Reviewer's report

Title: Fatal case of sorafenib-associated hepatotoxicity in the adjuvant treatment of a patient with Renal Cell Carcinoma

Version: 2 Date: 18 July 2012

Reviewer: Henning Wege

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Fairfax et al. report the first case of fatal immune-mediated sorafenib induced multi-organ failure. This is a case of very likely idiosyncratic hepatotoxicity associated to sorafenib. Since the successful completion of large phase III studies in patients with RCC and HCC, more patients receive sorafenib and it is not surprising that (as has been reported for many other drugs and even herbal remedies) sorafenib may cause an idiosyncratic drug reaction. Therefore, I agree with the authors’ conclusion that the reported case represents idiosyncrasy induced by sorafenib with acute liver toxicity triggering multi-organ failure and is of high importance to the field.

The case report is thoroughly written and comprehensive. Sufficient background information is provided to understand the case and the discussion. However, a few points are not entirely clear and should be addressed in a revised version.

Minor Essential Revisions
1. From the discussion and the pathology report it is not clear whether the authors classify the idiosyncrasy as allergic or non-allergic.
2. According to the danger hypothesis, possibility of background mild hepatic injury or concomitant infection (altered cytokine milieu triggering hapten formation) contributing to the fatal course should be addressed.
3. Currently it is unclear, why an early (e.g. transjugular) liver biopsy was not obtained and why treatment with steroids (as reported for the other discussed cases) was not initiated as rescue attempt in this patient.

Discretionary Revisions
1. I suggest including the term “idiosyncratic” in the title of the manuscript.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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

Declaration of competing interests:
I have received travel grants and lecture fees from Bayer HealthCare and are involved as principal investigator in phase III clinical studies investigating sorafenib in the treatment of patients with hepatocellular carcinoma.