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Characterizing Fatigue Associated with Sunitinib in Patients with Metastatic Renal Cell Carcinoma

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INTRODUCTION

- In advanced cancer, fatigue is the most frequent patient-endorsed priority symptom[1] and may adversely impact quality of life because of its effects on physical functioning, social functioning, activity level, and emotional well-being.
- Fatigue is also a common cancer adverse event (AE) associated with targeted therapies.[2,3]
- Sunitinib malate (SUTENT®), an orally administered multitargeted inhibitor of vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and other receptor tyrosine kinases, is a globally approved treatment for advanced renal cell carcinoma (RCC).
- Fatigue is the one of the most common sunitinib-associated AEs, reported in approximately 40–70% of patients with advanced RCC treated with sunitinib in clinical trials.[4–7].
- A better understanding of the pattern of sunitinib-associated fatigue may allow more timely and effective intervention to help manage fatigue and minimize its impact on patient quality of life related to sunitinib treatment.
- We investigated patient-reported and physician-assessed fatigue using data from two clinical trials of sunitinib in patients with advanced RCC.

OBJECTIVES

- To investigate the time course of patient-reported fatigue and physician-assessed AE fatigue across cycles in patients receiving sunitinib for treatment of advanced RCC.
- To compare the change between adjacent visits in patient-reported fatigue in patients receiving sunitinib on two different dosing schedules.
- To provide a descriptive overview of the patient fatigue experience while undergoing sunitinib treatment.

METHODS

Study Designs and Treatment

- These retrospective analyses used data from patients with advanced RCC who received sunitinib in two clinical trials.[4–6]
- Study 1 was a randomized phase III study comparing sunitinib with interferon-α in treatment-naïve patients with advanced RCC;[4,5] only patients assigned to receive sunitinib (n=375) were included in analyses reported here. For these patients, treatment comprised sunitinib 50 mg once-daily for 4 consecutive weeks followed by 2 weeks off treatment (Schedule 4/2), in repeated 6-week cycles.
- Study 2 was a phase II study comparing sunitinib administered on two different dosing schedules as first-line treatment of advanced RCC.[6] Patients were randomized to receive sunitinib at either 50 mg once daily on Schedule 4/2 (n=146) or 37.5 mg on a continuous once-daily dosing (CDD) schedule (n=146). In both arms, a treatment cycle was defined as 6 weeks.
- Treatment in each study was continued until disease progression, significant toxicity, or withdrawal. In Study 2, the maximum treatment period was 2 years; however, responding patients were given the opportunity to roll over into a continuation protocol.

Patient Eligibility

- Key eligibility criteria for both studies included:
  - age 18 years or older
  - histologically confirmed advanced RCC (Study 1: metastatic; Study 2: locally recurrent or metastatic) with a clear-cell component
  - presence of measurable disease
  - no known brain metastases
  - Eastern Cooperative Oncology Group performance status 0 or 1 (Study 1) or Karnofsky performance status ≥70% (Study 2)
  - adequate organ function.

Fatigue Assessments

- In both studies, fatigue was self assessed by patients as part of the Functional Assessment of Cancer Therapy-Kidney Symptom Index–Disease-Related Symptoms (FKSI–DRS) subscale.[8,9]
  - Patients completed the questionnaire on days 1 and 28 (Study 1) or days 1 and 29 (Study 2).
  - Within the FKSI–DRS subscale, the item "I feel fatigued" was scored from 0 (very much) to 4 (not at all).
- AEs, including fatigue, were monitored throughout each study and were graded on a scale from 1 (lowest) to 4 (highest) by treating physicians using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0.

Analytical Methods

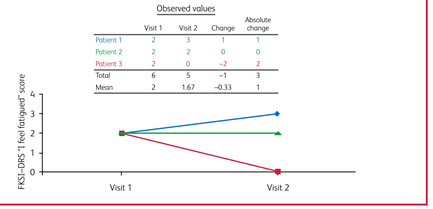
Study 1

- To study the profile of fatigue over time, two models were used, which included all available longitudinal data for every patient; both models were applied to the FKSI–DRS item "I feel fatigued" and to the AE fatigue.
  - In the repeated measures model, time was used as a categorical predictor, meaning that no functional relationship was imposed between outcome and time.
    - In this model, FKSI scores were averaged for each patient by cycle. Because of the small number of observations, data from cycles 22 to 30 were collapsed and represented as one (mean) value per patient.
  - In the random intercept-slope model, time was used as a continuous predictor, i.e., a linear relationship was imposed between outcome and time.
- Reported severity grades for AE fatigue were averaged by cycle for each patient. A value of 0 was assigned if a patient did not report fatigue as an AE during a cycle.

Study 2

- A repeated measures analysis comparing the affect of Schedule 4/2 and CDD on fatigue over time showed no significant difference between the two dosing regimens. However, to address the observed up-and-down pattern in mean fatigue scores with Schedule 4/2, two analyses were performed to examine whether patients on this schedule experienced greater change in patient-reported fatigue (the FKSI–DRS item "I feel fatigued") between adjacent visits (day 1 to day 29 within a cycle and day 29 to day 1 of the next cycle) than patients assigned to CDD.
  - The first analysis compared the absolute values of the mean changes between visits at the group level.
  - The second analysis drilled down to the individual patient level and compared the mean of the absolute changes between visits for individual patients.
  - An illustration of the mean change for the population, the mean absolute change for individual patients and the definition of absolute value is presented in Figure 1.
- The two-sample t-test was used to assess the difference between the treatment arms in both analyses.

Figure 1. Three individual patient trajectories for changes in FKSI–DRS "I feel fatigued" scores illustrating the mean change for a population and the mean absolute change for individual patients. Higher scores indicate better outcome (i.e., less fatigue).



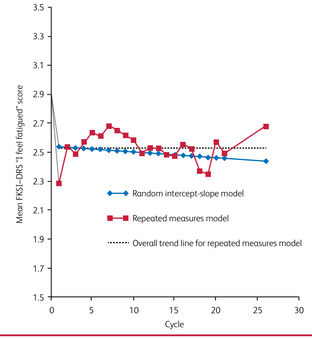
RESULTS

Study 1

Modeling the Time Course of Patient-Reported Fatigue

- Results from the repeated measures model with the FKSI–DRS item "I feel fatigued" (Figure 2) showed that:
  - the initial increase in patient-reported fatigue was worst during the first cycle
  - mean fatigue values for subsequent cycles were numerically better than (and for most comparisons, also statistically different from) the value in the first cycle.
- Results from the random intercept-slope model showed that fatigue was stable over time (after the initial increase in fatigue during the first cycle); the overall trend (slope) for the FKSI–DRS item "I feel fatigued" was not statistically different from zero (Figure 2).
- For illustrative purposes, a regression line (or overall trend line) was fitted to the results obtained with the repeated measures model. This demonstrated that the repeated measures model results were consistent with those obtained using the random intercept-slope model (Figure 2), that is, showing no increase in fatigue.

Figure 2. Study 1: Modeling the time course of the FKSI–DRS item "I feel fatigued" using the repeated measures and random intercept-slope models. Higher scores indicate better outcome (i.e., less fatigue).



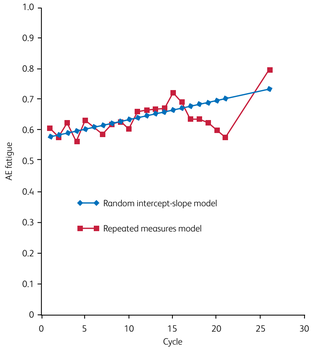
Modeling the Time Course of Physician-Assessed AE Fatigue

- Results from the repeated measures model showed some fluctuations in AE fatigue over time (Figure 3), but differences were small; pair-wise comparisons of the cycle mean values were not statistically significant (with one exception), indicating that the mean values at every cycle were actually not different from one other.
- Results from the random intercept-slope model showed that the overall trend (or slope) for AE fatigue was not statistically different from zero, indicating no significant change in AE fatigue over time (Figure 3).

Study 2

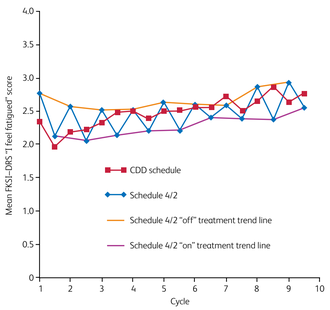
- During the first nine cycles of treatment, 133 patients (91%) and 132 patients (90%) assigned to the Schedule 4/2 and CDD schedule arms, respectively, completed at least two patient-reported outcomes measures.
- Figure 4 displays the observed mean scores for the FKSI–DRS item "I feel fatigued" from start to end of each cycle by treatment arm.
  - The figure suggests the possibility of an "on–off" effect in the Schedule 4/2 arm, with patients reporting less fatigue at the beginning of each treatment cycle (following the 2-week off treatment period) when compared to fatigue at day 29 following the 4-week on treatment period.

Figure 3. Study 1: Modeling the time course of the AE fatigue using the repeated measures and random intercept-slope models.



- In the first analysis, based on the absolute value of the group mean changes, the mean (standard deviation) of the changes between adjacent visits was 0.40 (0.13) and 0.14 (0.10) for the Schedule 4/2 and CDD arms, respectively. The two-sample t-test showed $t(32) = 6.82$ and $P<0.001$, indicating significantly greater fluctuation between adjacent visits with Schedule 4/2 than with CDD.
- In the second analysis, which drilled down to the individual patient level by using their absolute changes between visits, the mean (standard deviation) of the changes between visits was 0.86 (0.58) and 0.67 (0.56) for the Schedule 4/2 and CDD arms, respectively. The two-sample t-test showed $t(263) = 2.78$ and $P=0.006$, again, indicating significantly greater fluctuation between adjacent visits with Schedule 4/2 than with CDD.

Figure 4. Study 2: Observed mean FKSI–DRS "I feel fatigued" scores from start to end of each cycle by treatment arm. Higher scores indicate better outcome (i.e., less fatigue).



CONCLUSIONS

- Compared with baseline assessment, patients reported worse fatigue during the first cycle of sunitinib treatment; however, less fatigue was reported in all consecutive treatment cycles. The overall trend was stable, showing no significant increase in reported fatigue after the first follow-up assessment.
  - Physician-assessed fatigue, using the NCI CTCAE grading system, suggested no overall change in the AE fatigue over time for patients treated with sunitinib.
- Schedule 4/2 was associated with an "on–off" effect, with patients reporting more fatigue on day 29 of each cycle following 4 weeks on treatment and less fatigue on day 1 of each cycle following the 2-week off-treatment period.

CLINICAL IMPLICATIONS

- The finding that sunitinib-related fatigue occurs early (during the first treatment cycle), but is less pronounced in following cycles, may have been reported anecdotally by some clinicians experienced with sunitinib, but this is the first formal analysis to confirm this observation.
  - This can be used to enhance education and preparedness among patients who have been prescribed sunitinib for the treatment of advanced RCC.
  - This highlights the importance of setting up-front expectations regarding the fatigue experience so that patients do not prematurely withdraw from treatment, failing to take advantage of potential clinical benefit with sunitinib.[10]
- The observation of an "on–off" effect for fatigue with Schedule 4/2, combined with the discovery of a greater change in fatigue between adjacent visits using this schedule, may have been intuitive, but this is the first time that such data have been reported for sunitinib both across and within treatment cycles.
  - This highlights the time points within a treatment cycle that patients are most vulnerable to fatigue and emphasizes the importance of monitoring fatigue when the patient is both on and off treatment in order to capture the patient's overall experience within a cycle.
  - A better awareness of this fatigue pattern may better enable the clinician to effectively manage any additional contributing factors, such as thyroid abnormalities, anemia, cardiac function, or depression.
- Finally, the overview of the patient fatigue experience with sunitinib, made possible by these analyses, may lead to improved implementation of fatigue-specific coping strategies (e.g., rescheduling activities from the beginning of treatment, and from on- to off-treatment periods)[11] by both the patient and those involved with his/her care, thus motivating the patient to remain on sunitinib therapy in order to maximize therapeutic benefit.

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