

ARTICLE

Patient-Level Adverse Event Patterns in a Single-Institution Study of the Multi-Kinase Inhibitor Sorafenib

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Novel characterization of patterns of adverse events (AEs) of kinase inhibitors (KIs) could reveal new insights on human molecular physiology and methods to improve the therapeutic index of KIs. Incidence and severity of AEs for each of 157 patients enrolled in sorafenib clinical trials were determined for three clinically relevant treatment intervals: weeks 0–3, weeks 3–7, and after 7 weeks. The most common within patient co-occurrences were mucositis with dermatologic events: hand-foot syndrome (HFS; odds ratio [OR] = 4.36; $p = 0.0017$) and rash (OR = 5.32; $p < 0.001$). Prevalence of severe: alopecia ($p = 0.02$), diarrhea ($p < 0.001$), and fatigue ($p = 0.005$) increased over the course of therapy. Incidence of HFS (60%) and diarrhea (25%) increased up to a minimum steady-state concentration (approximately 5 mcg mL⁻¹) and plateaued thereafter. Common AEs of sorafenib occur in distinct temporal and tissue distribution patterns and this analysis identified unrecognized relationships among mechanism-dependent and independent effects of a KI.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Sorafenib is a small molecule kinase inhibitor (KI) with relative potency for inhibition of c-Raf and the platelet-derived growth factor and vascular endothelial growth factor receptor kinases. It has been approved for the treatment of patients with hepatocellular, renal, and thyroid carcinoma. It has a population spectrum of adverse events (AEs) with unique elements and overlap with other KIs.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ Which common distinct AEs occur together.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE?

✓ Total sorafenib concentrations in plasma above a specific threshold were associated with peak incidence of hand-foot syndrome (HFS) and diarrhea, but other AEs did not have such quantile relationships.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✓ This method of analysis may provide new insights on the mechanistic basis for KI toxicities and improve the therapeutic index for these drugs.

Kinase inhibitors (KIs) have improved therapeutic outcomes for patients with cancer. Initially considered “targeted therapy” intended to inhibit specific aberrantly activated signaling pathways in cancer, most agents are competitive reversible inhibitors for the adenosine triphosphate binding site in protein kinases. Consequently, these agents typically inhibit multiple kinases with multiple downstream therapeutic antiproliferative, antiangiogenic, and proapoptotic effects.^{1,2}

These agents have been developed for particular indications based on relative selectivity for specific sets of kinases. However, KIs have routinely caused patients unanticipated

adverse events (AEs). Examining the relationships among specific pharmacological effects, signaling pathways, and organ functions provides a unique opportunity. Phase III trials of anticancer agents typically report the incidence of more severe AEs in summary tables. Closer examination of the temporal and co-occurrence patterns of these common AEs could lead to new testable hypotheses regarding previously unrecognized cellular and molecular determinants of kinase inhibitor-induced organ dysfunction. Through better understanding of these mechanistic relationships, investigators developing new KIs should achieve better therapeutic indexes for patients.

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Sorafenib (Nexavar) was originally developed to target the Raf kinases,³ but *in vitro* kinase binding assays have shown that sorafenib binds to many other kinase targets, including platelet-derived growth factor receptors, fms-related tyrosine kinase 3, vascular endothelial growth factor receptors (VEGFRs), and c-KIT.^{2,4} Its broad preclinical and clinical activity may be attributed to its multiple molecular targets. Sorafenib is indicated for treatment of hepatocellular, renal, and thyroid carcinoma. Sorafenib might also have therapeutic benefit in leukemia with aberrant fms-related tyrosine kinase 3 activation.⁵ The US Food and Drug Administration label lists the most common AEs occurring in over 20% of patients on sorafenib treatment as fatigue, diarrhea, nausea, rash, hand-foot syndrome (HFS), alopecia, weight loss, anorexia, and abdominal pain.⁶ Other less common, dose-limiting AEs include: cardiac ischemia and infarction, hypertension, hemorrhage, and gastrointestinal perforation. Common laboratory abnormalities include: hypophosphatemia, elevated lipase and amylase, and hypoalbuminemia. Some AEs are class effects with clear mechanistic basis (e.g., cardiovascular AEs due to vascular endothelial growth factor/VEGFR inhibition),⁷ some have evidence-based, plausible, but unconfirmed mechanisms (e.g., hand-foot skin reaction),⁸ whereas others have uncharacterized mechanisms (e.g., hypophosphatemia).

These population profiles of AEs and their frequencies provide general descriptive information to infer the therapeutic index of cancer drugs. However, current studies and technologies promise to better predict and personalize therapy for individual patients. Past studies have examined clinical predictors and pharmacological data for specific individual AEs caused by sorafenib.^{9,10} Bioinformatic strategies have been piloted to discover potential molecular mechanisms by which KIs cause various AEs.^{11–13} To better infer the mechanisms of KI-induced AEs, to determine their relationships to drug exposure, and to develop predictive markers for KI-induced AEs, alternative methods of evaluating and reporting the incidence of AEs could also be helpful.

Empirically, individual patients tend to experience specific subsets of the total reported AEs, and we hypothesized that the predictable reproducible patterns of AE manifestation could be identified objectively. The purpose of this investigation was to study the time course and co-occurrence of AEs of one KI, sorafenib, at the individual patient level. Over a 7-year period, our institution enrolled more than 150 subjects on two investigational studies of sorafenib pharmacodynamics (PDs). Patients were treated by a small group of physicians and nurses consistently over this time frame, and AE data were collected prospectively in relatively standardized fashion throughout the course of these investigations. As an initial effort, we determined the patterns of AE co-occurrence and mutually exclusive occurrences over clinically relevant time intervals. We further examined evidence of exposure-toxicity relationships between plasma concentrations of sorafenib and AE occurrence.

METHODS

Patients and trials

Two clinical trials of sorafenib monotherapy enrolled 157 patients with solid tumors at the University of Chicago.

The first trial, conducted from October 2004 to October 2006, examined ambulatory blood pressure monitoring as a PD biomarker of VEGFR pathway inhibition.⁹ The second trial enrolled patients from April 2007 to July 2011 and investigated the effect of dose escalations on safety and PD responses.¹⁴ All patients received the standard dose of 400 mg twice daily through day 7 on trial. Patients underwent clinical evaluations by treating physicians every 2–3 weeks according to protocols for the first 8 weeks of therapy. For patients who remained on study to that point, computed tomography imaging evaluations of tumor burden were also performed. Subjects with stable or responsive disease by Response Evaluation Criteria in Solid Tumors¹⁵ remained on study. All patients with disease progression by Response Evaluation Criteria in Solid Tumors criteria discontinued treatment, and final AE evaluations were completed 30 days later. Both study protocols were approved by the institutional review board of the Biological Sciences Division of the University of Chicago.

AEs were typically recorded by the treating physicians on standardized checklists at the time of each patient evaluation, as were the attributions to sorafenib (by the Naranjo criteria¹⁶). Physicians recorded all AEs consistent with institutional standards for assessments of patients on early phase clinical trials without prespecification. These data and additional clinical chart notes and laboratory assay results were independently reviewed by one of the study authors (S.K.). All AEs were graded systematically according to the Common Terminology Criteria for Adverse Events version 3.¹⁷ When absent or conflicting documentation were identified, treating physicians received queries and provided clarification typically within 10 days of the event.

The details of the study designs were previously described. Briefly, in the first trial, patients received 400 mg twice daily continuously as tolerated. Doses were typically held when grade two or more AEs occurred. Grades 3 and 4 AEs and grade 2 AEs that did not resolve after withholding sorafenib prompted systematic dose reductions as described in the current FDA label. In the second trial, as a dose-escalation and pharmacodynamic biomarker study, all patients discontinued treatment for the second week of treatment and restarted in the third week with the standard dose or an escalated dose of either 400 mg three times daily or 600 mg twice daily. Thereafter, the same procedures for AE evaluation and dose reduction were maintained, except for the patients receiving escalated doses of sorafenib. In those cases, the first dose reduction was to the standard dose, 400 mg twice daily. Sorafenib pharmacokinetics (PKs) have unusually high intraindividual and interindividual variability.^{10,18,19} We therefore performed PK analyses exclusively on patients in the second trial in which sparse, but multiple samples were collected at initial steady-state on treatment days 7 and 8. Briefly, four separate plasma samples were collected at estimated peak and trough concentration time points on each of 2 days. For the purpose of the analyses here, the mean of the four measured concentrations among 56 patients who had complete data was used. As patients with advanced metastatic diseases were enrolled on these studies for the primary purposes of studying blood pressure as a PD biomarker, additional PK sampling was

deemed too onerous to add to ambulatory blood pressure monitoring.

Adverse event data restructuring

We used a multistep procedure to restructure the Common Terminology Criteria for Adverse Events classification and ratings to support our further analysis. Because we focused on sorafenib-attributable AEs, the first step was to exclude all events that were deemed “not related” and “unlikely,” whereas observations that were “possible,” “probable,” and “definitely” attributed to the drug were retained. As novel anticancer drugs are developed, there is a tendency for the same AEs to be classified under different terms; for example, “pruritus” and “itching.” The next step therefore entailed identifying all AE occurrences that were likely to have been documented using multiple terminologies. For instance, similar dermatologic events, such as “rash,” “rash desquamating,” “dermatitis exfoliative not otherwise specified,” and “dry skin” were collapsed into a single category. During this curation step, we re-reviewed the source documents (study charts and clinic notes) to achieve consistent classification of the same events among all patients.

Temporal cut-points

We related the time course and rating of AEs to clinically and scientifically meaningful time intervals: weeks 0 to 3 (initial treatment), weeks 3 to 7 (treatment prior to initial evaluation of disease status), and after week 7 of sorafenib therapy (continued treatment after initial evidence of potential clinical benefit). We were primarily interested in events during the first interval, when early AEs began to emerge but before clinical intervention typically began. These early AEs tend to be the most severe, difficult to predict, and important for subsequent dosage adjustment and administration of supportive agents.^{10,20} Also, focusing on data during this interval allowed us to minimize potential biases of censored data as patients subsequently discontinued their participation in the trial (most commonly for worsening malignant disease). In summary, we analyzed inpatient co-occurrence of AEs at each of the three intervals, but focused on the apparent mechanistic basis for the AEs in the initial treatment interval.

Statistical and exposure-response analyses

Frequencies and distributions of AEs were analyzed with the R statistical software environment version 2.15.1 (**Supplementary Information**). McNemar’s test was performed with Stata 13.1 (StataCorp LP, College Station, TX, USA) and applied to assess increase in prevalence of AEs in the first (0–3 weeks) and the third (after 7 weeks) interval. Pairwise co-occurrences and associations of these AE pairs were performed with Fisher’s exact test, as well as the chi-square association test when sample sizes permitted. All statistical tests were two-sided. The p values < 0.05 were considered to be statistically significant. To determine relationships between AEs and drug exposure, we used the method of Mehrotra *et al.*²¹ The 56 patients with evaluable plasma PKs were divided into quintiles based on minimum measured plasma total sorafenib concentra-

tions at steady state on days 7–8, and the relationship between plasma sorafenib exposure and incidence of AEs was plotted. Figures were generated with GraphPad Prism version 6.00 for Windows (GraphPad Software, La Jolla, CA, USA).

RESULTS

The prevalence of sorafenib AEs in this study was similar to other reported studies. Each of the 157 patients typically experienced six different AEs. The median duration for patients to remain on study therapy was 11 weeks. Consistent with the data supporting the FDA label, the most common AEs ($>10\%$ any grade) attributed to sorafenib (**Figure 1**) were fatigue (64%), HFS (59%), hypophosphatemia (57%), diarrhea (45%), rash (41%), alopecia (35%), anorexia (32%), elevated lipase (27%), mucositis (26%), hypertension (21%), and nausea (21%). The common severe AEs (grade ≥ 2) included hypophosphatemia (50%), HFS (36%), fatigue (20%), and hypertension (18%). There were no grade 4 or 5 AEs attributable to sorafenib.

Temporal patterns of AEs

In part, as a function of the trial designs, most grade ≥ 2 AEs manifested within the first few weeks of the study (**Figure 2**) and were managed with appropriate temporary withholding of sorafenib, dose reductions, or use of supportive care. However, a few of the common AEs had a distinctly different pattern. The prevalence of both total and grade ≥ 2 alopecia (p [total] < 0.001 ; p [severe] = 0.02), diarrhea (p [total] = 0.015; p [severe] < 0.001), and fatigue (p [total] = 0.03; p [severe] = 0.005) increased over the course of treatment.

AE pairwise association tests

We further examined occurrence patterns among AEs that typically appeared in the first time interval and that had potential PK or PD significance, such as HFS, hypophosphatemia, rash, elevated lipase, mucositis, and hypertension. Two different patterns became apparent (**Figure 3**). Mucositis and dermatologic AEs co-occurred more frequently than expected by chance: HFS (**Figure 3a**; odds ratio [OR] = 4.4; $p = 0.0017$; 95% confidence interval = 1.6–14.4) and rash (**Figure 3b**; OR = 5.3; $p < 0.001$; 95% confidence interval = 1.9–15.5).

Sorafenib exposure-adverse event relationships

Sorafenib plasma concentrations at day 8 were collected for 56 patients. Distribution of drug levels on study revealed typical high variability in drug exposure. The median drug concentration was 6.03 mcg mL⁻¹, and the minimum and maximum were 2.2 and 17.1 mcg mL⁻¹, respectively. Per previously published methods of analysis,²¹ patients were divided into five quintiles based on mean plasma concentration at steady state: 2.2–3.6, 4.3–5.8, 6.0–7.3, 7.8–9.1, and 10.3–17.1 mcg mL⁻¹. Threshold exposure-response relationships were detected with HFS and diarrhea (**Figure 4**). The frequency of HFS increased by almost threefold between the second and third group to the peak prevalence of approximately 60%. Only 2 of the 14 patients with steady-state

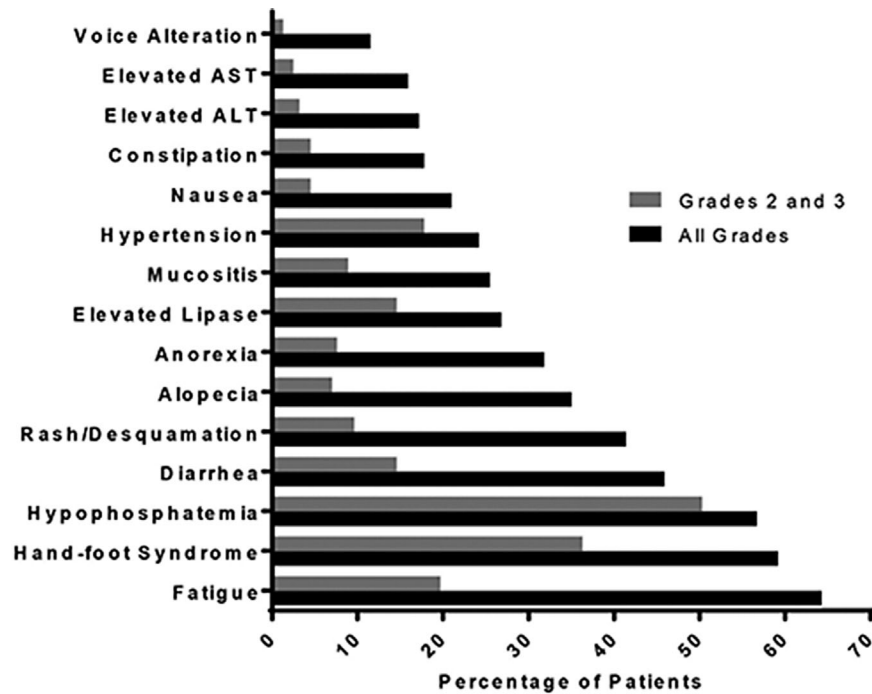


Figure 1 Most common adverse events (AEs) are attributed to sorafenib. Incidence of the most common AEs (>10% any grade) are displayed for all grades in black bars and for grades ≥ 2 in gray bars.

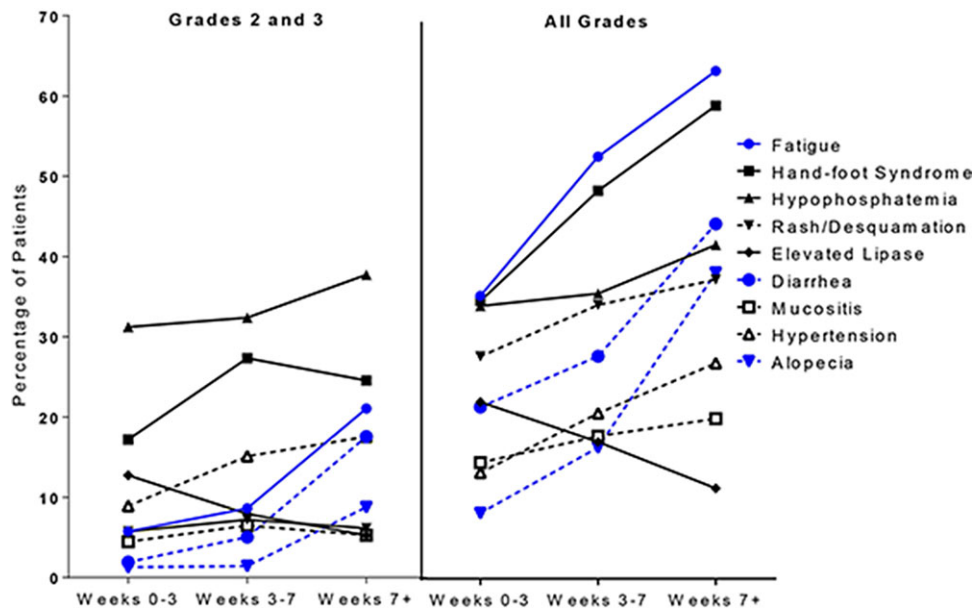


Figure 2 Prevalence of common adverse events (AEs) over three treatment intervals. Prevalences of specific AEs of interest were plotted across the three time intervals with two different grading criteria. Prevalence was adjusted for patient attrition for the last two time intervals: weeks 0–3 ($n = 157$), weeks 3–7 ($n = 138$), and weeks 7+ ($n = 113$). Each AE has a different color. Dramatic increases were found in the prevalences of fatigue, hand-foot syndrome, diarrhea, and alopecia over time, whereas modest increases were observed with hypophosphatemia, rash, and hypertension.

sorafenib plasma concentrations below 5.0 mcg mL^{-1} reported any HFS, and in these cases, it was grade 1. The exposure-response plot for diarrhea displays a similar threshold concentration effect. Although the “jump” in prevalence appears between the first and second group, all three

subjects in the second quintile had average steady-state plasma concentrations above 5.0 mcg mL^{-1} . The remaining AEs showed no striking relationship between exposure and frequency or were too infrequent to consider for presentation.

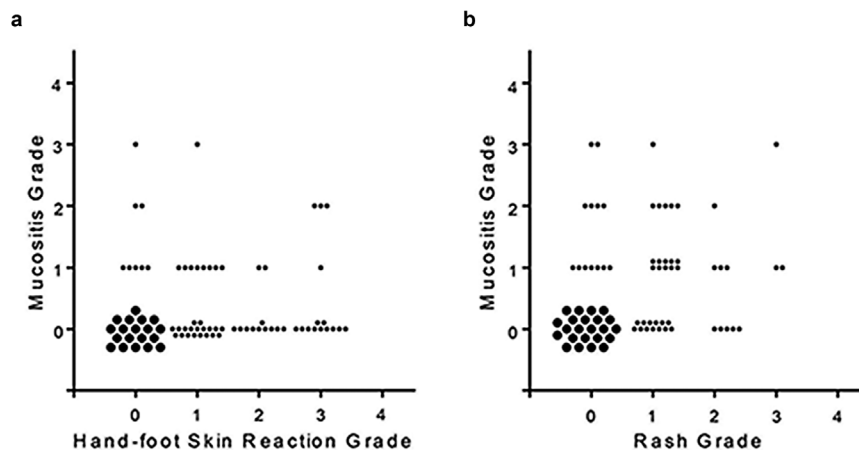


Figure 3 Pairwise occurrence of selected adverse event (AE) pairs during weeks 0–3 on study. Observations of separate AE occurrence are depicted next to the axes, whereas co-occurrences are shown closer to the middle of the dot plots. A small dot represents one patient, whereas the larger dot represents about five patients. (a) Mucositis and hand-foot syndrome. The likelihood of these two AEs occurring together in a patient is high and statistically significant (odds ratio [OR] = 4.36; $p = 0.0017$). (b) The likelihood of mucositis and rash co-occurring is also statistically significant (OR = 5.3; $p < 0.001$).

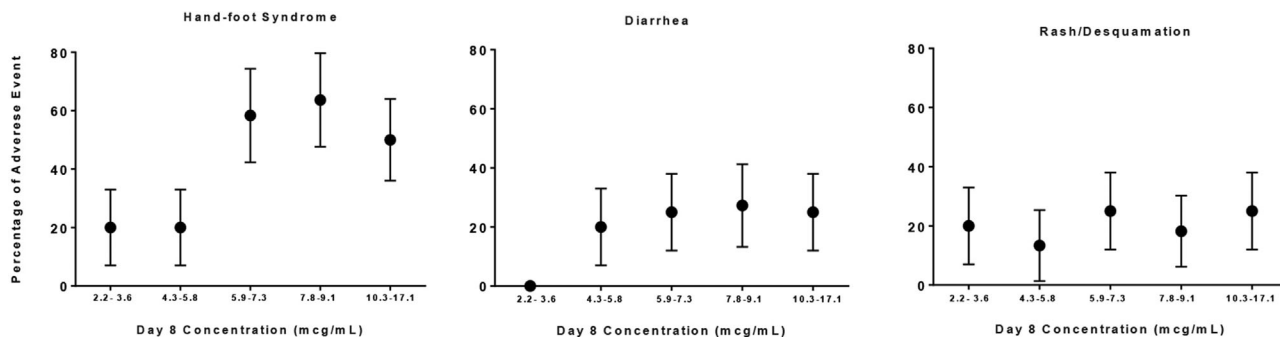


Figure 4 Sorafenib exposure-adverse event relationships. (Left panel) Prevalence of hand-foot syndrome jumped from 20% to almost 60% between the second and third bins. (Center panel) Prevalence of diarrhea increased 20–30% from the first bin to the other bins of higher concentrations. (Right panel) The reporting of low grade rash shows no striking association with drug exposure.

DISCUSSION

This analysis of the time course and co-occurrence of AEs from the KI sorafenib demonstrated previously unappreciated temporal and tissue distribution patterns. Interrater variance and misspecification are common challenges to conducting analyses like this in multicenter trials or observational data. With subjects enrolled in clinical trials at a single institution and systematic curation of the AE data, we minimized these subjective and operational factors that make study of toxicity in cancer KI therapy challenging. The empiric findings of increasing prevalence over time of alopecia, diarrhea, and fatigue, co-occurrence of mucositis with dermatologic AEs, and threshold exposure relationships for diarrhea and HFS all imply mechanism-based hypotheses.

For KIs in general and specifically for antiangiogenic treatments, incomplete understanding of the therapeutic index hinders wider more effective use.²² Some patients tolerate treatment much more readily than others. As demonstrated in this cohort, each patient develops a limited subset of AEs, but which of the AEs a particular patient will experience cannot be predicted at present. Additionally, treatment with these agents can be prolonged, but optimal management

of worsening chronic and late-developing AEs has not been well studied. Suttle *et al.*³ recently published analysis of a phase II multicenter trial of pazopanib in renal cell carcinoma. They identified a linear relationship between exposure and efficacy up to a trough concentration of approximately 25 mcg mL⁻¹, but some AEs, such as elevated liver enzymes and HFS, continued to increase in frequency as trough concentrations continued to increase in the supratherapeutic range. The investigators suggested that therapeutic drug monitoring for pazopanib trough concentrations might improve the therapeutic index for this KI. As in our investigation, the prevalence of HFS demonstrated a threshold effect.

Two shortcomings of this study were the 7-year period required to enroll these patients and that patients had diverse tumor types. This raises concerns about the capacity to conduct such investigations in a timely fashion to guide development of future compounds. We were unable to relate therapeutic effects of sorafenib to plasma exposure. Our overall enrollment limited power to detect uncommon, even if clinically meaningful, effects. Furthermore, we have only studied a single KI to date. However, as an initial pilot investigation, we identified several relevant findings to guide future research.

Kinome-wide bioinformatics-based association studies have been a popular method for discovering mechanism-based toxicities and novel targets of pharmacologic agents, especially KIs.^{12,23,24} There is a relationship between the atomic-level characteristics of a compound and the population-level reported clinical effects, such as AE rates.²⁵ Closer examination of the temporal occurrence and tissue distributions of AEs could help us more quickly and effectively recognize true associations and determine the mechanistic basis for these observations. For example, the increasing prevalence over time of alopecia, diarrhea, and fatigue suggests a potential common underlying mechanism related to chronic suppression of VEGFR2 signaling. Vascular rarefaction (the diminished presence of patent microvessels in tissue) has been associated with alopecia (a basis for use of minoxidil as hair follicle-sustaining therapy), diarrhea (diminished pancreas exocrine function),²⁶ and fatigue (diminished perfusion of skeletal muscle and sarcopenia).²⁷ Rarefaction has been demonstrated in multiple organs of rodents treated with VEGFR KIs,^{28,29} and inhibition of vascular endothelial growth factor signaling over time has also been associated with rarefaction of subcutaneous microvessels in human patients with cancer.³⁰

In contrast, the early co-occurrence of dermatologic effects and mucositis supports competing hypotheses with important considerations in larger kinome-wide studies. A keratinocyte-specific kinase inhibited by sorafenib could explain these effects, but as the threshold exposure is a determinant of the HFS, an alternative hypothesis is that keratinocytes may transport sorafenib to the intracellular space more efficiently than other cells.³¹ If this is true for sorafenib and not for other KIs, the sorafenib-AE relationship would diverge in frequency and severity from similar KIs even if they all have similar potency for inhibiting the same target. We also uncovered nonlinear relationships among sorafenib exposure and prevalence of AEs. Peak risk for both HFS and diarrhea occurs at the threshold exposure of 5.0 mcg mL⁻¹. In contrast, there was no evidence of apparent exposure-response relationship with rash. Our findings demonstrate that the incidence of these AEs among similar drugs is not due exclusively to differences in the *in vitro* profiles of kinase inhibition, but that the distribution and disposition of the drug and its metabolites likely play important roles as well.

In conclusion, this investigation revealed previously unrecognized patterns of temporal and spatial distribution of AEs due to sorafenib exposure among individual patients. Future investigations of KIs that use these methods might be more effective in developing methods to predict the occurrence of AEs and determination of the optimal dose for individual patients.

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S.K., and M.L.M. performed the research. S.K., E.F.S., H.C., and M.L.M. analyzed the data.

Conflict of Interest. The authors declared no conflict of interest.

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