Severe gastrointestinal bleeding due to erlotinib and celecoxib therapy: additional effect?

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ABSTRACT

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related dead worldwide and accounts for over 85% of all lung cancers. Furthermore, the majority of patients with NSCLC present with advanced, metastatic disease at the time of diagnosis. For most patients with non-small cell lung cancer, current treatments do not cure the cancer. Therefore, there is a great need for development of more effective therapies. The epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) like erlotinib and gefitinib have been recognized as an important molecular target in cancer therapy and they are approved for the treatment of refractory advanced NSCLC patients. EGFR TKIs are generally well tolerated. The two most common toxicities include dermatologic and gastrointestinal side effects. Cases of gastrointestinal perforation, some of which were fatal, have also been reported in patients receiving erlotinib. Patients at increased risk include those taking concomitant anti-angiogenic agents, corticosteroids, non-steroidal anti-inflammatory drugs, and/or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease.

Introduction

Over the past few years, research has showed that non-small cell lung cancer (NSCLC) is a heterogeneous disease, with a number of biological events that drive tumor growth and progression. This has led to the identification of several molecular targets involved in the uncontrolled growth of lung cancer cells, such as the epidermal growth factor receptor (EGFR) pathway, which includes a family of genes encoding widely expressed trans-membrane protein tyrosine kinase implicated in the development and the progression of cancer in humans.[1] The epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) like erlotinib and gefitinib have been recognized as an important molecular target in cancer therapy and they are approved for the treatment of refractory advanced NSCLC patients.[2]

Moreover, activation of *EGFR* gene mutation has emerged as the most clinically relevant predictor of response to EGFR TKIs.[3] Data show that patients with the tumor EGFR-activating mutation had superior survival, compared to patients with EGFR wild-type tumors.[4]

Therefore, according to the international guidelines, erlotinib is recommended as the treatment in patients with advanced metastatic non-squamous, non-small cells lung cancer with EGFR activating mutations (EGFR M+).[4] Cyclooxygenase 2 (COX-2)-dependent signaling represents a potential mechanism of resistance to therapy with EGFR tyrosine kinase inhibitors.[5,6] Patients with EGFR wild-type status may benefit from the combination of erlotinib and celecoxib. Celecoxib is a selective COX-2 inhibitor commonly used for osteoarthritis pain. Celecoxib inhibit the production *via* COX-2 of prostaglandinis (PGs) mediating pain and inflammation while preserving COX-1-mediated production of PGs. As a result, this

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agent might be expected to offer a more favorable safety profile than non-selective non-steroidal anti-inflammatory drugs (NSAIDs) with respect to upper gastrointestinal bleeding.

Case Report

A 68-year-old non-smoker male with advanced non-small cell lung cancer EGFR M+ was referred to our Unit for melena. The patient was in the second-line treatment with Erlotinib (150 mg/daily), in addition to celecoxib (COX-2 inhibitor) at 400 mg twice daily by seven weeks because the first therapy with cisplatin and pemetrexed was administered unresponsive for up to eight months.

Laboratory studies revealed reduction in hemoglobin (8.4 mg/dL, range 13-15 mg/dL). An anamnestic history did not reveal previous diagnosis of upper gastrointestinal bleeding. Urgent upper endoscopy, performed until the second duodenal portion, revealed the presence of several longitudinal wide ulcers in the antrum (Forrest IIc) (Figure 1A). In the bulb, were found a wide ulcer located in the posterior wall, with recent signs of bleeding and adherent clot (Forrest IIb), and another wide ulcer, located in the anterior wall with active bleeding (Forrest Ib) that were treated with sclerotherapy (dilution adrenaline 10 cc) (Figure 1B). Therapy with intravenous proton pump inhibitors was started. The *Helicobacter pylori* infection was not found. The patient recovered well and was discharged five days later. A gastroscopy of follow-up, performed 3 weeks later, was negative for gastric and duodenal peptic lesions. The only therapy with erlotinib at 150 mg/daily was resumed. After six months of follow-up, the patient is in good conditions and the hemoglobin level is 13.2 g/dL.

Discussion

Generally, erlotinib therapy is safe and well tolerated. The most common adverse reactions in patient receiving erlotinib are diarrhea and skin rash.[7] Grade 3 and 4 of rash and diarrhea occurred in 9% and 7% of erlotinib-treated patients respectively, but only 6% and 1% of patients need a dose reduction for rash and diarrhea.[8] Liver function test abnormalities are observed. This elevation is transient or associated with liver metastasis. Interstitial lung disease as interstitial pneumonia, pneumonitis, acute respiratory distress syndrome, pulmonary fibrosis and alveolitis can be observed rarely with an overall incidence of about 0.8%. Conjunctivitis and keratitis are reported infrequently in patient receiving erlotinib therapy while corneal ulceration may also occur.[8]

Very rare cases of gastrointestinal bleeding (GIB) are reported in clinical studies, some associated with concomitant warfarin administration and some with concurrent NSAIDs administration. No GIB is reported in literature when erlotinib is associated with COX-2-inhibitors (celecoxib).[8] The mechanism by which erlotinib can cause GIB is still unclear.[9]

The first study conducted by Reckamp *et al.*[10] to determine the optimal biological dosage of celecoxib when combined with erlotinib in advanced NSCLC did not reveal GIB or severe gastro-intestinal toxicity.

Subsequently another study enrolled twenty-six patients evaluating the potential predictive value of COX-2 expression and increased risk of gastrointesti-

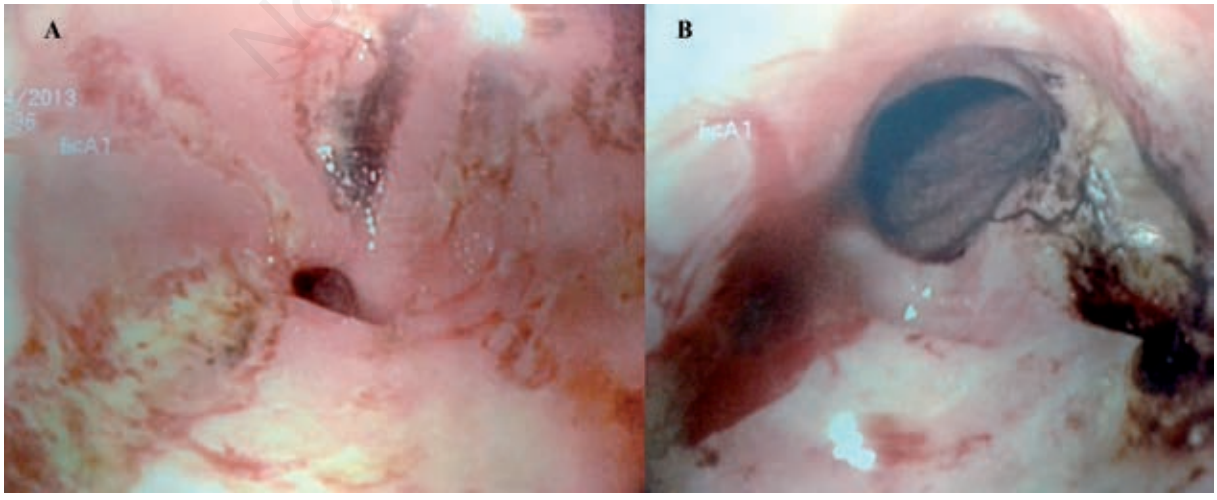

Figure 1. Endoscopic view showed: A) longitudinal wide ulcers in the antrum; B) in the bulb, were found a wide ulcer located in the posterior wall with recent signs of bleeding, and another wide ulcer located in the anterior wall with active bleeding.

nal hemorrhage in advanced NSCLC patients treated with erlotinib and celecoxib.[11] The combination of erlotinib and celecoxib did not seem to be superior to erlotinib alone in unselected patients.

Conclusions

In conclusion, EGFR TKIs in association with COX-2 inhibitors are promising anticancer drugs for the future, but further research is warranted to select the patient group that will optimally benefit from this therapy, also in terms of safety and tolerability. GIB occurred under erlotinib and celecoxib treatment is rare and this clinical scenario can be fatal especially in patients with a history of peptic ulcer or requiring anticoagulant therapy. Maybe these two last conditions should be considered before starting the treatment in order to reduce the incidence of this complication.

References

1. Baselga J, Arteaga CL. Critical update and emerging trends in epidermal growth factor receptor targeting in cancer. J Clin Oncol 2005;23:2445-59.
2. Mok TS, D'arcangelo M, Califano R. Clinical outcomes with erlotinib in patients with epidermal growth factor receptor mutation. Drugs 2012;72:3-10.
3. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancer from "never smokers" and are associated with sensitivity of tumors to gefinitib and erlotinib. Proc Natl Acad Sci U S A 2004;101:13306-11.
4. Wu WS, Chen YM, Tsai CM, et al. The epidermal growth factor receptor-tyrosine kinase inhibitor era has changed the causes of death of patients with advanced non-small-cell lung cancer. J Chin Med Assoc 2013;pii: S1726-4901(13)00204-9.
5. Csiki I, Johnson DH. Did targeted therapy fail cyclooxygenase too? J Clin Oncol 2006;24:4798-800.
6. Dohadwala M, Yang SC, Luo J, et al. Cyclooxygenase-2-dependent regulatin of E-cadherin: prostaglandin E(2) induces transcriptional repressors ZEB1 and snail in non-small cell lung cancer. Cancer Res 2006;66:5338-45.
7. Gridelli C, Bareschino MA, Schettino C, et al. Erlotinib in non-small cell lung cancer treatment: current status and future development. Oncologist 2007;12:840-9.
8. Cohen MH, Johnson JR, Chen YF, et al. FDA drug approval summary: erlotinib (tarceva) Tablets. Oncologist 2005;10:461-6.
9. Bai H, Liu Q, Shi M, Zhang J. Erlotinib and gefitinib treatments of the lung cancer in an elderly patient result in gastrointestinal bleeding. Pak J Med Sci 2013;29: 1278-9.
10. Reckamp KL, Krysan K, Morrow JD, et al. A phase I trial to determine the optimal biological dose of celecoxib when combined with erlotinib in advanced non-small cell lung cancer. Clin Cancer Res 2006;12:3381-8.
11. Fidler MJ, Argiris A, Patel JD, et al. The potential predictive value of Cyclooxygenase-2 expression and increased risk of gastrointestinal hemorrhage in advanced non-small cell lung cancer patients treated with erlotinib and celecoxib. Clin Cancer Res 2008;14:2088-94.