Evaluating the Treatment Patterns of Chlormethine/Mechlorethamine Gel in Patients With Stage I-IIA Mycosis Fungoides: By-time Reanalysis of a Randomized Controlled Phase 2 Study

Larisa J. Geskin,[1] Ellen J. Kim,[2] James T. Angello,[3] Youn H. Kim[4]

Abstract

Chlormethine gel was approved for treatment of mycosis fungoides based on the pivotal 201 Study. This by-time analysis of the 201 Study data provides complementary information about response patterns over time. Peak response was achieved at 10 months, with early, intermittent, and late response patterns observed. This information should help physicians and patients set expectations regarding response patterns and times.

Background: The pivotal 201 Study investigated chlormethine/mechlorethamine gel treatment for patients with early stage disease mycosis fungoides and demonstrated the treatment was not inferior to chlormethine ointment. However, overall response rates do not provide information about response patterns. The study objective was to assess the value of by-time analysis of clinical response data in visualizing response over time. **Methods:** This post hoc analysis re-evaluated chlormethine efficacy using a by-time approach that investigated the trend to treatment response and permitted assessment of response, both monthly between 1 and 6 months, and once every 2 months between 7 and 12 months, over the course of 1 year. In addition, very good partial response was redefined as a $\geq$ 75% response. **Results:** By-time analyses of Composite Assessment of Index Lesion Severity (CAILS) and modified severity-weighted assessment tool (mSWAT) showed response rates at 1 month (respectively, 8.5% and 5.9%) that increased over time to peak at 10 months (78.9% and 54.4%). Early, intermittent, and late response patterns were observed. In total, 32.5% of patients experienced very good partial response over 2 consecutive visits, indicating that $\sim$ 33% of patients could expect to have very good to complete response within 1 year. **Conclusion:** By-time analysis for clinical response provides complementary information to traditional overall response rate data regarding response peak time and changes over time.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 21, No. 2, 119-24

Keywords: By-time analysis, Composite assessment of index lesion severity, Cutaneous T-cell lymphoma, Efficacy, Modified severity-weighted assessment tool

Introduction

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphomas. For patients with early stage MF (stage IA-IIA), the use of skin-directed therapy, such as chlormethine (also known as mechlorethamine), is recommended.[1-3] Chlormethine is a bifunctional alkylating agent that inhibits rapidly proliferating cells, resulting in cell death.[4] Topical chlormethine gel (chlormethine 0.016% w/w, equivalent to 0.02% chlormethine HCl) has been specifically developed for the treatment of MF and is recommended

[1]Department of Dermatology, Columbia University, New York, NY
[2]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
[3]Medical Affairs and Research, Helsinn Therapeutics (US) Inc, Iselin, NJ
[4]Department of Dermatology, Stanford Cancer Institute, Stanford, CA

Submitted: Nov 6, 2020; Accepted: Nov 27, 2020; Epub: Dec 3, 2020

Address for correspondence: Larisa J. Geskin, MD, Columbia University Department of Dermatology, 161 Fort Washington Ave, 12th Floor, New York, NY 10032
E-mail contact: ljg2145@cumc.columbia.edu

https://doi.org/10.1016/j.clml.2020.11.022

as one of several first-line therapies for adults with MF by international guidelines.[1-3] Chlormethine gel is a stable, optimized, quick-drying, and nongreasy formulation that is centrally manufactured and is easier to apply than compounded aqueous and ointment formulations, which may enhance patient compliance.

The pivotal registration study (201 Study; NCT00168064) was a randomized, observer-blinded, controlled, noninferiority trial comparing the efficacy and safety of daily 0.02% chlormethine gel with 0.02% chlormethine compounded ointment over a 12-month period in patients with early stage MF.[5] The primary efficacy endpoint was the proportion of patients with $\geq$ 50% improvement in baseline Composite Assessment of Index Lesion Severity (CAILS) for at least 2 consecutive visits (complete response plus partial response). In total, 58.5% of patients treated with chlormethine gel and 47.7% of patients treated with chlormethine ointment experienced objective responses assessed by CAILS in the intent-to-treat (ITT) population. The prespecified criterion for noninferiority was met, with a ratio of 1.23 (95% confidence interval, 0.97-1.55) for the gel versus the ointment.[5] In addition, chlormethine gel was noninferior to the ointment in terms of modified severity-weighted assessment tool (mSWAT) (46.9% vs. 46.2%, respectively; response rate ratio, 1.02; 95% confidence interval, 0.78-1.32 in the ITT population) and body surface area (BSA) (44.6% vs. 43.1%, respectively; response rate ratio, 1.04; 95% confidence interval, 0.79-1.37 in the ITT population). In a time-to-response analysis, the gel resulted in a significantly shorter time to response of 26 weeks compared to the ointment (42 weeks; $P < .01$).[5]

Although the 201 Study data provided insight into the overall efficacy benefit of chlormethine gel treatment in patients with MF, it did not provide information regarding the natural course of responses over time or patterns of response, including timeline and durability of response over time. To gain a deeper understanding of response patterns, we used a novel statistical analysis, by-time analysis, to evaluate not only the overall proportion of those with response to chlormethine gel but also response over time. In addition, similar to evaluations in psoriasis and other chronic skin disorders, we looked at very good partial response (VGPR), which included patients who had $\geq$ 75% improvement from baseline in their skin disease as measured by CAILS, mSWAT, and BSA. Considering the original trial was designed over 10 years ago, in this analysis, we applied more rigorous modern criteria to investigate the rate of durable long-term responses. We calculated the responses lasting for at least 2 or 4 consecutive months (overall response rate [ORR] 2 and ORR4). The overall objective was to obtain practical information that would help both patients and health care practitioners set realistic expectations regarding typical response patterns and times.

Methods

Patients and Study Design

The 201 Study was a randomized, controlled, observer-blinded, multicenter clinical trial that compared a once-daily treatment of chlormethine gel (0.02%) to chlormethine ointment (0.02%) in patients with MF. Details of the study including design, patient population, and interventions have been previously published.[5] The primary endpoint was response, defined as $\geq$ 50% improvement in baseline CAILS for $\geq$ 2 consecutive visits. Secondary endpoints included $\geq$ 50% improvement in mSWAT, BSA percentage (%BSA), and time to CAILS response. Study visits were every month for the first 6 months, and then every 2 months until the final visit at 12 months (9 postbaseline study visits total). Institutional review board approval of the clinical trial was obtained at all study sites, and all patients provided written informed consent before enrollment.

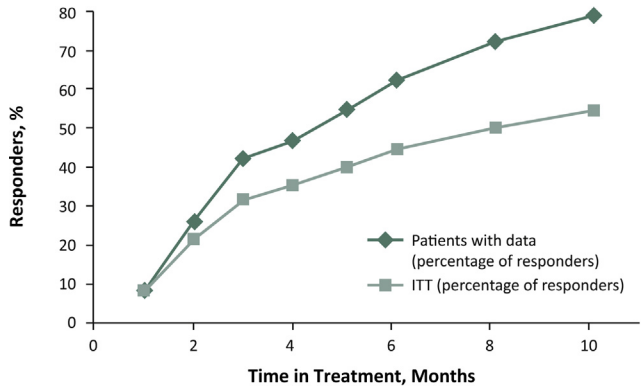
Post Hoc Analysis

The by-time analysis shows the proportion of patients with clinically responsive disease ($\geq$50% reduction from baseline in CAILS, mSWAT, or %BSA score, respectively) at each visit. The by-time analyses were conducted for the ITT and patients with postbaseline data (PBD) populations. For the ITT analysis, the proportion of patients with clinical response was calculated by dividing the number of those with response by the total randomized population (N = 130) for each visit. For the PBD analysis, the number of those with response was divided by the number of patients contributing postbaseline data at the relevant visit, which declines with time as a result of accumulation of early treatment discontinuations. Over the 12-month study duration, a total of 49 patients discontinued therapy for a variety of reasons: 26 discontinuations were due to dermatitis reactions; 2 due to patient's best interest (1 before receipt of study medication and 1 due to facial lesions in untreated area); 4 due to concurrent illness unrelated to study drug; 3 withdrew consent; 2 due to noncompliance; 4 lost to follow-up; 4 for other (1 before receipt of study medication, 2 for other treatments that disqualified further participation, 1 for disease progression); and 4 for lack of efficacy. Of these, only patients in the 2 final categories discontinued therapy for reasons associated with a decline in clinical response during chlormethine treatment (5 patients total). Therefore, these 5 patients were kept in the denominators for each visit data point in the PBD analysis, which effectively counts them as having nonresponse throughout.

Adding the 5 patients with declining clinical response was done to control for a potential selection bias in the PBD analysis. The ITT and PBD analyses are presented side by side to show the clinical responses over time and to illustrate the impact on clinical response rates when all 49 discontinuations are kept in the denominator for each visit with the ITT (all patients are included; always N = 130 for each data point) versus PBD (all patients are included until they leave the study, except those who leave for disease progression or lack of efficacy) populations. The bulk of discontinuations (n = 26) were due to dermal irritation reactions, which have been reported to correlate with earlier complete clearance[6] and can be therapeutically beneficial.[7] Therefore, counting these and other non—efficacy-related discontinuations as nonresponse is more likely to underestimate the true clinical response profile of chlormethine, which explains the rationale for adding the PBD approach. Finally, the response rates for the final visit are not reported in either by-time analysis. The last-visit mean treatment time was shorter than the planned 12 months as a result of early discontinuations. Final visit results were similar to the 10-month results.

The ORR2 and ORR4, defined as a reduction of $\geq$ 50% in CAILS or mSWAT lasting for at least 2 or 4 consecutive months, respectively, were also determined. VGPR was redefined as a $\geq$ 75% response in CAILS, mSWAT, or %BSA. In addition, a 1× or 2× designation was added to identify patients with a VGPR for at least 1 or for 2 or more consecutive postbaseline visits, respectively.

Figure 1 By-Time Graph of CAILS Clinical Response Data



Abbreviations: CAILS = Composite Assessment of Index Lesion Severity; ITT = intent to treat.

Results

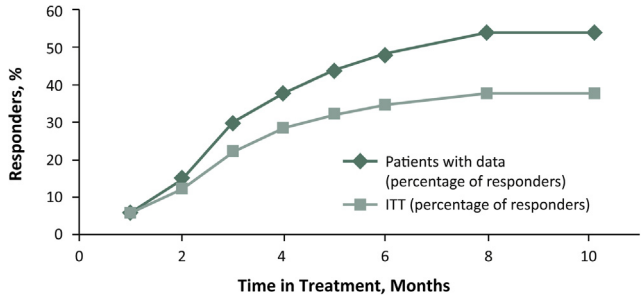
The by-time analysis of the CAILS clinical response data for patients with data showed that there was a modest level of clinical response (8.5%) at 1 month after treatment initiation, with a steady increase in response rates over time. Peak response occurred at 10 months (visit 8) and was 78.9% (Figure 1, Supplemental Table 1 in the online version). The corresponding ITT response rates were 7.7% at 1 month and 54.6% at 10 months (visit 8). Last-visit response rates for patients with data and the ITT population were 67.5% and 59.2%, respectively (data on file).

The by-time analysis of the mSWAT response data showed a modest proportion of patients with response (5.9%) 1 month after treatment initiation for patients with data, with a steady increase over time and a response rate of 54.4% at 10 months (visit 8) (Figure 2, Supplemental Table 2 in the online version). Response rates for the ITT population were 5.4% and 37.7% at 1 and 10 months, respectively. The last-visit response rates were 60.7% for patients with data, and 50.0% for patients in the ITT group (data on file).

A modest level of response was similarly seen at 1 month (5.0%) for patients with data in the by-time analysis of the %BSA response data, with a steady increase over time and a response rate of 51.1% at 10 months (visit 8). The corresponding ITT response rates were 4.6% and 35.4% at 1 and 10 months, respectively (Supplemental Figure 1 and Supplemental Table 3 in the online version). Last-visit response rates for patients with data and the ITT population were 55.7% and 37.7%, respectively (data on file).

The post hoc analyses revealed different response patterns in the 201 Study data (Table 1). Twelve patients were identified who met the criteria for response status early, then subsequently lost this status or discontinued for other reasons (Supplemental Table 4 in the online version). For example, 1 patient discontinued early because of non-efficacy of the treatment but was counted as having overall responsive disease in the traditional ORR2 analysis as a result of the 50% reduction threshold just being reached at 2 early time point visits (Supplemental Table 4 in the online version, patient M). The by-time analyses also showed variety in the time to response to chlormethine gel treatment, with some patients experiencing early response and maintaining their response status over time, while others experienced intermittent responses, or had disease that did not respond until late (≥6 months after treatment initiation) in the study (Table 1; Supplemental Table 5 in the

Figure 2 By-Time Graph of mSWAT Clinical Response Data



Abbreviations: ITT = intent-to-treat; mSWAT = modified Severity-Weighted Assessment Tool.

Table 1 Composite Assessment of Index Lesion Severity (CAILS) Percentage Change From Baseline Scores of Varying Responders in 201 Study

Patient	Visit								
	1	2	3	4	5	6	7	8	9
A	**−52.5**	**−57.6**	**−64.4**	**−72.9**	**−57.6**	**−59.3**	**−57.6**	**−69.5**	**−83.1**
B	−44.4	**−66.7**	**−58.3**	**−83.3**	**−72.2**	**−75.0**	**−72.2**	**−63.9**	**−69.4**
C	−32.4	**−51.4**	**−67.6**	**−70.3**	**−56.8**	−45.9	−48.6	**−62.2**	**−62.2**
D	−10.3	−36.8	−36.8	**−51.5**	−41.2	**−60.3**	**−58.8**	**−55.9**	**−70.6**
E	−28.6	−32.1	−35.7	−28.6	−21.4	−35.7	**−75.0**	**−71.4**	**−64.3**
F	33.3	57.1	57.1	76.2	57.1	**−52.4**	**−66.7**	**−76.2**	**−100**
G	33.3	13.3	0	−13.3	13.3	20	0	13.3	**−100**
H	−6.3	37.5	25.0	37.5	18.8	12.5	−6.3	−6.3	**−100**

Bold values represent patients with ≥50% reduction from baseline in CAILS.
Rows A, B indicate early response; C, D, intermittent response; E, F, later response; and G, H, extremely late response.

online version) or at their final study visit (Table 1; Supplemental Table 6 in the online version).

The ORR2 for the CAILS response data was 61.8% using the patients with data denominator and 58.5% using the ITT denominator. For mSWAT, the ORR2 was 48.4% and 46.2% for patients with data and ITT, respectively (Table 2). The ORR4 for the CAILS response was 43.9% for patients with data and 41.5% for ITT, while the ORR4 for the mSWAT response data was 29.8% and 28.5% for patients with data and ITT, respectively (Table 2).

In total, 30.8% (ITT) and 32.5% (patients with data) of patients had VGPR for at least 2 consecutive visits (2×) by CAILS; 21.5% (ITT) and 22.6% (patients with data) had VGPR 2× by mSWAT (Table 3). VGPR 1× was achieved for 49.2% (ITT) and 52.0% (patients with data) by CAILS and 36.9% (ITT) and 38.7% (patients with data) by mSWAT.

Discussion

This post hoc analysis of the 201 Study data re-evaluated the efficacy of chlormethine gel treatment using a by-time approach, which investigates the trend to treatment response and allows assessment of response, monthly between 1 and 6 months and bimonthly between 7 and 12 months, over the course of 1 year. By-time analyses of clinical response data provide complementary data to the traditional ORR analysis, and have enabled visualization of the changing response rates over time. Such information sheds light on the typical response timelines.

By-time analyses showed that for CAILS, an increase in the response rate for patients with data was seen from 8.5% at 1 month (visit 1), to 46.9% at 4 months (visit 4), and 78.9% at 10 months (visit 8). The mSWAT response rate increased from 5.9% at 1 month (visit 1), to 37.8% at 4 months (visit 4), and 54.4% at 10 months (visit 8). Peak responses were seen at 10 months for both CAILS and mSWAT. Conversely, the traditional ORR analysis provides only a single measure of response over the whole treatment interval and does not provide a granular view on response timing, response rate changes, or whether response status was maintained or lost. The by-time analysis provides more detail about the different types of response patterns seen with chlormethine gel treatment. Some patients had an early response that was sustained throughout the study, while others had intermittent responses and lost response status during the study (Table 1 and Supplemental Table 5 in the online version). Late responses were observed as well, where patients did not respond to chlormethine gel treatment until ≥ 6 months after treatment initiation. Because the primary endpoint of the 201 Study required patients to maintain response status for 2 consecutive visits,[5] this post hoc analysis also visualized those patients who had a response at the last visit, where confirmation of ORR2 status was not possible because of the data cutoff at the end of the study. These patients had responses well above the 50% threshold (83%-100%) at their final visit and may have maintained response status after the study ended (Table 1 and Supplemental Table 6 in the online version).

Table 2 Overall Response Rate by Assessment Tool

Characteristic	CAILS		mSWAT	
	ITT	PBD	ITT	PBD
ORR2				
Total no.	130	123	130	124
Response, n (%)	76 (58.5)	76 (61.8)	60 (46.2)	60 (48.4)
ORR4				
Total no.	130	123	130	124
Response, n (%)	54 (41.5)	54 (43.9)	37 (28.5)	37 (29.8)

Data refer to cutaneous assessments that were aligned with those performed in patients with stage IA-IB mycosis fungoides in the registration study.
Abbreviations: CAILS = Composite Assessment of Index Lesion Severity; ITT = intent-to-treat denominator; MF = mycosis fungoides; mSWAT = modified severity-weighted assessment tool; ORR2/4 = response lasting for at least 2/4 consecutive months; PBD = patients with postbaseline data denominator.

Table 3 Very Good Partial Response Rates by Assessment Tool

Characteristic	CAILS		mSWAT	
	ITT	PBD	ITT	PBD
VGPR 1×	49.2%	52.0%	36.9%	38.7%
VGPR 2×	30.8%	32.5%	21.5%	22.6%

Abbreviations: CAILS = Composite Assessment of Index Lesion Severity; CR = complete response; ITT = intent-to-treat denominator (N = 130); mSWAT = modified severity-weighted assessment tool; PBD = patients with postbaseline data denominator; VGPR 1/2× = very good partial response (≥75% improvement from baseline) for at least 1 visit/at least 2 consecutive visits.

Although by-time analyses provide additional insight into responses over time, there is the potential for both positive and negative bias with this approach. The inclusion of patients who discontinued treatment either for lack of efficacy or early responses at later analysis time points could affect response rates in opposite directions. This emphasizes the importance of choosing the appropriate denominator in by-time analyses. To prevent selection bias, it is important to include those patients who discontinued treatment early as a result of disease progression or lack of efficacy in the denominator at later time points, as was done in the current analysis (patients with data). If patients discontinued treatment early for other reasons, such as a complete response (CR) or adverse events, they were not carried forward to later time points even if their final response exceeded the 50% threshold for responses, because it was not determined whether they maintained response status. During the 201 Study, the majority of patients (n = 44) discontinued treatment for reasons other than poor clinical response (n = 5). Because positive response results were not carried forward, the increasing response rates over time indicate there was a higher proportion of responses among patients who continued chlormethine gel treatment for longer (Supplemental Table 4 in the online version). The traditional ORR focuses on the response status of a patient at the best point in their treatment course and will therefore include as having overall response patients who lost their response status after an early response. Considerably higher response rates were seen for patients with data, compared to the secondary ITT analysis, where all 49 patients who discontinued were included in the denominator for the by-time analyses. For CAILS, the response rates at 10 months (visit 8) were 78.9% for patients with data and 54.6% for the ITT population, while for mSWAT the 10-month response rates were 54.4% and 37.7%, respectively. Because most patients who discontinued did so for reasons unrelated to efficacy, including them as nonresponsive at later time points likely underestimates the clinical response profile of chlormethine gel.

Results for the traditional ORR and for VGPR rates were similar between patients with data and ITT because these endpoints are impacted less by early discontinuation. In total, 18 (13.8%) of 130 had CR by CAILS during the 201 Study.[5] In this post hoc analysis, 32.5% of patients with data had VGPR 2×, defined as ≥ 75% reduction from baseline for at least 2 consecutive visits. The VGPR rate visualizes those patients who had a substantially better response than the 50% threshold for partial response, but fell short of the 100% required for CR. This indicates that approximately one third of patients with MF treated with chlormethine gel may expect to have a very good to CR within 1 year.

Ensuring precision and accuracy of clinical response estimates were the drivers to count all discontinuations due to disease progression or lack of efficacy as nonresponse. In addition, the avoidance of any data-censoring techniques for missing sequential data was applied to the by-time analysis for the same reasons. Nonetheless, there is always potential with any endpoint construction to introduce unexpected artifacts.

In conclusion, using a by-time approach to analyze response to chlormethine gel treatment provides more detail about response patterns and timelines. These data can help emphasize the importance of continued chlormethine gel treatment to patients and health care practitioners because peak clinical response rates occurred past 6 months. Because dermatitis cases tend to occur early after treatment initiation (1-3 months), the knowledge that clinical response may occur later can help motivate patients to continue treatment. Combining both the traditional ORR and by-time analyses for clinical response analysis provides clinicians with complementary information regarding sustained response, as well as changes in response over time.

Clinical Practice Points

- Mycosis fungoides (MF) is a challenging disease to treat, with no curative options aside from allogeneic stem-cell transplantation.
- Chlormethine gel (also known as mechlorethamine) was approved for the treatment of patients with MF after outcomes of the pivotal 201 Study, which demonstrated noninferiority to chlormethine ointment.
- The current by-time analysis of 201 Study data was undertaken to provide further information regarding typical response patterns and times.
- Three by-time analyses showing the proportion of patients who experienced clinical response at each visit were undertaken (≥50% reduction from baseline in Composite Assessment of Index Lesion Severity [CAILS], modified Severity-Weighted Assessment Tool [mSWAT], and body surface area percentage [%BSA]).
- These data revealed that responses were seen at 1 month and that these increased over time to a peak response at 10 months. Moreover, early, intermittent, and late response patterns were observed.
- To gain a deeper understanding of the high overall proportion of those with response to chlormethine gel, a new set of very good partial response (VGPR) analyses, which included patients who had ≥ 75% improvement from baseline in their skin disease as measured by CAILS, mSWAT, and body surface area, were also undertaken. In total, 32.5% of patients had VGPR over 2 consecutive visits, indicating that ~33% of patients could expect to have very good to complete response within 1 year.
- Our results enabled visualization of the changing response rates and peak response and emphasize the importance of continued chlormethine gel treatment. Such information should help physicians and patients set expectations regarding typical response timelines and motivate patients to continue treatment.

Acknowledgments

This work was supported by Helsinn Healthcare SA. Writing and editorial assistance was funded by Helsinn Healthcare SA. The authors would like to acknowledge and thank the volunteers, investigators, and study teams at the centers participating in this study. Statistical programming and analysis were overseen by Michael J. Williams, PhD, and David Mink, MS, from ICON Commercialization & Outcomes, Dublin, Ireland. Editorial and medical writing assistance was provided by Joanne Franklin, PhD, CMPP, from Aptitude Health, The Hague, the Netherlands, funded by Helsinn Healthcare SA. The authors are fully responsible for all content and editorial decisions for this manuscript.

Disclosure

L.J.G. reports research support/PI for Helsinn Group, J&J, Mallinckrodt, Kyowa Kirin, Soligenix, Innate, miRagen, Galderma, Merck, BMS, and Stratpharma; speakers' bureau for Helsinn Group and J&J; and scientific advisory board for Helsinn Group, J&J, Mallinckrodt, and Kyowa Kirin. E.J.K. reports research support/PI for Actelion, Galderma, MedImmune, and Soligenix; consultant work for Actelion, Galderma, and Helsinn Group; and scientific advisory board for Helsinn Group and Kyowa Kirin. J.T.A. is an employee of Helsinn Group Therapeutics (US) Inc. Y.H.K. reports steering committee and advisory board for Eisai; research funding and advisory board for Forty Seven and Seattle Genetics Inc; steering committee member and research funding for Kyowa Hakko Kirin and Millennium Pharmaceuticals Inc; consultant for Portola and Horizon; and PI on current trials for miRagen, Merck, Soligenix, TetraLogic, Neumedicines, Innate, KHK, Eisai, Millennium Pharmaceuticals Inc, and Forty Seven.

Supplemental Data

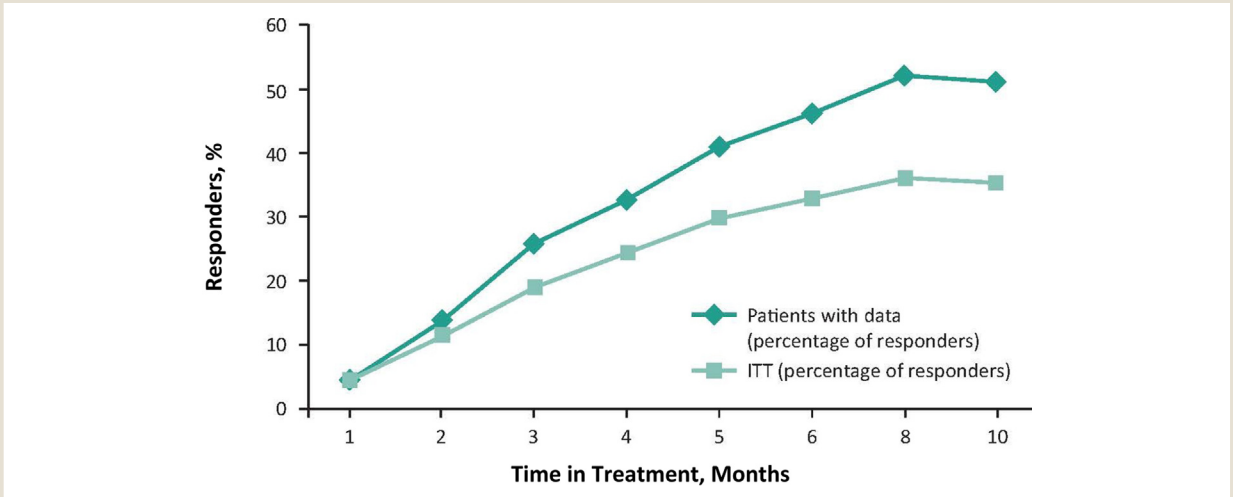
Supplemental tables and figure accompanying this article can be found in the online version https://doi.org/10.1016/j.clml.2020.11.022.

References

1. Trautinger F, Eder J, Assaf C, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome—update 2017. *Eur J Cancer* 2017; 77: 57-74.
2. Willemze R, Hodak E, Zinzani PL, et al. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; 29:iv30-40.
3. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: primary cutaneous lymphomas. Version 2.2020. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed: June 5, 2020.
4. Denis D, Beneton N, Laribi K, et al. Management of mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL): focus on chlormethine gel. *Cancer Manag Res* 2019; 11:2241-51.
5. Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. *JAMA Dermatol* 2013; 149:25-32.
6. Kim YH, Martinez G, Varghese A, et al. Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol* 2003; 139:165-73.
7. Vonderheid EC, Ekbote SK, Kerrigan K, et al. The prognostic significance of delayed hypersensitivity to dinitrochlorobenzene and mechlorethamine hydrochloride in cutaneous T cell lymphoma. *J Invest Dermatol* 1998; 110:946-50.

Supplemental Data

Supplemental Figure 1 By-Time Graph of BSA Clinical Response Data



Abbreviations: BSA = body surface area; ITT = intent to treat.

Supplemental Table 1 CAILS Response Data

	Visit							
CAILS Outcome	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Mean treatment time (months)	1.0	2.0	3.0	4.0	5.0	6.0	8.0	10.1
No. patients with ≥ 50% reduction	10	28	41	46	52	58	65	71
No. patients with PBD	113	103	92	93	90	88	85	85
No. patients with PBD + early termination due to lack of efficacy and/or disease progression	118	108	97	98	95	93	90	90
By-time response rates, PBD denominator (variable denominator)	8.5%	25.9%	42.3%	46.9%	54.7%	62.4%	72.2%	78.9%
By-time response rates, ITT denominator (fixed denominator at N = 130)	7.7%	21.5%	31.5%	35.4%	40.0%	44.6%	50.0%	54.6%

Abbreviations: CAILS = Composite Assessment of Index Lesion Severity; ITT = intent to treat; PBD = postbaseline data.

Supplemental Table 2 mSWAT Response Data

mSWAT Outcome	Visit							
	1	2	3	4	5	6	7	8
Mean treatment time (months)	1.0	2.0	3.0	4.0	5.0	6.0	8.0	10.1
No. patients with ≥ 50% reduction	7	16	29	37	42	45	49	49
No. patients with data	114	103	92	93	90	88	85	85
No. patients with data + early termination due to lack of efficacy and/or disease progression	119	108	97	98	95	93	90	90
By-time response rates, PBD denominator	5.9%	14.8%	29.9%	37.8%	44.2%	48.4%	54.4%	54.4%
By-time response rates, ITT denominator	5.4%	12.3%	22.3%	28.5%	32.3%	34.6%	37.7%	37.7%

Abbreviations: ITT = intent to treat denominator; mSWAT = modified severity-weighted assessment tool; PBD = patients with postbaseline data.

Supplemental Table 3 BSA Response Data

BSA Outcome	Visit							
	1	2	3	4	5	6	7	8
Mean treatment time (months)	1.0	2.0	3.0	4.0	5.0	6.0	8.0	10.1
No. patients with ≥ 50% reduction	6	15	25	32	39	43	47	46
No. patients with data	114	103	92	93	90	88	85	85
No. patients with data + early termination due to lack of efficacy and/or disease progression	119	108	97	98	95	93	90	90
By-time response rates, PBD denominator	5.0%	13.9%	25.8%	32.7%	41.1%	46.2%	52.2%	51.1%
By-time response rates, ITT denominator	4.6%	11.5%	19.2%	24.6%	30.0%	33.1%	36.2%	35.4%

Abbreviations: BSA = body surface area; ITT = intent-to-treat denominator; PBD = patients with postbaseline data.

Supplemental Table 4 CAILS Percentage Change From Baselines Scores in Patients With ORR Response Status Early and Subsequently Lost Response or Discontinued Treatment Early

Patient	Visit								
	1	2	3	4	5	6	7	8	9
I	−5.1	**−71.2**	**−100**	**−64.4**	**−61**	**−84.7**	−67.8	NRBT	NRBT
J	−12.5	−30	**−55**	**−75**	**−77.5**	NRBT	NRBT	NRBT	NRBT
K	**−76.9**	**−100**	−41	**−66.7**	**−100**	**−100**	**−92.3**	NRBT	NRBT
L	−22	**−53.7**	**−65.9**	NRBT	NRBT	NRBT	NRBT	NRBT	NRBT
M	−8.3	−41.7	**−50**	**−50**	−33.3	−33.3	0	NRBT	NRBT
N	−18.5	−38.5	−47.7	**−50.8**	**−50.8**	**−72.3**	**−86.2**	NRBT	NRBT
O	−35.6	**−55.6**	**−71.1**	**−68.9**	NRBT	NRBT	NRBT	NRBT	NRBT
P	0	57.1	−42.9	**−57.1**	**−57.1**	**−57.1**	**−71.4**	NRBT	NRBT
Q	−37.5	**−75**	**−75**	**−50**	**−50**	**−50**	NRBT	NRBT	NRBT
R	66.7	60	0	53.3	−33.3	**−66.7**	**−60**	−20	53.3
S	−31.3	**−50**	**−50**	−31.3	−37.5	−37.5	−37.5	**−50**	−43.8
T	−39.1	−43.5	−52.2	−21.7	**−69.6**	**−73.9**	**−73.9**	**−60.9**	−43.5

Bold values represent patients with ≥50% reduction from baseline in CAILS.
Two patients terminated the study protocol early as a result of skin irritation reactions associated with chlormethine (patients M and R). Other reasons for discontinuation were concurrent illness (patient K), concurrent chemotherapy (patient L), lack of efficacy (patient N), and loss to follow-up (patient Q).
Abbreviations: CAILS = Composite Assessment of Index Lesion Severity; NRBT = not counted as responders using by-time analysis approach; ORR = overall response rate.

Supplemental Table 5 Patients With Early, Intermittent, and Late Responses

CAILS, Percentage Change From Baseline (Visits 1 Through 9)								
Examples of Early Response								
1	2	3	4	5	6	7	8	9
−52.5	**−57.6**	**−64.4**	**−72.9**	**−57.6**	−59.3	**−57.6**	**−69.5**	**−83.1**
−44.4	**−66.7**	**−58.3**	**−83.3**	**−72.2**	**−75**	**−72.2**	**−63.9**	**−69.4**
−50	**−100**	**−100**	**−100**	**−100**	**−100**	**−100**	**−100**	**−100**
−25	**−50**	**−100**	**−100**	**−100**	**−100**	**−100**	**−100**	**−100**
−20	**−100**	**−100**	**−100**	**−100**	**−100**	**−100**	**−100**	**−100**
Examples of Intermittent Response								
1	2	3	4	5	6	7	8	9
−32.4	**−51.4**	**−67.6**	**−70.3**	**−56.8**	−45.9	−48.6	**−62.2**	**−62.2**
−19.4	−29	−22.6	−19.4	**−80.6**	−35.5	**−74.2**	**−90.3**	**−90.3**
−10.3	−36.8	−36.8	**−51.5**	−41.2	**−60.3**	**−58.8**	**−55.9**	**−70.6**
−20	−40	−24	**−52**	**−76**	**−68**	−48	**−72**	**−100**
−48	**−52**	NRBT	−48	**−72**	**−76**	**−76**	**−100**	**−100**
Examples of Late Response								
1	2	3	4	5	6	7	8	9
−28.6	−32.1	−35.7	−28.6	−21.4	−35.7	**−75**	**−71.4**	**−64.3**
−27.8	−38.9	−22.2	−22.2	−27.8	−33.3	−44.4	**−55.6**	**−100**
2.9	4.4	−19.1	−23.5	−26.5	**−60.3**	**−58.8**	**−57.4**	**−57.4**
−20	−16	−34	−32	−32	−36	**−60**	**−60**	**−100**
33.3	57.1	57.1	76.2	57.1	**−52.4**	**−66.7**	**−76.2**	**−100**

Bold values represent patients with ≥50% reduction from baseline in CAILS.
Abbreviations: CAILS = Composite Assessment of Index Lesion Severity; NRBT = not counted as responders using by-time analysis approach.

Supplemental Table 6 Final Visit Response

CAILS, Percentage Change From Baseline (Visits 1 Through 9)								
Examples of Final Visit Unconfirmed Response								
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
17.2	−10.3	−55.2	−27.6	−24.1	−20.7	−13.8	6.9	**−93.1**
−6.3	37.5	25	37.5	18.8	12.5	−6.3	−6.3	**−100**
33.3	13.3	0	−13.3	13.3	20	0	13.3	**−100**

Bold values represent patients with ≥50% reduction from baseline in CAILS.
Abbreviations: CAILS = Composite Assessment of Index Lesion Severity.