Reviewer's report

Title: Fatal interstitial lung disease associated with oral erlotinib therapy: Case report

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Reviewer: Christopher Azzoli

Reviewer's report:

General

This is a case report of a single patient who developed lethal interstitial lung disease (ILD) coincident with erlotinib chemotherapy for metastatic NSCLC. This condition is a diagnosis of exclusion. The authors establish the diagnosis by providing information regarding the timing of erlotinib administration and development of the condition, and also explaining that an, "extensive work-up failed to reveal pulmonary infection or heart failure." There is also a post-mortem examination of lung tissue with findings consistent with erlotinib-induced ILD. No pre-treatment studies (CT scans, tissue analysis, or pulmonary function tests) are presented to establish whether the patient had underlying interstitial lung disease prior to erlotinib therapy.

An unusual aspect of the case is that he was noted to have bilateral diffuse ground-glass opacities on a chest CT prior to the development of symptoms, and his condition worsened over the next two weeks despite discontinuing the drug. This calls into question the temporal association of the condition and drug effect.

While the incidence of erlotinib-induced ILD is < 1%, this syndrome is an extremely important clinical phenomenon for the management of patients with metastatic NSCLC. This case report is certainly worthy of publication, but it needs some changes.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

I have the following major criticisms which merit response by the author:

1) In the abstract and discussion sections, the authors allude to the necessity to, "treat," ILD in patients on erlotinib. Nothing in their case suggests that any treatment is effective, other than stopping the drug. In fact, the case which they present suggests that even stopping the drug doesn't help!

While corticosteroids seem reasonable once infection has been ruled out, I do not agree with the use of cyclophosphamide in this setting. I suggest the authors drop any and all allusions to "treatment" of this condition. If they insist on recommending a treatment, they must provide a more thorough literature review which might suggest an effective treatment for this condition. (I am not aware of data in the literature which supports one treatment over another, other than immediately stopping erlotinib).

2) This patient received several drugs in sequence which are toxic to the lungs-- gemcitabine, docetaxel and mitomycin. The authors do not present any information about potential lung damage from these agents. They report that his, "lung function tests were normal," prior to erlotinib. They must present the FEV1, FVC, FEV1/FVC ratio and DLCO from contemporary pulmonary function tests (PFTs) in order for me to believe this. Ideally, they should also present PFTs before and after the other chemotherapies, and some baseline CT images to confirm the lung infiltrates developed while on the erlotinib, and not before.

3) Given erlotinib ILD is a diagnosis of exclusion, the authors must present more detailed information regarding tests which ruled out intercurrent infection, congestive heart failure, and multiple pulmonary emboli/infarction rather than just referring to, "an extensive work-up."

4) The authors state that none of the factors typically associated with ILD (such as pre-existing ILD, radiation, or infection) were present in this case. Given that this patient has received prior gemcitabine, docetaxel and mitomycin, I think he may have had underlying lung damage which made him susceptible to erlotinib-induced ILD. As such, the authors must review the literature on lung damage from these agents,
and comment on whether treatment with these agents (which are all commonly used for the treatment of NSCLC) may increase risk of erlotinib ILD.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I have no conflicts of interest with regards to any relationship with the makers of erlotinib.

I am co-author on a manuscript which details a case report of erlotinib-induced ILD in a patient with underlying idiopathic pulmonary fibrosis (IPF). This case report was not accepted for submission to the Journal of Clinical Oncology, and is currently under review for submission to the journal Chest.

Given I have not submitted any manuscripts for publication in this journal, I declare that I have no competing interests.