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Research article

Varying Doses of Sorafenib may have Non-Significant Differences in Bioavailability and Overall Survival

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Abstract

Aim: Sorafenib is the first FDA-approved agent for the treatment of unresectable hepatocellular carcinoma (HCC). The approved dose is 400 mg BID. Anecdotal experience has suggested that many Asian-American (AA) patients are unable to tolerate this recommended dosing. This is a pilot study aimed at evaluating the pharmacokinetics (PK) of sorafenib at various doses. Methods: A cohort of 21 patients completed the study, two of whom were analyzed twice. The PK of Sorafenib and its main metabolite M2 were analyzed at 0, 1, 2, 4, 9 and 12 hours. A subset analysis comparing high dose (>400mg daily) vs. low dose (≤400mg daily), high body surface area (BSA>1.9) vs. low body surface area (BSA≤1.9) and AA vs. non-AA patients. Results: There were no significant differences in the PK of Sorafenib and M2 between the high and low dose groups nor the high and low BSA groups. Despite the difference in dose, the mean sorafenib area under curve (AUC) and Cmax of the low dose group was at least 70% of the high dose group at steady state. Furthermore, the mean Sorafenib AUC and Cmax of the low BSA cohort was at least 75% of the high BSA group at steady state. There were no significant differences in the PK between the AA and NA groups. In addition, the two cohorts did not show a difference in overall survival (OS). Conclusion: Our analysis demonstrates comparable PK and OS with sorafenib treatment despite lower doses than the FDA-approved recommendation. These findings suggest that a lower, more tolerable dose of sorafenib in AA patients may not compromise drug efficacy. Large, population-based studies are needed to validate these findings.

Introduction

The SHARP trial established the efficacy of on overall survival in patients with unresectable hepatocellular carcinoma and led to its FDA-approval [1]. Sorafenib, however, has a long list of potential side effects that can reduce tolerability. These include hand-foot syndrome, pruritis, diarrhea, hypertension, and leukopenia.

Currently, there is no dose adjustment of sorafenib for weight, age or gender. Several studies have explored the possibility of reduced doses to decrease the side effect profile without impacting overall survival (OS). Hepatocellular is the sixth most common cause of cancer and third most common cause of cancer death worldwide, with an increased prevalence in Asia [2]. Additional studies to examine the differences in pharmacokinetics and bioavailability among patient populations that differ in areas such as weight and ethnicity can help lead to dosing protocols optimized for each patient to maximize survival and quality of life and minimize toxicity.

It has been our institution's experience that a significant percentage of AA patients are unable to tolerate the recommended daily dose of 400 mg twice daily. If a lower daily dose can still achieve therapeutic levels of sorafenib and the M2 metabolite, which has been demonstrated in vitro to have pharmacologic efficacy, [3] patients may have a more tolerable therapeutic option. For this reason we conducted a pilot study to examine the pharmacokinetics of a lower-dose regimen of sorafenib.

Methods

This protocol was conducted under IRB approval. To be eligible for the study patients were required to be on a stable dose for a minimum of 30 days. Subjects were divided into a high-dose cohort receiving 600 or 800 mg/day and a low-dose cohort receiving 200 or 400 mg/day. Blood draws were taken at 1, 2, 4, 9, and 12 hours post-infusion to measure levels of sorafenib and the M2 metabolite in each cohort; samples were measured by mass spectroscopy at Northeast Bioanalytical

Laboratories. Twenty-one patients in total completed the study; four in the high-dose cohort and seventeen in the low-dose cohort. One patient in each dosage cohort underwent analysis twice. Subjects were further divided into subsets of high BSA and low BSA as well as AA patients and non-AA patients. A summary of the demographics of the high-dose and low-dose cohorts can be found in table 1.

In addition, patients were followed-up until October 2018 to assess overall survival. Each subject continued treatment as per the dosage they received within the study.

Table 1. Demographics of the high-dose and low-dose cohorts

Characteristic	High Dose	Low Dose	p-value
Total patients	4	17	
Age (median, mean, standard error)	54, 56 +/- 4.1	69, 69 +/- 2.5	
Gender			
Male	4	12	
Female	0	5	
Ethnicity			
Asian-American	1	9	
Non-Asian	3	8	
BSA (m2)(median, mean, standard error)	1.75, 1.87 +/- 0.17	1.78, 1.79 +/- 0.06	
Hepatitis B +ve	0	6	
Hepatitis C +ve	3	7	
History of alcoholism	1	0	
Non-alcoholic steatohepatitis	0	2	
Idiopathic	0	2	
Extra-hepatic disease present	2	6	
AFP >200			
>200	2	8	
<200	2	9	
Length of time on drug (days) (median, mean, standard error)	160, 214 +/- 98	126, 172 +/- 34	
Received previous HCC treatment	3	15	
Sorafenib AUC (mean +/- standard error)	42,729 +/- 5684	31,314 +/- 3683	NS
M-2 AUC (mean +/- standard error)	5972+/-751	6320 +/- 1679	NS

Results

For measurements of sorafenib levels across all patient cohorts, bioavailability curves followed expected trends. The high-dose cohort had an AUC of 42,729 mg*h/L compared to 31,314 mg*h/L; the high-BSA patients had an AUC of 41,477 compared to the low-BSA patients' 31,662 mg*h/L; the non-Asian patients had an AUC of 37,914 compared to 28,443. However, given the wide variability between individual patients these differences were not statistically significant (p=NS).

AUC measurements followed similar trends for the M2 metabolites across the BSA and ethnicity. High and low-BSA cohorts had a mean AUC of 9,852 and 5,242, respectively. The non-Asian cohort's AUC was measured at 7,961 mg*h/L compared to 4,012 mg*h/L. However, the cohort receiving high dose sorafenib was actually measured to have an M2 AUC lower than that of the low-dose cohort, 5,972 mg*h/L and 6,320 mg*h/L respectively. Comparisons of each dosage cohort's AUC for sorafenib and M2 are displayed at the bottom of Table 1.

Overall, the mean sorafenib AUC of the low dose group was at least 75% of the high dose group at steady state and was actually greater for the M2 metabolite. A scatter plot comparing sorafenib bioavailability yielded an R2 of 0.174; changing the x-axis to be a function of dose over body surface area further yielded an R2 of 0.1094 (Figure 1). The same analysis of the AUC for the M2 metabolite yields R2 values of 0.0198 and 0.003 (Figure 2), respectively; combining the AUCs of both sorafenib and the M2 metabolite yielded R2 values of 0.1227 and 0.68 (Figure 3), respectively. These data suggest a significant variance in not only the absorption of sorafenib, but its metabolism after reaching tissue and eventual excretion.

All but one of the Asian patients in this study was part of the low-dose cohort. The Asian cohort averaged 28,443 mg*h/L and 4,012 mg*h/L for sorafenib and M2 respectively; the non-Asian cohort averaged 37,914 mg*h/L and 7,961 mg*h/L. A one-tailed t-test did not show a statistically significant difference.

The max concentration (Cmax) of sorafenib and the M2 metabolite were also measured. The low-dose cohort's average Cmax for sorafenib and the M2 metabolite were 4705.63 mg/L and 844.72 mg/L, respectively. The high-dose cohort's average Cmax for the two measured levels were 5,652.45 mg/L and 704.47 mg/L. For

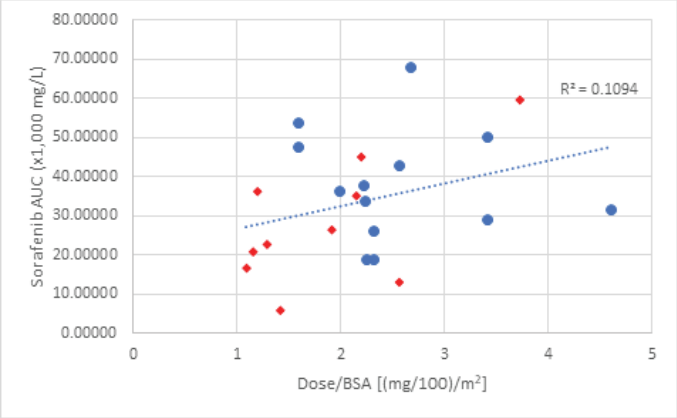


Figure 1. Sorafenib AUC compared to dose/BSA

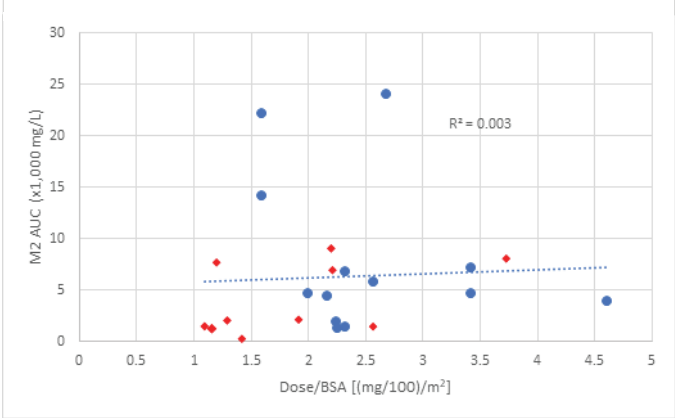


Figure 2. M2 AUC compared to dose/BSA

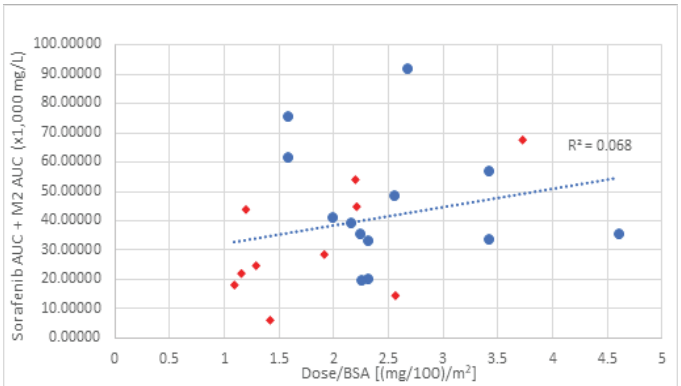


Figure 3. Sorafenib and M2 combined compared to dose/BSA

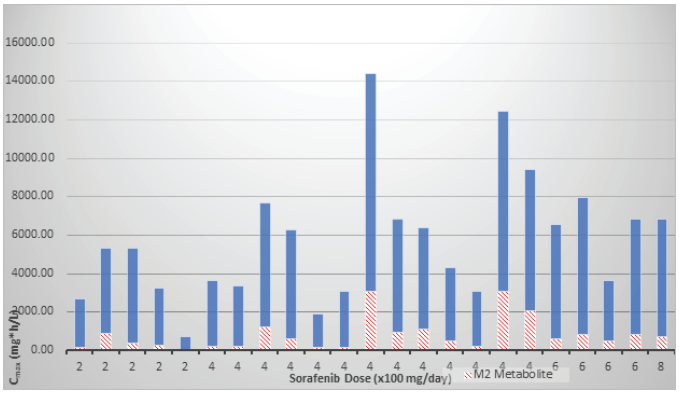


Figure 4. Cmax (mg*h/L) against dose

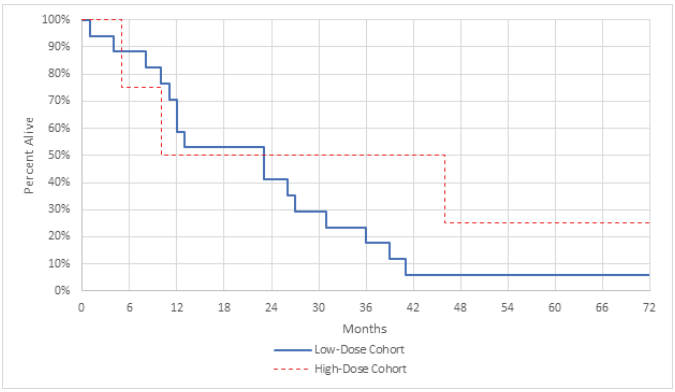
Survival

For the purposes of this study, survival was defined as from the time of consent for the study to the end of follow-up or death, whichever came first. All the patients in this study continued on the dose they received for bioavailability analysis for the duration of their treatment for HCC. Five patients received 200 mg/day, twelve patients received 400 mg/day, 3 patients received 600 mg/day, and one patient received 800 mg.

For the patients receiving 200 mg/day, they survived a mean of 19 months at this dosage. Median survival was 22.1 months with a standard error of ± 7.3 months. All of these patients were Asian-American and categorized as low-BSA (<1.9 m2).

Twelve patients received 400 mg/day. The mean survival for this cohort was 23.8 months. Median survival was 17.6 months with a standard error of ±5.4 months. Four of these patients were Asian-American and all but one of them exceeded the mean OS for this cohort.

Four patients were in the high-dose cohort, three of whom received 600 mg/day and one of whom received 800 mg/day. The mean survival of this cohort was 27.9 months; the one Asian-American patient in this cohort did not reach the mean survival time. Median survival was 27.2 months with a standard error of ±12.1 months. A one-tailed t-test of the survival of the low- and high-dose cohorts showed no difference in survival between the two groups, yielding a value of 0.35. The survival of the two cohorts over time is plotted in figure 5. There was no statistical difference in survival between the two groups.



Low dose	1	5	12	10	9	7	6	3	3	3	3	3	3
High dose	3	2	2	2	2	2	2	1	1	1	1	1	1

Figure 5. Overall Survival

Discussion

Sorafenib is the first systemic therapy shown to improve survival in unresectable HCC. The SHARP trial showed an improvement of three months in OS and time to progression (TTP) over placebo, [1] and further Phase IV trials have been able to reproduce those findings. Shi-Meng et al studied sorafenib's use in Taiwanese patients, and their results showed an OS benefit of 8.6 months and TTP benefit of 3.8 months [4]. This was a small pilot study exploring the possibility of lower dosages of sorafenib achieving favorable pharmacokinetics for patients suffering from unresectable hepatocellular carcinoma. Previous studies have examined the relationship between dose

and various clinical parameters. Furuse et al. examined the use of sorafenib in Japanese patients at various doses; they found the current recommended dosage to be generally tolerable though one of the fourteen patients treated at that dose suffered dose-limiting toxicity (DLT) [5]. Haixing et al found a dose-dependent relationship between dosage and adverse drug reactions (ADRs) in metastatic renal cell carcinoma (RCC), with severe ADRs being particularly associated with a steady-state concentration >10,000 ng/mL [6]. Fakudo et al. recommend that sorafenib concentration can be used as a benchmark to avoid the development of hypertension and other adverse effects in the treatment of both HCC and RCC.7 One of the biggest challenges facing clinicians treating HCC is the management of these adverse effects. Hand-foot syndrome (HFS) can be an extremely painful ADR associated with sorafenib treatment. Though Yada et al determined that the development of HFS is associated with a longer TTP, [8] many patients may opt to go without treatment if HFS proves too painful.

An individualized approach to each patient's treatment is the best way to maximize patient compliance, quality of life, and survival. Reiss et al found that initiating sorafenib treatment at a reduced starting dose is linked to reduced pill burden, reduced treatment cost, and reduced treatment discontinuation.[9] We set out to demonstrate how the pharmacokinetics of sorafenib make reduced dosages viable for treatment. Our data shows sorafenib dosage does not correlate strongly enough with its own bioavailability or that of the active M2 metabolite to justify a single dosing regimen; several low-dose patients achieved an AUC and Cmax similar to or significantly higher than those of the high-dose patients. Even combining AUCs for both sorafenib and the M2 metabolite showed a weak association with dosage; the association becomes even weaker when factoring dose with patient BSA. These results are shown in figures 2 and 3; they suggest that both metabolism and excretion of sorafenib are unpredictable from one patient to the next, even at the same dosage. These results were not statistically significant but do suggest a need for further research into the rationale behind dosing for patients of different sizes. Additionally, Ye et al demonstrated that the metabolism of sorafenib is much slower in tumor tissue than in normal liver tissue [10]. Sorafenib may have a significantly longer half-life in patients with a high tumor burden, warranting an individualized approach for their dosage. This is significant to clinical practice differing levels in sorafenib and its metabolites may impact the side effects seen and tolerability of the drug in individual patients.

Subjects were also grouped into high- and low-BSA cohorts. BSA has been a classic tool in the dosing of chemotherapy agents for decades, starting with its use for scaling doses from animal subjects to human subjects in phase I trials [11,12]. However, it has since been shown to be unreliable, with different formulae yielding significantly different results for the same patient [13]. For the purposes of our study, it was used to further characterize the difference between the patients typically seen in our practice at UCI and the population at large. As expected, both measured AUCs were higher for patients with a BSA of >2 m2 as they were receiving higher doses on average. However, when the AUC is compared to the dose per unit of surface area, any correlation between the dose and AUC weakens, almost disappearing outright in the case of the M2 metabolite. Where we had set out to examine the pharmacokinetics of sorafenib at varying doses in patients of various sizes, our data suggests that one of the most popular methods of scaling doses does not reduce pharmacokinetic variability.

Patient size is not the only potential factor influencing the pharmacokinetics of sorafenib. Chao et al analyzed several genes found that several polymorphisms in various genes such as VEGF and VEGFR2 were associated with different OS times and probabilities of suffering ADRs and DLTs [14].

HCC is an extremely common tumor in Asia, owing largely to generally higher rates of hepatitis B infection. The proportion to which it affects Asian patients makes it one of the most common cancer types worldwide [2]. Our hepatobiliary surgery practice is located in Orange County, California, which is home to many first- and second-generation Asian immigrants. These people constitute at least a significant minority of our HCC patients. It is thus worth examining how to best optimize care for this patient population. Kane et al already found that the pharmacokinetics for sorafenib demonstrate a 30% reduced AUC for Asian subjects in comparison to Caucasian subjects [15]. It is important to note that the Asian patients in our study were not paired with a non-Asian patient for dosage. In figures 1, 2, and 3, the data points corresponding to Asian patients are diamond-shaped. When directly comparing Asian-American and non-Asian patients, no significant difference could be detected in the AUC or Cmax regardless of dosage or the size of the patient. In addition, the survival of the Asian patients exceeded what is typically expected of uHCC patients being treated with sorafenib, despite all of them receiving lower doses than the recommended 400 mg BID. Considering the pharmacokinetics and OS of Asian patients receiving lower dosages than the current recommended dosage, it is clear more studies are needed.

Conclusion

Sorafenib has been an effective drug in prolonging the lives of patients with uHCC. However, variability in its tolerability for patients of varying sizes and ethnicities warrants a customized treatment approach to maximize benefit and tolerance while minimizing toxicity in individual patients. We recommend further study with larger patient populations exploring different dosing regimens and optimizing protocols for patient populations clinicians are most likely to be treating.

Consent

All human investigations were performed with the approval of the local Institutional Review Board. The investigators gained the consent of each subject before any investigations were carried out.

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