Author’s response to reviews

Title: Imatinib Induced Severe Skin Reactions and Neutropenia in a Patient with Gastrointestinal Stromal Tumor

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Version: 2 Date: 29 April 2010

Author’s response to reviews: see over
Dear Editor

We have enclosed a revised manuscript entitled “Imatinib Induced Severe Skin Reactions and Neutropenia in a Patient with Gastrointestinal Stromal Tumor” which we would like to submit to "BMC cancer" for consideration as a case report. We would be grateful if the manuscript could be reviewed and considered for publication in “BMC cancer”.

We are very inspired and thank you for your review.

Sincerely yours,

Ik-Joo Chung, M.D., Ph.D.

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Response to reviewer’s report (Reviewer: Pascal Wolter)

OP 1. Title: The authors use the term “hypersensitivity” to resume the observed side effect, however it is not clear neither in the abstract nor in the text what their definition of “hypersensitivity” is: are they talking about a hypersensitivity syndrome, also described as a drug reaction with eosinophilia and systemic symptoms (DRESS, some of the diagnostic criteria can be found in the case report, others such as lymphadenopathy are not mentioned, it is also not mentioned whether oral or mucosal lesions were observed), are they talking about a IgE-mediated reaction to imatinib,... this is needs further comment. This might be important because some of these “hypersensitivity reactions are not-dose dependent, the fact that in the described case the skin rash apparently was dose dependent might give insight into the possible pathomechanism.

->Thank you for your comment, I agree with your opinion. The patient had no lymphadenopathy and there were no oral mucosal lesions. The skin rash was exfoliative type. Eosinophilia was not above 1.5X10^9/L. A dose related skin toxicity was observed. Therefore, we could not think of DRESS syndrome. Manuscript was changed and added as follows “several studies have reported a dose related skin toxicity of imatinib, indicating a pharmacological effect of imatinib. This case can also mainly be related to the pharmacological effects of imatinib, but the delayed type hypersensitivity might be involved in some aspects like other skin rashes considering eosinophilia and pruritus.”

OP 2. Unfortunately, the author do not mention whether a molecular analysis of the GIST at initial diagnosis was performed although in most international guidelines mutational analysis for known mutations involving KIT and PDGFR genes are recommended and have become standard clinical practice.
We planned the molecular analysis but the patient refused the test

OP 3. We can not follow the authors in their conclusion that “the optimal dose of imatinib for the treatment of GIST is still unclear”, for the huge majority of patients a starting dose of 400mg seems adequate (see also recent publication of the MetaGIST group in J Clin Oncol). The value of pharmacokinetic studies in routine clinical practice is still under investigation.

I agree with your opinion. Manuscript was changed and added as follows. “ The current recommended daily dose of imatinib is 400mg, however, patients at risk for adverse drug reactions may benefit from lower doses. Individualized treatment is needed for such patients, and we may also try sunitinib as an alternative drug.

OP 4. At the initial presentation the patient had also neutropenic fever, the authors do not report on a possible underlying infection which might at least have contributed to the clinical presentation. The indication of G-CSF in this situation is at least doubtful.

We performed the microbiologic test, but the result of blood culture was negative. There were no infection foci. As the patient condition was so grave that we had to use G-CSF prophylactically.

OP 5. It might be useful to give references of the laboratory tests mentioned in the text, I am not sure that the standard references are the same in Korea, Europe and the United State? The authors do not mention whether specific test (skin test?) to exclude/confirm and allergic constitution were performed, this might be discussed with an allergologist.

We added the reference value in the manuscript. I think the standard references may be similar. We consulted allergic department and they recommended gradual dose escalation of imatinib. We did not performed the specific test.

OP 6. How do the authors explain the elevated liver function test?
We might think the liver enzyme elevation was due to the adverse effects of imatinib. As mentioned above, we could not think of DRESS syndrome.

OP 7. Did the dermatologist perform a skin biopsy – might deliver further interesting information.

-> We also think so, but a skin biopsy was not performed due to the potential risk of the wound not being able to heal.

OP 8. “Severe skin lesions that were resistant to supportive measures have been the most frequent cause for permanent discontinuation of imatinib therapy” Could the authors give us the reference for this statement?

We wonder whether imatinib-induced cutaneous side effect are as frequent in CML as in GIST? It would be better in this paper to refer only to imatinib induced cutaneous side effects in GIST patients, at least some side effect under imatinib seems to be more or less prominent in different diseases.

-> J Clin Oncol 2003, 21:1644. We extrapolated from imatinib data of CML.

-> High grade skin reactions were similarly reported with an incidence of 2-3% with imatinib in CML (Best Pract Res Clin Haematol 2009, 22:409-429)

-> We deleted the following paragraph according to your comments.

“Myelosuppression is particularly common in patients with CML treated with imatinib. Grade 3-4 neutropenia may occur in about 25% of patients with chronic phase disease. In patients with CML, the majority of hematopoiesis is derived from Philadelphia chromosome positive stem cells; since, imatinib effectively targets Bcr-Abl, a degree of myelosuppression is expected. Myelosuppression can also develop as imatinib inhibits c-KIT in the normal stem cell. However, imatinib does not severely affect normal hematopoiesis. Therefore, neutropenia is less common in patients with GIST”

OP 9. We wonder whether eosinophilia (only once assessed?) and recurrence of the skin
rash are sufficient to establish the diagnosis of “hypersensitivity”? For exam, were other possible reasons for eosinophilia excluded?

-> We performed the parasite exam including cellophane thick smear of stool and serum ELISA. the test was negative. We agreed with your comments but we could not completely exclude the delayed type hypersensitivity. The manuscript was changed as follows. “several studies have reported a dose related skin toxicity of imatinib, indicating a pharmacological effect of imatinib. This case can also mainly be related to the pharmacological effects of imatinib, but the delayed type hypersensitivity might be involved in some aspects like other skin rashes considering eosinophilia and pruritus.”

OP 10. It would be interesting to get to know how the authors measured the plasma level of imatinib, what are their references? If they have the same methods and references as in the cited paper of Demetri et al, than the imatinib concentration at steady state with 331 ng/ml is far infratherapeutic and it would be very surprising that the patient is still responding to treatment – why should the patient be so sensitive to Glivec?

-> We checked the plasma level of imatinib with similar method in the cited paper. We do not know why the patient should be so sensitive to Glivec. We thought it was extremely unusual case, therefore we decided to report this case.
Response to reviewer’s report (Reviewer: Peter Reichardt)

Major compulsory revisions:

Title should refer to the side effect discussed and not to optimal dose of imatinib

-> The title was changed as follows “Imatinib induced severe skin reactions and neutropenia in a patient with gastrointestinal stromal tumor”

Abstract is too long.

-> We shortened the abstract.

In background it is mentioned that no alternatives to imatinib exist in GIST. In this context the availability of sunitinib should be discussed.

-> We added the following sentences “Sunitinib has demonstrated efficacy in treating patients with GIST who have experienced disease progression on or intolerance to imatinib.

Case presentation : how was overdosing or interaction with food components or alternative treatments ruled out? Why was blood level testing not done?

-> The patient had good compliance. He took the medicine on a regular basis in accordance with a doctor’s directions. He never drinks alcohol and we could not think of any other interaction with food.

-> The patient had good tumor response to imatinib, therefore we tried to maintain the imatinib.

-> We could not think of drug overdosing because imatinib 800mg/day was even tolerable in other patients. Therefore, we did not performed the blood level testing. Demetri et al. Suggested that imatinib trough levels at steady state were associated with a clinical benefit recently.

Conclusions: discussion of basic data on GIST can be omitted.
-> We omitted the discussion of basic data on GIST

Substantial overlap with “background”.

-> We tried to shortened the conclusion.

Page 8, last line: data on overall survival incorrect and out of place here.

Conclusions must be shortened and restricted to the key message of skin toxicity management.

-> We deleted the data on overall survival and tried to shortened the conclusions according to reviewer’s comments

Final page: speculations on future course of the disease are not useful.

Discussion of “optimal dose of imatinib” should be deleted.

Summary: the manuscript should be revised to a concise discussion of the management of severe skin toxicity.

-> The manuscript was revised according to reviewer’s comments