Author's response to reviews

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

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Author's response to reviews: see over
To:
The Editor, BMC Cancer
April 23th, 2007

Dear Sir

We would like to submit a revised version of our manuscript entitled ‘Fatal interstitial lung disease associated with oral erlotinib therapy: Case report’.

As you will see in the enclosed answers to the reviewer we made a point by point response and when necessary changed the text accordingly.

We hope that this revised version will be considered as suitable for publication

Yours Sincerely,

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Dear Sir,

Thank you so much for the thorough reviewing you did and the constructive and helpful comments you made that helped us to improve by far our manuscript. Please find a point-by-point response to your comments. Page and line numbers relate to the word file.

**COMMENTS TO THE AUTHOR (IN CAPITALS)**

Response of the authors (lowercase in blue)

**REVIEWER**

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.

Thank you very much for your structural comment. You are right that our diagnosis was based on post mortem examination of the lungs which provided evidence for ILD and help to exclude definitely congestive cardiac failure and pulmonary embolism whereas it was not suggestive for infection.

In light of your comment we now provid Chest CT data (Figure 1) and baseline lung function tests (page 4, lines 17-18) obtained before initiating erlotinib. These studies were definitely not suggestive of underlying interstitial lung disease (ILD).

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 WORSENGED OVER THE NEXT TWO WEEKS DESPITE DISCONTINUING THE DRUG. THIS CALLS INTO QUESTION THE TEMPORAL ASSOCIATION OF THE CONDITION AND DRUG EFFECT.

Gas exchanges at rest and on exercise may be preserved at least for a while in ILD and the disease may remain indolent, at least during its early phase. In the present case CT assessment of tumor response was scheduled at predetermined time and not performed on a symptoms related basis. Thus, provided the disease developed sub-acutely, it is not surprising that chest CT caught the disease before symptoms were clinically apparent.

Unfortunately drug related ILD do not always respond to discontinuation of therapy, especially when the mechanism by which the drug induces ILD is not known. Although one case report suggested that erlotinib-related ILD may improve after drug
discontinuation (Ref 2) it should be emphasised that for the other EGFR inhibitor (gefitinib-Iressa) fatalities have been reported despite drug discontinuation (Ref 3).

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.

Thank you for this encouraging comment and most of all for the excellent and thorough reviewing you did.

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).

The treatment sequence in the present case (i.e. discontinuation of erlotinib, followed by corticosteroids followed by corticosteroids boluses followed by cyclophosphamide) was dictated by the severity of the symptoms and inexorable progression of the disease. You are right that in our case the therapeutic strategy was not effective and yet no data are available to support optimal treatment for this condition. In light of your comment we dropped any allusions to treatment of this condition. Abstract and discussion were modified accordingly.

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.
We agree that prior chemotherapy has the potential to result in significant pulmonary toxicity; however, this usually occurs early after administration of these agents [ref 4-8]. Our patient underwent chemotherapy with mitomycin – navelbine seven months before any sign of ILD could be radiologically or clinically detected. Unfortunately there is no DLCO test available since clinical and radiological examinations have never suggested interstitial disease and thus, this test has been never asked for. We regret for using the term ‘normal’ for lung function tests which was completely inappropriate here. Although there was no restrictive pattern that might indicate interstitial disease, lung function tests demonstrated an obstructive pattern due to underlying COPD; oxygen saturation and Karnofski index were normal. To confirm that there was no significant pulmonary damage suggestive of ILD before erlotinib administration Chest CT data, available lung function and Karnofski index were provided (Figure 1; page 4, lines 17-18 and page 5 first line).

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.”

You are certainly right. We should provide more information for tests used to rule out other possible causes of ILD. In light of your comment text was modified (page 5, lines 5 and 10-12).
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.

We have reviewed the current literature and in light of your comment and we have commented on whether treatment with these agents may increase the risk of erlotinib related ILD in the new version of the manuscript.