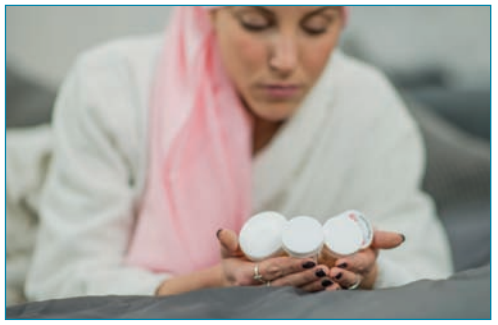
Management of TKI Anticancer Agents With Gastric Acid Medications

BY LISA LOHR, PHARMD, BCOP, BCPS

Oral chemotherapy agents often are used in patients with concomitant medications that may interact with the anti-cancer treatment, and successful management of the interaction is needed for optimal treatment. The most common types of interactions include CYP3A4 inhibitors and inducers, anticoagulants, agents that prolong the QTc interval of the ECG, and gastric acid suppressing medications. Some methods of managing drug-drug interactions (DDIs) include stopping or changing the interacting medication, increased monitoring for toxicity or efficacy, changing the dose of the oral chemotherapy agent, or in rare circumstances, changing to a different chemotherapy treatment.

Gastric acid suppressing (GAS) medications are commonly prescribed for patients receiving cancer treatment. GAS agents include proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H_2RAs), and antacid liquids/tabs. In addition, all of these GAS agents are available over-the-counter, and patients might not always report this usage. Hard indications for use of GAS medications include: 1) peptic ulcer disease, 2) gastroesophageal reflux disease (GERD) both as higher dose initial treatment and lower dose maintenance treatment, 3) Barrett's esophagus, 4) Zollinger-Ellison syndrome, 5) NSAID-associated ulcers, and 6) eradication of *Helicobacter pylori* infections.



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In addition, these agents are also used for softer indications, such as 1) prevention of gastritis in those receiving corticosteroids or NSAIDs, 2) stress ulcer prophylaxis after discharge from hospital, 3) endoscopy-negative reflux symptoms, and 4) symptoms of laryngopharyngeal reflux such as hoarse voice or coughing.

Based on data from several surveys, as many as 20-55 percent of people with cancer are taking GAS agents. The actual rate may be higher, because as these agents are available over the counter, the oncology team may not be aware of this usage.

Most orally available tyrosine kinase inhibitor (TKI) anticancer treatments exhibit incomplete and variable absorption. This stems, in part, from incomplete dissolution and thus can be the rate-limiting factor for absorption. As weakly basic molecules, the dissolution is improved in acidic gastric fluids. When the stomach pH is increased up over 4, the TKI absorption is reduced, resulting in a lower C_{max} and AUC of the TKI. Therapy with GAS agents increases the gastric pH, contributing to lower TKI absorption. With some TKIs, this change in absorption is inconsequential, but is very large with other agents.

Different GAS agents have different potencies and durations of effect on the gastric pH. Oral antacids, such as magnesium/aluminum hydroxide, change the pH for a couple of hours. The effects of H_2RAs, such as ranitidine and famotidine, have an onset of about 30-60 minutes and a duration of about 10-12 hours. PPIs, such as omeprazole and pantoprazole, show a variable and delayed increase in the gastric pH (to >4) of about 3-4 hours. Although the half-lives are about 1-2 hours, the duration of significant effects on the stomach pH is about 12-14 hours assuming once daily administration. Twice daily administration of PPIs often result in pH elevations during most of the day. A summary of PPI and H_2RA medications is shown in **Table 1**.

Increasing the dose of the TKI to overcome the reduced dissolution/absorption would be successful if there is saturable absorption.

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CME/CNE Article

In addition, the effect of food intake on the TKI absorption as well as the gastric pH is complicated.

A further complexity in the dosing of TKIs is the concept of "therapeutic range." For most medications, it is not clear what would be the ideal blood level of the TKI that would ensure optimal anti-cancer effects. The intent of most phase I drug trials is to determine the maximum-tolerated dose, not the minimally effective dose. As such, the recommended dose of a TKI might be higher than actually required. Only more complex studies could show the effect of a DDI on actual patient outcomes. In addition, studies of DDIs are highly dependent on the actual trial design. Such factors of when the GAS agent and TKI were given in relation to each other, the actual dose and schedule of the PPI or H_2RA, and the duration of the study period all could contribute to conflicting results.

Sharma and associates reviewed SEERs and Medicare data of over 12, 000 patients between 2007 and 2012 who received a TKI (erlotinib, sunitinib, imatinib, dasatinib, lapatinib, sorafenib, or nilotinib) and who were diagnosed with lung cancer, renal cell cancer, CML, pancreatic cancer, or liver cancer. The primary exposure variable was the concurrent receipt of a TKI and a PPI with at least 30 days of overlap in the first 90 days of TKI treatment. In this study, the prevalence of overlapping use of TKI and PPI was a little over 22 percent of people. One of the outcome measures, death in 90 days, showed an adjusted hazard

Continued on page 20

Table 1: Summary of GAS Medications

	Name	Usual treatment dose	Maximum dose	Usual low (maintenance or prophylaxis) dose
H_2RAs				
	Ranitidine (Zantac)	150 mg BID	300 mg per day	75 mg 1-2 times daily
	Famotidine (Pepcid)	10-20 mg daily or BID	NA	20 mg daily
	Cimetidine (Tagamet)	300 mg QID or 400 mg BID	2,400 mg per day	200 mg daily as needed
PPIs				
	Omeprazole (Prilosec)	20-40 mg daily	Up to 360 mg per day	10 mg daily
	Lansoprazole (Prevacid)	30 mg	Up to 180 mg per day	15 mg daily
	Rabeprazole (Aciphex)	20 mg	Up to 120 mg per day	5-10 mg daily
	Pantoprazole (Protonix)	40 mg daily or BID	Up to 240 mg per day	20 mg daily
	Esomeprazole (Nexium)	20-40 mg	Up to 240 mg per day	20 mg daily
	Dexlansoprazole (Dexilant)	60 mg	NA	30 mg daily

continued from page 19

ratio of 1.16 (95% CI 1.05-1.28). In addition, there was an increased risk of death at 1 year with a hazard ratio of 1.10 (95% CI 1.04-1.17). The increased risk of death was particularly striking for patients with lung cancer receiving erlotinib. The authors concluded that PPI use with one of these TKIs impacted survival, and PPI used should be reassessed when TKIs are started (*Cancer* 2019;125:1155-1162).

Mir and associates performed a retrospective review of participants in two trials of pazopanib treatment in patients with soft tissue sarcoma. The first trial, EORTC 62043, was a single-arm study and the second, EORTC 62072, was a placebo controlled phase III trial. Of the 333 evaluable patients, nearly 18 percent received concurrent GAS agents for ≥ 80 percent of the treatment duration. The median PFS was shorter in those receiving GAS agents (2.8 months) compared to those who did not (4.6 months) [HR, 1.49; 95% CI 1.11-1.99; p=0.01]. In addition, a shorter overall survival was seen in those with concomitant GAS usage (8.0 months) compared to those without GAS agent usage (12.6 months [HR, 1.81; 95% CI 1.31-2.49; p=0.01]. To control for the possible confounder of presence of GI disease, they studied the participants in the placebo arm of the controlled trial, and there was no observable difference in survival between those who did take GAS agents and those that did not. The authors concluded that administration of long-term GAS medications was associated with shortened survival in these patients. (*Clin Cancer Res* 2019;25:1479-1485)

In caring for a patient already on a PPI or H_2RA about to start an affected TKI, the clinician should start by determining the indication for the GAS agent, the length of treatment, and whether the person has attempted to stop the GAS agent in the past. When PPIs are abruptly discontinued, especially in those on a PPI for a long time, the gastric acid output may rebound significantly, due to hypergastrinemia. This often leads to rebound symptoms, making PPI discontinuation very difficult. To avoid this, one or more methods of deprescribing can be recommended.

One method is to step down to "on demand" or PRN dosing, in which the person takes the PPI only when significant symptoms (unresolved by OTC AAs) are present. Unfortunately, this could still lead to erratic TKI absorption.

Another two-step method is to first reduce the PPI dose to once daily administration of the lowest available dosage for a few days, then switch to a once daily H_2RA dose. This would allow for some GAS therapy while initiating TKI treatment in most cases. There would still be a DDI, but this might be mitigated through us of the less potent H_2RA.

The ideal method, if there's enough time, is the tapering and complete discontinuation of the PPI. One way is to 1) reduce the PPI dose to the lowest dosage given once daily for 1-2 weeks, 2) then change to

Continued on page 21

Table 2: Summary of TKI Medications

Name	Recommendation
Acalabrutinib (Calquence)	PPIs = X, recc change to H_2RA/AA. H_2RA = D, separate by giving acalabrutinib 2 hrs before H2B. AA = D, separate by giving AA 2 hrs pre/post acalabrutinib.
Bosutinib (Bosulif)	PPIs = D, recc change to H_2RA/AA. H_2RAs = D, separate by giving H2Bs more than 2 hrs before or after bosutinib. AA = D, separate by giving AA more than 2 hrs before or after bosutinib.
Dacomitinib (Vizimpro)	PPIs = X, recc change to H_2RA/AA. H_2RAs = D, separate by giving dacomitinib at least 6 hrs before or 10 hrs after H_2RAs.
Dasatinib (Sprycel)	PPIs = X, recc change to AA, taken 2 hrs before or after dasatinib. H_2RAs = X, recc change to AA, taken 2 hrs before or after dasatinib. AA = separate by taking AA 2 hrs before or after dasatinib.
Erlotinib (Tarceva)	PPIs = X, recc change to H_2RA/AAs, although there are conflicting data. H_2RAs = D, recc give erlotinib 10 hrs after and at least 2 hrs before H_2RA. AA = D, recc separate by several hours.
Gefitinib (Iressa)	PPIs = D, recc administer gefitinib 12 hrs after PPI or 12 hrs before next dose of PPI. H_2RAs = D, recc administer gefitinib at least 6 hrs before or after administration of H_2RAs. AA = D, recc separate by at least 6 hrs before/after AA.
Neratinib (Nerlynx)	PPIs = X, change to H_2RAs. H_2RAs = X, administer neratinib at least 2 hrs before or 10 hrs after H_2RAs. AA = D, separate by giving neratinib at least 3 hrs after AA.
Nilotinib (Tasigna)	PPIs = D, avoid use, separation of doses not likely to be adequate. H_2RAs = D, separate by giving nilotinib 10 hrs after or 2 hrs before H_2RAs. AA = D, separate by giving nilotinib 2 hrs before or 2 hrs after the AA.
Pazopanib (Votrient)	PPIs = X, avoid use. H_2RAs = X: avoid use. AAs = D, separate by several hours if AA is necessary.
Pexidartinib (Turalio)	PPIs = X, recc change to H_2RAs or AA. H_2RAs = D, recc administer pexidartinib at least 2 hrs before or 10 hrs after H2B. AAs = D, recc separate by at least 2 hrs before or after pexidartinib.

X = contraindicated, D = therapy change needed, recc = recommend.
PPIs = proton pump inhibitors, H_2RAs= histamine-2 receptor antagonists, AAs = antacids.
Source: Lexicomp.

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Learning Objectives for This Month's CME Activity:

After participating in this CME/CNE activity, readers should be better able to: 1. Summarize the indications for gastric acid suppressing (GAS) medications and the prevalence of their use among people with cancer. 2. Analyze the implications of research findings on the effects of GAS agents on patients who also received tyrosine kinase inhibitor (TKI) anticancer treatments.

Disclosure: The author(s), faculty, staff, and planners, including spouses/partners (if any), in any position to control the content of this activity have disclosed that they have no financial relationships with, or financial interests in, any commercial companies relevant to this educational activity.

Breast Cancer Can Form Sleeper Cells After Drug Treatment

Breast cancer medicines may force some cancer cells into "sleeper mode," allowing them to potentially come back to life years after initial treatment.

These are the early-stage findings from scientists at Imperial College London, who studied human breast cancer cells in the laboratory.

The team, who studied hormone treatments, say their research opens avenues for finding ways of keeping the cancer cells dormant for longer, or even potentially finding a way of awakening the cells so they can then be killed by the treatment.

"For a long time, scientists have debated whether hormone therapies—which are a very effective treatment and save millions of lives—work by killing breast cancer cells or whether the drugs flip them into a dormant 'sleeper' state," explained Luca Magnani, PhD, lead author of the study from Imperial College London Department of Surgery and Cancer.

"This is an important question as hormone treatments are used on the majority of breast cancers. Our findings suggest the drugs may actually kill some cells and switch others into this sleeper state. If we can unlock the secrets of these dormant cells, we may be able to find a way of preventing cancer coming back, either by holding the cells in permanent sleep mode, or by waking them up and killing them."

Study Details

In the study, published in the journal *Nature Communications* (2019; doi: 10.1038/s41467-019-11721-9) and funded by Cancer Research UK and the NIHR Imperial Biomedical Research Centre, the team studied around 50,000 human breast cancer single cells in the lab and found that treating them with hormone treatment exposed a small proportion of them as being in a dormant state.

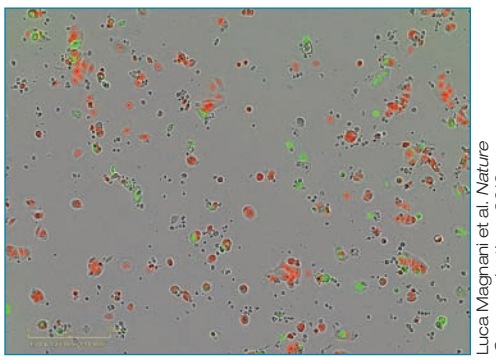
The team noted the "sleeper cells" may also provide clues as to why some breast cancer cells become resistant to treatment, causing a patient's drugs to stop working, and their cancer to return.

Hormone therapies are used to treat estrogen-receptor positive breast cancer. These make up over 70 percent of all breast cancers, and are fueled by the hormone estrogen. These cancers are usually treated with surgery to remove the tumor, followed by a course of targeted hormone therapy—usually either aromatase inhibitors or tamoxifen, which target estrogen receptors.

However, around 30 percent of breast cancer patients taking hormone therapies see their cancer eventually return—sometimes as long as 20 years after treatment. This returning cancer is usually metastatic and the tumors are often now resistant to medication.

Previous work by the same team has investigated why breast cancer cells become resistant to hormone treatment, with findings suggesting cells can make their own "fuel," allowing them to avoid being "starved" by cancer treatment.

This new research provides another piece in the puzzle, explained Iros Barozzi, PhD, co-author of the study, also from the Department of Surgery and Cancer. "These sleeper cells seem to be an intermediate stage to the cells becoming resistant to the cancer drugs. The findings also suggest the drugs actually trigger the cancer cells to enter this sleeper state."



Luca Magnani et al. *Nature Communications 2019*

Breast cancer sleeper cells: Dormant "sleeper" cells (red) and active cancer cells (green).

The research also revealed cells in this dormant sleeper state were more likely to spread around the body, explained Sung Pil Hong, PhD, study co-author from Imperial. "Our experiments suggest these sleeper cells are more likely to travel around the body. They could then 'awaken' once in other organs of the body, and cause secondary cancers. However, we still don't know how these cells switch themselves into sleep mode—and what would cause them to wake up. These are questions that need to be addressed with further research."

The team added that hormone therapies remain one of the most effective treatments against breast cancer, and that further patient research will explore whether taking hormone therapies for longer after initial cancer treatment could prevent cancer cells from waking from their sleeping state.

"Although treatments for breast cancer are usually successful, cancer returns for some women, often bringing with it a poorer prognosis," noted Rachel Shaw, PhD, from Cancer Research UK. "Figuring out why breast cancer sometimes comes back is essential to help us develop better treatments and prevent this from happening. This study highlights a key route researchers can now explore to tackle 'sleeping' cancer cells that can wake up years after treatment, which could potentially save the lives of many more women with the disease." OT

TKI ANTICANCER AGENTS

continued from page 20

every-other-day dosing for about 2 weeks, 3) then change to two times per week dosing for about 2 weeks, and 4) then discontinue. Residual symptoms can be managed with OTC AAs. Non-drug remedies for symptoms include elevation of the head of the bed, avoidance of meals for 2-3 hours prior to bedtime, and avoidance of dietary triggers of symptoms.

One of the first steps in managing patients about to start TKI treatment is to check for DDIs. A DDI check is only as good as the accuracy of the medication list, and patients should be specifically asked about the use of GAS agents. If a clinically significant DDI is found, then it should be determined if a deprescribing/step-down method would be appropriate based on the indication for GAS treatment. For example, if the patient has Zollinger-Ellison syndrome, then deprescribing would be inappropriate, and an alternate cancer treatment might be necessary, depending on the cancer diagnosis. However, this situation is rare and for most patients a deprescribing/step-down approach will likely be successful, allowing for TKI treatment to start.

Specific DDI management recommendations are found in **Table 2**, for those TKIs agents with likely clinically significant absorption changes when used with GAS medications. OT

Article Resources

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