Evaluation of Symptom and Side Effect Bother in Cutaneous T-cell Lymphoma Patients Treated with Mogamulizumab or Vorinostat

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Abstract

Background: Cutaneous T-cell lymphomas, including mycosis fungoides or Sézary syndrome, are rare non-Hodgkin lymphomas that can be serious and life-threatening with significant morbidity and impaired quality of life. The purpose of this study was to determine whether patient-reported outcome individual items on skin symptoms and toxicity bother show significant treatment differences for patients with mycosis fungoides or Sézary syndrome.

Methods: Health-related quality of life was assessed during the MAVORIC clinical trial of mogamulizumab for treatment of cutaneous T-cell lymphomas compared to vorinostat using the Skindex-29 (measures emotions, symptoms, and functioning) and Functional Assessment of Cancer Therapy – General (FACT-G) (assesses physical, social/family, emotional, and functional well-being). Pruritus was assessed with the ItchyQoL (measures symptoms, functioning, and emotions) and Likert Scale for level of itching. Item analyses used longitudinal generalized estimation equations of the post-baseline, treated period assessments to estimate likelihood of improvement. Forest plots of odds ratios (OR) characterized the likelihood of a 1- and 2-grade categorical improvement on individual items.

Results: Patients treated with mogamulizumab were more likely to observe a 1-grade improvement in painful skin (OR = 1.74, CI: 1.180–2.572), irritated skin (OR = 1.34, CI: 0.909–1.978), lack of energy (OR = 2.20, CI: 1.461–3.309), side effect bother (OR = 1.28, CI: 0.810–2.020), and general cancer pain (OR = 1.38, CI: 0.922–2.063). Patients treated with mogamulizumab were more likely to observe a 2-grade improvement in burning or stinging skin (OR = 1.62, CI: 1.013–2.591, $P < 0.05$) and more likely to observe improvement in painful skin (OR = 1.78, CI: 1.045–3.021, $P < 0.05$).

Conclusions: Single item analyses suggest a mogamulizumab symptom benefit during treatment compared to vorinostat for items on the skin symptoms of Skindex-29 and toxicity bother items of FACT-G.

Trial registration: NCT01728805

Background

Cutaneous T-cell lymphomas (CTCLs) represent a rare form of non-Hodgkin lymphomas that primarily affects the skin, presenting as patches, plaques, tumors or erythroderma, and may be associated with severe pruritus [1, 2]. The two most common subtypes, accounting for approximately 50% of all CTCL, are mycosis fungoides (MF) and Sézary syndrome (SS) [3]. MF is a mature T-cell non-Hodgkin lymphoma with presentation in the skin and potential involvement of the nodes, blood, and viscera. SS is defined as an erythrodermic CTCL with a leukemic involvement of malignant T-cells clonally matching that in the skin. In contrast to patch/plaque MF, SS is much more symptomatic, has a lower potential for remission, and lower expected survival. Advanced CTCL can be a serious, life-threatening disease associated with significant morbidity and impaired health-quality of life (HRQoL) [4–6].

MAVORIC was the first pivotal trial in CTCL to use progression free survival (PFS) as a primary endpoint. It was also the largest randomized study to compare systemic therapies in MF and SS subtypes of CTCL. MAVORIC evaluated the efficacy of the anti-CC chemokine receptor type 4 (CCR4)-targeted antibody, mogamulizumab, for the treatment of MF or SS compared to that of vorinostat (NCT01728805) [7]. Mogamulizumab had significantly better PFS compared to vorinostat (median PFS of 7.7 months for mogamulizumab and 3.1 months for vorinostat [$P < 0.0001$]). Global overall response rate was significantly improved in the patients randomized to mogamulizumab at 28.0% versus 4.8% for vorinostat ($P < 0.0001$). The most common treatment-emergent adverse events (TEAEs) in the mogamulizumab arm included infusion-related reactions (33.2% versus 0.5% in the vorinostat arm) and drug rash (23.9% versus 0.5%). Common TEAEs reported more often with vorinostat included diarrhea (61.8% versus 23.4% in the mogamulizumab arm), nausea (42.5% versus 15.2%), thrombocytopenia (30.6% versus 11.4%), dysgeusia (29.0% versus 3.3%), and increased blood creatinine (28.0% versus 3.3%). Preplanned analyses of patient reported outcomes found mogamulizumab had a greater improvement in HRQoL measures at the 6-month assessment than did vorinostat treated patients ($P > 0.05$) [7].

The objective of this analysis was to determine whether individual items related with skin symptoms and safety profile on patient-reported outcome measures show significant differences over the course of treatment for patients with CTCL.

Methods

Details of the study design have been published (NCT01728805) [7]. Briefly, this was a large, open-label, multi-center, randomized, Phase 3 study that compared mogamulizumab versus vorinostat in 372 patients who had failed ≥ 1 prior systemic therapy for MF or SS (Figure 1). Eligible patients were at least 18 years of age, had an Eastern Cooperative Oncology Group performance score of ≤ 1 , and had adequate hematologic, hepatic, and renal function. Patients were randomly assigned (1:1) to mogamulizumab (1.0 mg/kg intravenously weekly for 4 weeks of the first 28-day cycle, then on Days 1 and 15 of subsequent cycles) or vorinostat (400 mg daily). Stratification was by cutaneous T-cell lymphoma subtype (MF versus SS) and disease stage (IB–II versus III–IV).

Study Instruments

Health-related quality of life was assessed using the Skindex-29 and Functional Assessment of Cancer Therapy – General (FACT-G). Evaluation of pruritus was assessed using the ItchyQoL and the Pruritus Likert scale. The Skindex-29 and FACT-G were evaluated at Baseline (Cycle 1, Day 1), end of Cycle 1, then every 8 weeks (ie, end of Cycle 3, 5, ..., 25) through Cycle 25, and at the End of Treatment visit. The ItchyQoL and the Pruritus Likert scale were evaluated every 4 weeks at each cycle. Measurements at the end of Cycle 1 were defined as the latest value obtained from Cycle 1 (Days 26 through 28) or Cycle 2 (Day 1). Measurements at the end of Cycle X, where $x = 1, 2, 3, \dots, 25$ were defined as the latest value

obtained from Cycle X (Days 26 through 28), Cycle X every 8 weeks, or Cycle (X+1) Day 1. Clinical HRQoL measurements included Skindex-29, FACT-G, and two measures of pruritus (a Likert Scale and ItchyQoL; not included in this presentation).

The Skindex-29 is a validated instrument to measure the effect of skin disease on HRQoL [8]. It is composed of 29 items assessing three domains: emotions, symptoms, and functioning. The items are scored on a 5-point Likert-type scale (never, rarely, sometimes, often, or all the time). Responses to each item are transformed to a linear scale of 100 (where 0 = never, 25 = rarely, 50 = sometimes, 75 = often, and 100 = all the time) for the purpose of scale score calculation. A scale score is the mean of a subject's responses to the items in a given scale and the composite Skindex-29 score is calculated as the average of the three scale scores to measure the overall impact on HRQoL. Higher scores indicate a higher impact of skin disease on emotions, symptoms, and functioning.

The FACT-G questionnaire is used to assess effects of underlying disease and its treatment on patient HRQoL [9]. As a generic cancer-related core, the FACT-G includes the 27-item FACT-General (FACT-G) to assess symptoms and treatment related effects impacting physical well-being (seven items), social/family well-being (seven items), emotional well-being (six items), and functional well-being (seven items). Scores for the domain subscales can be combined to produce a FACT-G total score, which provides an overall indicant of generic HRQoL. The recall period is 1 week. Each question is assessed on a 5-point Likert scale: 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much. The FACT-G scoring guide identifies those items that must be reversed before being added to obtain subscale totals. Negatively stated items are reversed by subtracting the response from "4." After reversing proper items, all subscale items are summed to a total, which is the subscale score. For scales and symptom indices, higher scores represent better HRQoL.

Statistical Analysis

The analytic population was defined as patients with clinical outcome assessments at any time point within the intent-to-treat population. These exploratory post-hoc analyses were performed using the Statistical Analysis System Version 9.4.

Analyses on identified individual symptom items of Skindex-29 and toxicity items of FACT-G were conducted using descriptive, categorical change from baseline as well as longitudinal generalized estimation equations (GEE) of the post-baseline, treated period assessments (through Cycles 5 or 6, depending on collection schedule) for these items. Generalized estimation equations of logistic regression models were used to estimate the likelihood of improvement. The GEE model of an "improved" binary event was regressed on fixed effects of treatment arm, time point, and their interaction terms, as well as an R-side random effect with autoregressive correlation structure to account for repeated measures. Model results were used to generate the odds ratios and the 95% confidence interval to compare the likelihood of "improvement" between treatment groups. The proportion of patients

experiencing a 1-grade and 2-grade improvement is presented in terms of frequency and percentage by treatment arm.

Forest plots of odds ratios (OR) and associated confidence intervals (CI) from the GEE analyses were generated to characterize the likelihood of a 1-grade (eg, improvement by 1 category on the verbal response scale) and 2-grade (eg, improvement by two categories on the verbal response scale) categorical improvement on individual items for patients treated with mogamulizumab compared to vorinostat during the first 6 cycles of therapy.

Results

Treatment groups were balanced with respect to demographic and physical characteristics, disease characteristics, and previous therapies for MF/SS without statistically significant differences (Table 1).

Table 1

Baseline Characteristics

Demographic or Clinical Item	Mogamulizumab (n = 186)	Vorinostat (n = 186)	Total (N = 372)
Age group			
< 65	99 (53.2%)	89 (47.8%)	188 (50.5%)
≥ 65	87 (46.8%)	97 (52.2%)	184 (49.5%)
Gender			
Female	77 (41.4%)	79 (42.5%)	156 (41.9%)
Male	109 (58.6%)	107 (57.5%)	216 (58.1%)
Race			
Black/African American	24 (12.9%)	13 (7.0%)	37 (9.9%)
White	125 (67.2%)	135 (72.6%)	260 (69.9%)
Other	37 (19.9%)	38 (20.4%)	75 (20.2%)
Disease type			
MF	105 (56.5%)	99 (53.2%)	204 (54.8%)
SS	81 (43.5%)	87 (46.8%)	168 (45.2%)
Disease stage			
IB or II	68 (36.6%)	72 (38.7%)	140 (37.6%)
III or IV	118 (63.4%)	114 (61.3%)	232 (62.4%)
Blood involvement			
Yes	123 (66.1%)	122 (66.3%)	245 (66.2%)
No	63 (33.9%)	62 (33.7%)	125 (33.8%)
Missing/no response ^a	0	2	2
Region			
US	98 (52.7%)	103 (55.4%)	201 (54.0%)
Japan	9 (4.8%)	6 (3.2%)	15 (4.0%)
Rest of World ^b	79 (42.5%)	77 (41.4%)	156 (41.9%)

Demographic or Clinical Item	Mogamulizumab (n = 186)	Vorinostat (n = 186)	Total (N = 372)
Abbreviations: MF = mycosis fungoides; SS = Sézary syndrome; US = United States			
^a Percent missing is overall by treatment group and are not included in the calculation of response proportions.			
^b European Union and Australia.			

Data demonstrated that subjects treated with mogamulizumab more often showed an improvement in or no worsening of their HRQoL versus those treated with vorinostat (OR > 1.0). Patients treated with mogamulizumab were more likely to observe a 1-grade improvement in painful skin (OR = 1.74, CI: 1.180–2.572), irritated skin (OR = 1.34, CI: 0.909–1.978), lack of energy (OR = 2.20, CI: 1.461–3.309), side effect bother (OR = 1.28, CI: 0.810–2.020), and general cancer pain (OR = 1.38, CI: 0.922–2.063) within 6 cycles of therapy (Figure 2A). Patients treated with mogamulizumab were 62% more likely to observe a 2-grade improvement in burning or stinging skin (OR = 1.62, CI: 1.013–2.591, P < 0.05) and 78% more likely to observe this level of improvement in painful skin (OR = 1.78, CI: 1.045–3.021, P < 0.05) within 6 cycles of therapy (Figure 2B). While not statistically significant, mogamulizumab patients were 60% more likely to report 2-grade improvement in side effect bother associated with treatment (OR = 1.60, CI: 0.85–3.009, P < 0.05) within 5 cycles of therapy.

The single item descriptive and proportion analysis of 1-grade and 2-grade improvement at Cycle 5 from baseline favors mogamulizumab compared with vorinostat (Table 2). Data demonstrate that subjects treated with mogamulizumab more often showed an improvement in or no worsening of their quality of life versus those subjects treated with vorinostat. For the 1-grade improvement, mogamulizumab-treated patients had significant improvements versus vorinostat for the items: skin hurts (P = 0.02); bothered by side effects (P = 0.01); and lack of energy (P = 0.05). For the 2-grade improvement, mogamulizumab-treated patients had significant improvements versus vorinostat for the items: skin hurts (P < 0.05) and pain (P = 0.02).

Table 2
Single Item Analysis of Improvement at Cycle 5 or 6 from Baseline

Item Name	Mogamulizumab ^a	Vorinostat ^a	P-value
1-grade improvement			
SKINDEX-29: My skin condition bleeds	38 (40.9%)	20 (37.7%)	0.7106
SKINDEX-29: My skin is irritated	56 (59.6%)	26 (49.1%)	0.2176
SKINDEX-29: My skin itches	53 (56.4%)	30 (56.6%)	0.9793
SKINDEX-29: My skin condition burns or stings	49 (52.1%)	27 (50.9%)	0.8903
SKINDEX-29: My skin hurts	53 (56.4%)	19 (36.5%)	0.0216
FACT-G: I am bothered by side effects of treatment	32 (33.3%)	7 (14.0%)	0.0122
FACT-G: I have pain	43 (43.4%)	15 (28.8%)	0.0799
FACT-G: I have nausea	10 (10.1%)	4 (7.4%)	0.7713
FACT-G: I have a lack of energy	43 (43.9%)	15 (27.8%)	0.0505
2-grade improvement			
SKINDEX-29: My skin condition bleeds	15 (16.1%)	3 (5.7%)	0.0721
SKINDEX-29: My skin is irritated	32 (34.0%)	14 (26.4%)	0.3382
SKINDEX-29: My skin itches	28 (29.8%)	11 (20.8%)	0.2336
SKINDEX-29: My skin condition burns or stings	29 (30.9%)	14 (26.4%)	0.5703
SKINDEX-29: My skin hurts	26 (27.7%)	7 (13.5%)	0.0495
FACT-G: I am bothered by side effects of treatment	14 (14.6%)	2 (4.0%)	0.0562
FACT-G: I have pain	22 (22.2%)	4 (7.7%)	0.0249
FACT-G: I have nausea	3 (3.0%)	1 (1.9%)	1.0000
FACT-G: I have a lack of energy	11 (11.2%)	4 (7.4%)	0.5754
^a Percentages are based on those who adhered or remained in the study up until Cycle 5 or 6.			

Discussion

Patient reported outcome measures included in this study were multi-item scales that represent uni- or multi-dimensional concepts related to symptomatic manifestation, cancer-related quality of life, and tolerability. Interpretation of the individual items further supports the overall interpretability of the domain-level scores on the respective domains. More specifically, while the Skindex items represent the

core skin symptom manifestations (eg, bleeding, irritation, itching, burning, or hurting), the individual symptoms may respond to treatment differently and should be assessed individually.

Understanding the specific items that are contributing most to the total score is important in evaluating treatment efficacy as the individual items represent cardinal components of HRQoL. By isolating each item in a categorical analysis and setting a threshold for meaningful categorical change, which in this analysis was 1-grade change threshold on the respective 5-point Skindex and 4-point FACT-G verbal response scales, analogous to 20% and 25% categorical improvement, with sensitivity testing using a more conservative 2-grade change (40% and 50% categorical improvement), it is possible to determine how the overall symptoms move on the total score, thus enhancing the interpretability [10,11].

In a previous study, mogamulizumab was found to gain a greater improvement in HRQoL measures at the 6-month assessment than did vorinostat [7]. In the present analysis, we confirm that mogamulizumab was able to induce a significant greater improvement on individual items related with skin symptoms and safety profile in the same patient cohort.

These results provide a detailed account of the magnitude at which HRQoL was affected by treatment with mogamulizumab.

A limitation of the analysis is a lack of data in the later cycles of treatment, such as post-progression, as well as reasons for missing PRO data. Further data on durability of symptomatic and functional improvements in HRQoL and influence of progression on these patient outcomes could prove valuable for considering the long-term ramifications of treatment selection. Future prospective studies using single-item analyses should focus on long-term changes in HRQoL.

Conclusion

Single item analyses provide detailed information on the cumulative probability of categorical improvement of individual items on the skin symptoms of Skindex-29 and the toxicity bother items of FACT-G. These results suggest a symptom benefit of mogamulizumab over the course of treatment compared to vorinostat.

Abbreviations

CI – confidence interval; CTCL, cutaneous T-cell lymphoma; HRQoL – health related quality of life; LCL – lower confidence limit; MF – mycosis fungoides; OR – odds ratio; PFS – progression free survival; SS – Sézary syndrome; TEAEs – treatment-emergent adverse events; UCL – upper confidence limit; US – United States

Declarations

Ethics Approval

All study procedures were in accordance with ethical standards of the 1964 Helsinki Declaration and its later amendments, relevant laws, institutional guidelines, and approved by an institutional review board (IRB). The protocol was reviewed and approved by institutional review boards or independent ethics committees at each study center.

Participant Consent for Publication

Not applicable

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Competing Interests

KD is an employee of Kyowa Kirin Pharmaceutical, Inc. SH, PP, PQ, AH, LF, and MD declare no competing interests.

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Authors' contributions

All authors contributed to the conception, analysis, interpretation, and revised manuscript content. All authors read and approved the final manuscript.

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Figures

Figure 1

MAVORIC Study Design Abbreviations: IV = intravenous; MF = mycosis fungoides; PD = progression of disease; PO = orally; SS = Sézary syndrome; US = United States

A. 1-Grade Improvement

B. 2-Grade Improvement

Figure 2

Probability of Observing Categorical Improvement on Individual Items Through Cycle 5 or 6
Abbreviations: FACT-G = Functional Assessment of Cancer Therapy – General; LCL = lower confidence limit; OR = odds ratio; UCL= upper confidence limit