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Lung cancer

ACID SUPPRESSORS AND TKI ABSORPTION

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TRIAL SUMMARY: Proton pump inhibitor use reduces TKI efficacy


Oral drug absorption is dependent on numerous factors including gastric acidity. This study aimed to determine if concurrent use of proton pump inhibitors (PPIs) and tyrosine kinase inhibitors (TKIs) impairs progression-free survival (PFS) and overall survival (OS). Advanced/metastatic non-small cell lung cancer (NSCLC) patients receiving erlotinib from 2007 to 2012 and renal cell cancer (RCC) patients receiving sunitinib from 2007 to 2013 at 2 Alberta cancer centres were retrospectively reviewed. The review included the Alberta outpatient/retail pharmacy databases. Patients (pts) were identified as concurrently receiving acid suppression if their pharmacy records included a PPI with prescription dates that overlapped by ≥20% with TKI treatment duration. PFS and OS were the primary endpoints. The concomitant use of PPIs with erlotinib was found to be detrimental to both PFS (hazard ratio [HR] 1.71, 95% CI: 1.39–2.11, p<0.0001) and OS (HR 1.29, 95% CI: 1.05–1.59, p=0.016). Use of PPIs alongside sunitinib also affected PFS (HR 1.42, 95% CI: 1.00–2.01, p=0.050) and OS (HR 1.27, 95% CI: 0.88–1.82, p=0.202). When considering performance status, acid suppression impaired PFS (HR 1.56, 95% CI: 1.31–1.87, p<0.0001) and OS (HR 1.24, 95% CI: 1.04–1.49, p=0.019) in both RCC and NSCLC. Results support the idea that PPIs impair TKI absorption, leading to poorer survival.

COMMENTARY: While oral chemotherapy agents have been available since the early 1950s, the explosion of new oral cytotoxic and small-molecule targeted inhibitors in the market over the last decade has significantly impacted the way cancer treatment is administered. It is suggested that the use of oral agents can improve a patient’s quality of life by avoiding lengthy visits for intravenous infusions and the need for invasive lines, which can pose an increased risk for infection and thromboembolic complications.1 As well, oral agents provide the patient with an element of control over treatment administration.2 The bioavailability of orally administered drugs can, however, be affected by their ability to be absorbed through the gut epithelium. Dissolution and passive diffusion of orally administered drugs is partially dependent on the pKa of the compound, as well as the gastric/intestinal pH. The latter, in turn, is affected by food and other drugs, which can result in a reduction in the level of the drug entering the bloodstream. In some cases, highly acidic environments can also lead to protonation of the drug, neutralizing its activity. One method to reduce acid levels in the gut is the utilization of PPIs such as omeprazole and rabeprazole. Due to the high rates of gastrointestinal reflux disease in the general population, the use of PPIs is widespread and many cancer patients are on PPIs at the time of diagnosis.

Acid suppression is known to affect the absorption of certain oral drugs. In fact, the product monographs for drugs such as erlotinib and dasatinib warn against coadministration of PPIs for this reason.3,4 A few studies have looked at the effect on patient outcome of PPIs administered in conjunction with oral small-molecule inhibitors; these have shown no adverse effects on efficacy.5,6 Chu et al embarked on a large retrospective study looking at the effect of coadministration of PPIs with the TKIs erlotinib and sunitinib on both OS and PFS in their advanced NSCLC and RCC patient population. Their results indicated that PPI usage impaired the efficacy of both TKIs, with a reduction in both PFS and OS. While given the product monograph recommenda-

IN BRIEF

Already known
• Acid suppression affects the absorption of certain oral drugs
• Product monographs for oral chemotherapy agents erlotinib and dasatinib warn against co-administration of proton pump inhibitors (PPIs)

What this study showed
• PPI co-administration impaired the efficacy of erlotinib and sunitinib, with a reduction in both PFS and OS

Next steps
• Undertake further research on PPI therapy and oral TKI administration
• Incorporate discussion of impact on OS and PFS in discussions between clinicians and patient to assure informed treatment decisions.
tions, this is not surprising for erlotinib, it is for sunitinib, which has no available data on PPI drug-drug interactions. Chu et al have thus highlighted a potential effect of acid-suppression therapy on sunitinib activity. Taken together, these important results illustrate the need for future work to be undertaken on PPI therapy and oral TKI administration, as the potential effect on survival is a critical piece of information that physicians and patients require to make informed treatment decisions.

References: