Association of gastric acid suppression and sorafenib efficacy in advanced hepatocellular carcinoma

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DOI:
10.1097/MCG.0000000000001375

Document Version
Peer reviewed version

Citation for published version (Harvard):
Razak, RA, Fletcher, P, Kunene, V & Ma, YT 2021, 'Association of gastric acid suppression and sorafenib efficacy in advanced hepatocellular carcinoma', *Journal of Clinical Gastroenterology*, vol. 55, no. 2, pp. 169-173. https://doi.org/10.1097/MCG.0000000000001375

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Abstract

Background

Recent studies have revealed that co-administration of gastric acid suppressants reduces the efficacy of the tyrosine kinase inhibitors erlotinib and sunitinib in patients with non-small cell lung cancer and renal cell carcinoma, respectively. We have therefore assessed if concurrent use of gastric acid suppressants and sorafenib impairs outcomes in patients with advanced hepatocellular carcinoma (HCC).

Methods

A retrospective analysis was conducted on all patients treated with sorafenib for advanced HCC at a single tertiary referral unit in the United Kingdom, between January 2008 and January 2014. A multivariate Cox' proportional hazard model was used to assess the effect of the concomitant use of gastric acid suppression and sorafenib on progression-free survival and overall survival.

Results

Data were collected from 197 patients, of which 182 could be assessed for this study; 77 (42%) were on concurrent gastric acid suppression therapy. After adjusting for imbalances between the groups, a Cox regression analysis gave an adjusted hazard ratio for the concurrent acid suppression group compared to the no acid suppression group of 5.4 (95% CI: 3.6-7.9) for progression-free survival and 1.85 (95% CI: 1.3-2.6) for overall survival.

Conclusions

Our single centre experience shows that patients with advanced HCC taking sorafenib and concomitant gastric acid suppression therapy have significantly inferior progression-free and overall survival. This is the first time this negative interaction has been reported and further prospective validation is warranted.

Key words

Gastric acid suppression; sorafenib; hepatocellular carcinoma.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most common cause of cancer-related death worldwide[1]. Although most of the burden occurs in developing countries, the incidence in the West has tripled over the last 3 decades, in parallel with the increasing burden of chronic liver disease due to the rising incidences of chronic hepatitis C virus infection and fatty liver disease related to obesity and type II diabetes[2].

For patients with advanced HCC, the orally active multikinase inhibitor, sorafenib, was the first systemic agent to demonstrate a survival benefit[3,4]. Sorafenib blocks both tumour cell proliferation by targeting the RAF/MEK/ERK signalling pathway at the level of the serine-threonine kinases Raf-1 and B-Raf, and tumour angiogenesis by inhibition of the receptor tyrosine kinase activity of the vascular endothelial growth factor receptor-2/3 and platelet derived growth factor receptor beta[5].

Sorafenib has a low solubility and high *in vitro* permeability and is thus classified as a Biopharmaceutics Classification System and Biopharmaceutical Drug Disposition Classification System class II compound[6]. The bioavailability of sorafenib is therefore limited by its solvation rate. Co-administration of sorafenib with a high fat meal has been demonstrated to reduce its bioavailability by 29% compared to dosing under fasting conditions, thus the Summary of Product Characteristics recommends sorafenib to be taken without food[7,8].

The solubility of sorafenib also decreases with increasing pH (the solubility of sorafenib ranges from 0.34mg/100ml at pH 1.0 to 0.013mg/ml at pH 4.5), thus elevation of gastric pH with acid reducing therapy has the potential to reduce its absorption and consequently its efficacy[6]. The potential interaction of acid suppressing agents on sorafenib bioavailability has subsequently been studied by Bayer in twenty-four healthy male subjects[9]. Pre-treatment of subjects with omeprazole, administered at a dose of 40 mg once daily for 5 days, increased the gastric pH but had no effect on sorafenib pharmacokinetics compared to fasting conditions[9]. It is therefore recommended that no sorafenib dose adjustments are necessary in patients taking acid-suppressing agents.

However, sorafenib is characterised by a high degree of interpatient variability in its pharmacokinetics after both single and multiple dosing[10-13]. The area under the curve (AUC) and the maximum concentration (C_{max}) also increase less than proportionally with increasing dose[10-13]. Thus, it is likely that a much larger healthy volunteer study is required in order to be confident that no interaction between sorafenib and acid suppressing agents actually exists.

The potential drug-drug interaction with acid suppressing agents is not unique to sorafenib. In a recent review article, Budha et al demonstrate that the majority of approved orally administered, small molecule, molecularly targeted drugs are weak bases characterised by pH dependent solubility[6]. Thus elevation of gastric pH with gastric suppressing agents has the potential to reduce their absorption and thus bioavailability. This is of particular relevance in this population as the prevalence of acid reducing agents use amongst patients with cancer ranges from 20-55%[6].

Two recent retrospective case reviews have demonstrated that the median progression-free survival (PFS) and overall survival (OS) of patients with non-small-cell lung cancer treated with erlotinib is significantly shorter amongst patients taking concomitant acid suppressing therapy compared to those without, and the median PFS and OS in patients with advanced or metastatic renal cell cancer was significantly shorter in those treated with sunitinib and concomitant acid suppressing therapy vs the no acid suppression group[14,15]. We therefore performed a single centre retrospective case review to assess the potential impact of co-administration of acid suppressing therapy with sorafenib in patients with advanced HCC.

Methods

Study population

We retrospectively collected data from all patients with advanced HCC who commenced treatment with sorafenib between January 2008 and January 2014 at the Queen Elizabeth Hospital Birmingham, United Kingdom. All patients were 18 years of age or older with a confirmed diagnosis of HCC, either histologically or radiologically as per internationally accepted American Association for Study of Liver Diseases criteria. Data was collected on baseline demographics, including age, sex, Child-Pugh score and ECOG performance status prior to start of sorafenib, disease characteristics, use of gastric acid suppression therapy, duration of sorafenib therapy and survival outcomes. This study was performed as a clinical audit and registered under the clinical audit number CARMS-12080 at our institution.

Patients with ≤ 1 week of sorafenib therapy or intermittent (taken as required) use only, were excluded. Patients were defined as receiving concurrent acid suppression therapy if their pharmacy records included a proton pump inhibitor (PPI) or histamine receptor antagonist (H2RA) with prescription dates that overlapped by ≥20% of sorafenib treatment duration.

Overall survival was measured from the date of starting sorafenib until the date of death from any cause. Patients who were lost to follow-up were censored at the last date they were known to be alive. Progression-free survival was measured from the date of starting sorafenib until the date of first documented disease progression.

Statistical analysis

Survival analyses were performed using the Kaplan-Meier method and Cox regression. All statistical analyses were performed in Stat14.

Results

Between January 2008 and January 2014, 197 patients with advanced HCC commenced sorafenib therapy. Fifteen patients were excluded from further analyses; 7 patients were on intermittent acid suppression therapy, 4 patients received sorafenib for less than 1 week and the remaining 4 patients were treated as part of a clinical trial. Of the remaining 182 patients, 77 (42%) were taking concurrent gastric acid suppression therapy, and 105 (58%) had no acid suppression.

Baseline characteristics

The median age of the patients was 68 years and 149 (82%) of patients were male. The two groups were generally balanced for sex, age, Child-Pugh class, alpha-foetoprotein (AFP) levels and presence of macrovascular invasion (MVI). Patients in the no acid suppression group had a slightly better performance status and less extra-hepatic spread (EHS) but less underlying hepatitis C virus (HCV) infection and higher BCLC stage compared to the continuous acid suppression group (Table 1). To adjust for any differences between the groups, the variables listed in Table 1 were included in the adjusted Hazard Ratio analysis (Cox regression).

Gastric acid suppression

Of the 77 (42%) patients who were receiving concurrent gastric acid suppression therapy, the most common agents used were PPIs (n=74, 96%) and only 4% (n=3) of patients were taking a histamine receptor antagonist (Supplementary Table 1). Seventy three patients (95%) receiving gastric acid suppression therapy were taking this concurrently for the entire duration of their sorafenib treatment.

Progression-free survival

The median PFS was 7.9 months (95% CI: 5.9-9.9 months) in the no acid suppression group compared with 1.9 months (95% CI: 1.5-2.4 months) in the continuous acid suppression group (Figure 1). A Cox regression analysis gave an adjusted Hazard Ratio for the continuous acid suppression group, compared to the no acid suppression group of 5.4 (95% CI: 3.6, 7.9, $p<0.001$). Covariates included in the Cox regression were age in years, sex, Child-Pugh class, performance status, ln(AFP), BCLC stage, aetiology of cirrhosis (HCV vs no HCV), presence of MVI and presence of EHS.

Overall survival

The median OS was 8.7 months (95% CI: 7.6-10.9 months) in the no acid suppression group compared with 5.8 months (95% CI: 4.1-7.2 months) in the continuous acid suppression group (Figure 2). A Cox regression analysis gave an adjusted Hazard Ratio for the continuous acid suppression group, compared to the no acid suppression group of 1.9 (95: CI: 1.3, 2.6, $p=0.001$). Covariates included in the adjusted Cox regression were as for the PFS analysis.

Discussion

Whilst it is known that the solubility of sorafenib decreases with increasing pH, a small healthy volunteer study demonstrated no impact on sorafenib pharmacokinetics following 5 days of oral omeprazole[9] and it is therefore recommended that no sorafenib dose adjustments are necessary in patients talking acid-suppressing agents. To the best of our knowledge, ours is the first study demonstrating a potential significant negative clinical impact from co-administration of gastric acid suppressants with sorafenib in patients with advanced HCC.

Given the high degree of interpatient variability in sorafenib pharmacokinetics following both single and multiple dosing[10-13] it is possible that the small healthy volunteer study was simply underpowered to be able to identify the presence of a true negative relationship between sorafenib and acid-suppressing agents. This possibility is supported by the observed significantly lower sorafenib AUC and C_{max} in the individuals in this healthy volunteer study randomised to a moderate fat meal prior to sorafenib, which is contrary to previous findings[8,9]. The healthy volunteer study has also only assessed the potential interaction between omeprazole and sorafenib bioavailability following a single dose of sorafenib, whilst steady-state conditions are usually reached after 7 days of dosing. Furthermore, sorafenib is characterised by a delayed secondary peak in plasma concentrations indicating that it is also subject to enterohepatic circulation[10-13]. Most patients with HCC have underlying liver cirrhosis which is known to be associated with reduced hepatic circulation and hepatocyte function, both of which are important determinants of enterohepatic circulation[16,17].

Thus a healthy volunteer study may not accurately reflect the true clinical scenario of patients using sorafenib in advanced HCC.

Our results are consistent with the findings from a previous phase II study of erlotinib and sorafenib in chemotherapy naïve patients with advanced non-small cell lung cancer. It was observed that of the 15 patients taking a proton pump inhibitor concomitantly, the mean sorafenib levels were lower compared with those who were not[18].

Indeed, the majority of the approved orally administered, molecularly targeted drugs are weak bases characterised by pH dependent solubility like sorafenib and several retrospective case reviews have now demonstrated worse clinical outcomes among patients being treated with erlotinib for non-small cell lung cancer, or sunitinib in metastatic renal cell carcinoma, who are concurrently taking gastric acid suppressants[14,15,19].

Although a subsequent pooled analysis of 2188 patients with metastatic renal cell carcinoma treated with sunitinb (n=952), axitinib (n=626) or sorafenib (n=610) within phase II and III clinical trials observed no difference in the overall survival amongst patients using a PPI compared to those who did not, this analysis was limited by several major criticisms[20]. Firstly, only 120 patients (5.5%) within this pooled cohort were defined as taking a PPI which is much lower than in the normal cancer population. Patients were also classified as PPI users only if they were taking a PPI at baseline, and there is no data on duration of treatment and patients subsequently commenced on a PPI during therapy were also not recorded. This analysis also lacked

intragastric pH measurements. The other major criticism of this study is that patients taking H2RA or antacids were not included.

In the general population, gastroesophageal reflux disease (GERD) is common and among patients undergoing cancer treatment, gastric acid suppressants are frequently used not only to palliate GERD but also for palliation of dyspepsia or gastritis that may be associated with the cancer or the anticancer therapy[6]. A recent epidemiological study revealed that the prevalence of acid-reducing agent use amongst all cancer patients ranges from 20-55%[21]. Consistent with this, we have demonstrated 42% of patients in our cohort were taking gastric acid suppressants concurrently with their sorafenib. Given this high prevalence, it is clearly extremely important for clinicians and pharmacists to be aware of any potential interactions.

The most common gastric acid suppressants used are proton pump inhibitors. However PPIs are characterised by a long duration of action due to their irreversible binding to hydrogen potassium ATPase (H+/K+ ATPase) pumps[22]. For example, up to 80% of basal gastric acid secretion remains inhibited 24 hours after an oral dose of omeprazole (20mg)[23]. Thus separating the administration of the PPI and sorafenib is unlikely to eliminate this problem.

An alternative to PPIs for cancer patients may be to switch to H2RA. These drugs inhibit the histamine from binding to histamine-2 receptors on parietal cells and hence reduce the production of gastric acid. Their duration of action is shorter than PPIs[24]. It has been reported that separating the administration of ranitidine and erlotinib (eg erlotinib taken 2 hours before or 10 hours after administration of randitidine) or by

reducing its dose, can blunt the effect of ranitidine on erlotinib, although it does not completely abolish this interaction.

An alternative approach for patients may be to temporarily lower the stomach pH by taking the anticancer therapy with cola (an acidic beverage). A recent pharmacokinetic study demonstrated that cola intake led to a clinically relevant and statistically significant increase in the bioavailability of erlotinib in patients taking esomeprazole concurrently, whilst this effect was only marginal in patients not taking a PPI[25]. This finding needs validating with sorafenib but may represent a practical solution to manage this potential drug-drug interaction in patients who do need to remain on gastric acid suppressants.

The main limitation of this study is that it is a retrospective review thus we cannot be certain if patients were taking their gastric acid suppressants as prescribed. This study is also limited by the lack of intragastric pH measurements and pharmacokinetic measurements. Additionally, we cannot exclude if some of the observed effect may be due to PPIs known potential effect on the cytochrome P450 isoenzymes rather than just their effect on gastric pH. However an early phase pharmacokinetic interaction study found that concomitant administration of sorafenib and midazolam, dextromethorphan or omeprazole (substrates for cytochromes CYP3A4, CYP2D6 and CYP2C19 respectively) did not alter the exposure of these agents[26]. Therefore, clinical pharmacokinetic interactions of sorafenib with substrates of these enzymes are felt to be unlikely[26]. Furthermore, a review of 3 PPIs (omeprazole, lansoprazole and pantoprazole) concluded that these drugs have a very limited potential for drug interactions on the cytochrome p450 superfamily and the small effects observed are

usually of no clinical relevance[27]. Thus the impact of the PPIs on sorafenib metabolism is likely to be small and unlikely to account for the large effect size we have observed in our study. The findings from this study clearly need to be validated prospectively and in a larger cohort but given the large effect size observed, we recommend clinicians and pharmacists consider this potential drug-drug interaction in all patients with advanced HCC currently being treated with sorafenib.

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Figure Legends

Figure 1. Kaplan Meier curve showing progression free survival in patients with no acid suppression compared with patients with continuous acid suppression.

Figure 2. Kaplan Meier curve showing overall survival in patients with no acid suppression compared with patients with continuous acid suppression.