REFeree’S COMMENTS

• The paper adds to (already several) other case reports and reviews on cutaneous side-effects of Imatinib for the treatment of patients with metastatic GIST.

• The manuscript can be judged as being scientifically and methodologically more or less accurate, although some definitions remain vague and some additional investigations would have been useful.

• The figures are of moderate quality, and I am not sure that 6 figures are really needed to illustrate the case.

• The reference section is adequate, most references are up-to-date and appropriate.

• Some concrete comments/questions:

  o 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 needs further comment.

  o 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.

  o p. 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.

  o p. 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 400 mg 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.

  o p. 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.

o p. 5-6: 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 States? The authors do not mention whether specific test (skin tests?) to exclude/confirm and allergic constitution were performed, this might be discussed with an allergologist.

o p. 6: How do the authors explain the elevated liver function tests?

o p. 7: Did the dermatologist perform a skin biopsy – might deliver further interesting information.

o p. 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?

o 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.

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

o p. 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?

**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.