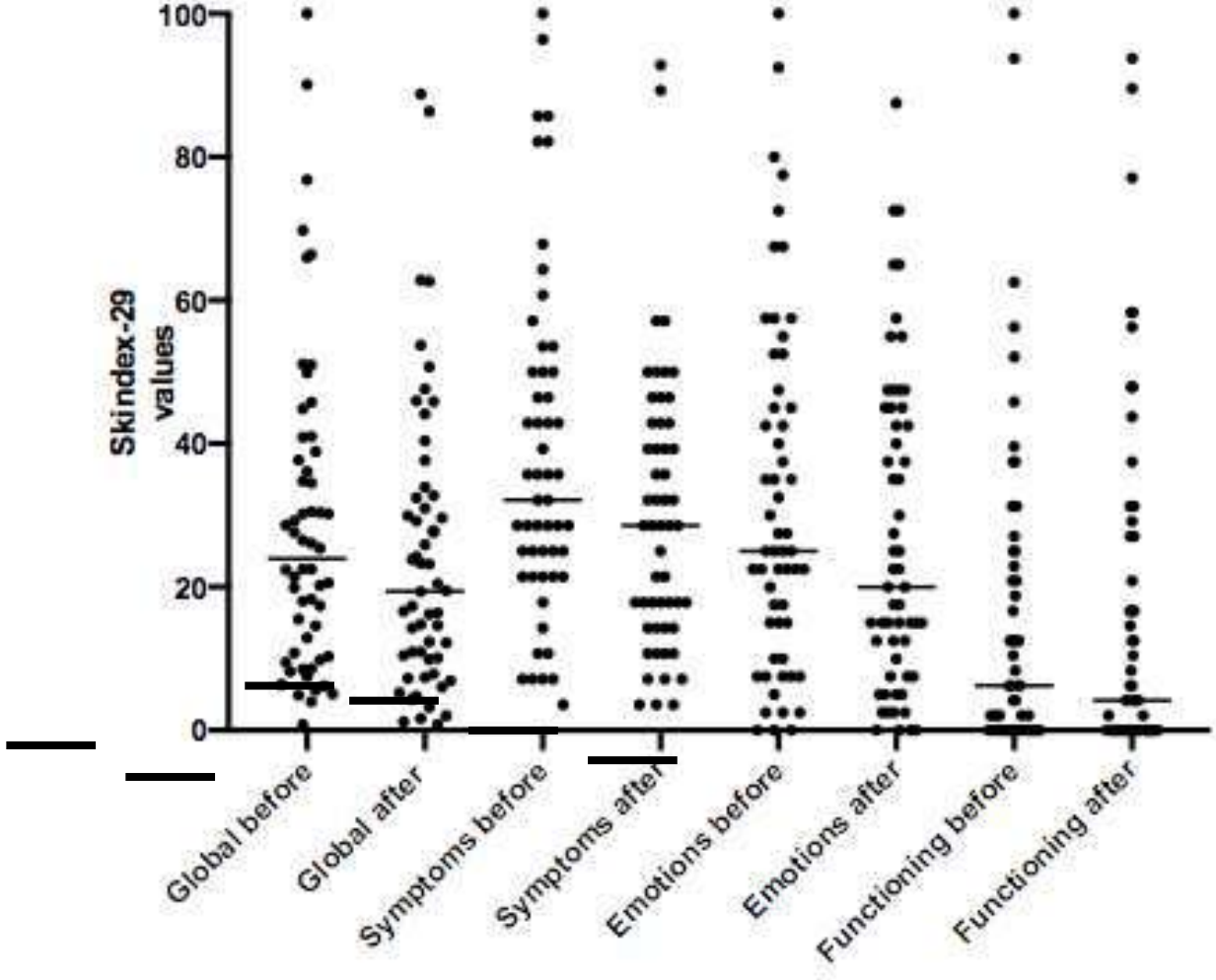

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