Author's response to reviews

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

Authors:

Benjamin P Fairfax (bfairfax@well.ox.ac.uk)
Sarah Pratap (Sarah.Pratap@ouh.nhs.uk)
Ian SD Roberts (Ian.Roberts@orh.nhs.uk)
Jane Collier (jane.collier1@nhs.net)
Rick Kaplan (RKaplan@ctu.mrc.ac.uk)
Angela M Meade (A.Meade@ctu.mrc.ac.uk)
Alistair W Ritchie (A.Ritchie@ctu.mrc.ac.uk)
Tim Eisen (tgqe2@medschl.cam.ac.uk)
Valentine Macaulay (valentine.macaulay@imm.ox.ac.uk)
Andrew Protheroe (andrew.protheroe@oncology.ox.ac.uk)

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‘Fatal case of sorafenib-associated hepatotoxicity in the adjuvant treatment of a patient with Renal Cell Carcinoma’
- Response to reviewers comments

August 28, 2012

1 General comments

We would like to thank both of the reviewers for their appraisal of this case report and their helpful comments. They are both in agreement that a report of this fatal drug reaction warrants publication and, where possible, we have attempted to address their individual concerns in a revised version of this manuscript.

2 Response to reviewer 1

We are grateful for this thorough review. We note the reviewer agrees with our conclusion that this case represented a fatal idiosyncratic drug reaction to sorafenib. The reviewer has mentioned some specific concerns that we take into account in our revised manuscript and are detailed in a point by point basis.

2.1 Point 1

‘From the discussion and the pathology report it is not clear whether the authors classify the idiosyncrasy as allergic or non-allergic.’

We adjudge this idiosyncratic reaction to have been immune based and allergic in nature. We have come to this conclusion based upon the delayed interval between exposure and initial symptoms, the nature of the clinical course including mild fever and the hepatic histology where an immune based inflammatory response was apparent. To make this clearer in our conclusions we have altered the initial line so that where previously it read:

‘We believe sorafenib-induced hepatotoxicity with associated renal impairment is the most likely cause of death,’

It now reads:
‘We believe the most likely cause of death to be an idiosyncratic allergic reaction to sorafenib manifesting as hepatotoxicity with associated renal impairment.’

2.2 Point 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.’

The danger hypothesis is a theory whereby molecular patterns released upon cell injury and death (DAMPs - Danger-Associated Molecular Patterns) trigger the immune system to manifest a secondary immune response. It is a theoretical framework for the way the immune system operates and has implications for idiosyncratic drug reactions. In the text we state ‘post-nephrectomy the patient was enrolled into the SORCE study. At this point he was well and physically active and his blood parameters were within normal range’. We have no evidence to suggest that the patient was unwell with a concomitant infection during the initial period of sorafenib and we were unable to detect presence of infection when he presented later. Whilst we cannot exclude intercurrent infection, there was no history of this and there was no suggestion of ‘background mild hepatic injury’. Indeed, underlying hepatic disease is not thought to play a significant role in the susceptibility to drug induced hepatotoxicity [1, 2]. We are unaware of evidence to suggest that the altered cytokine milieu may trigger hapten formation, although the possibility that direct hepatotoxicity leads to release of DAMPs and can then promulgate an immune response is plausible. Moreover, it is becoming increasingly apparent that a large proportion of adverse drug reactions are due to host genetics, with HLA type being of utmost importance in reactions to drugs including abacavir, flucloxacillin, coamoxiclav, carbamazepine and lumiracoxib amongst others. Whilst it is entirely possible that the state of the immune system alters the chances of a genetic predisposition become actuality, there is no data to suggest that this is required and we would not wish to speculate in this single case report where the mechanism is unclear.

2.3 Point 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.’

The reviewer has raised an important point. Whilst it is arguable that a liver biopsy would have been of aid in diagnosis, the rapidity of decline in the patient’s condition, becoming encephalopathic within 4 days of admission with deteriorating clotting, meant that a biopsy was not possible. Corticosteroids were only given in one of the other described cases of non-fatal sorafenib hepatotoxicity, with recovery in the other cases occurring upon sorafenib cessation alone. The rapidity of hepatic decline in the case we describe means that it is unlikely that steroids would have had any benefit. We suggest
clinicians consider the appropriateness of steroids on a case by case basis with the caveat that there exists no evidence to suggest steroids would indeed not be deleterious.

2.4 Discretionary Revisions

‘I suggest including the term “idiosyncratic” in the title of the manuscript.’

We have accepted this suggestion and the title now reflects this.

3 Response to reviewer 2

We thank reviewer 2 for his thorough review. We are pleased that he agrees that this case report is of importance when considering the use of sorafenib as a prophylactic drug against recurrence of RCC. Where we feel appropriate, we have acted upon his comments and have altered several sentences to take into account his concerns regarding language use, but as he states, this is a stylistic matter. Of note, all authors are native English speakers. Our revisions in response to his comments are listed on a point by point basis below:

3.1 Point 1

‘The reasons for concluding that sorafenib was the cause of the liver failure are not stated explicitly, and it is unclear which causality score was used, or why the score was ’5b.’

In our revised manuscript we have used the RUCAM scoring system and have now referenced it appropriately[3]. Of note, the score is 7 which is ‘probable’, although as the reviewer doubtless appreciates, the reliability of this accepted scoring method, as with others is debatable [4]. To reflect this and the comments of reviewer 1, the text which previously read:

We believe sorafenib-induced hepatotoxicity with associated renal impairment is the most likely cause of death, supported by a causality score consistent with the role of sorafenib being “highly probable”(5b).

Now reads: We believe the most likely cause of death to be an idiosyncratic allergic reaction to sorafenib manifesting as hepatotoxicity with associated renal impairment. This is supported by a RUCAM causality score of 7, consistent with sorafenib being the probable cause.

3.2 Point 2

The authors imply on page 6/16 that what they call ‘idiosyncratic reactions’ are not dose-dependent. Since delayed-type hypersensitivity reactions are demonstrably dose-dependent, and are assumed to lie behind adverse drug reactions of intermediate time-
course, this is almost certainly wrong. [Drug Saf. 2005;28(10):851-70] What the authors almost certainly mean is that those with relevant HLA type are more susceptible.

We did not wish to imply this although we agree that this is unclear. Although a linear relationship may not exist between drug dose and idiosyncratic adverse response, hypersensitivity reactions obviously have a dose dependence[1]. We have rephrased the text so as to remove this impression.

Previously: ‘Drug induced liver injury (DILI) is attributable to either dose dependent intrinsic hepatotoxicity typically occurring soon after drug exposure, or an idiosyncratic reaction.’

Revised: Drug induced liver injury (DILI) is attributable to either direct hepatotoxicity occurring soon after drug exposure, or a delayed idiosyncratic reaction.’

3.3 Point 3

‘3. The MHRA has a single fatal report of liver failure associated with sorafenib. Have the authors reported their own case? If not, what does the MHRA fatal case represent?’

Yes, the MHRA were informed regarding the case we report here.

3.4 Point 4

‘4. Page 2/16: The authors write: ‘Here we report the case of a patient on the SORCE trial who died from liver failure associated with sorafenib treatment. Although this is an extremely uncommon occurrence, this case has important implications in the treatment of patients who are entirely asymptomatic and may indeed be free of cancer as well as alerting clinicians to this rare side effect.’ This presupposes that the hepatic failure was drug-induced, and makes a statement about prevalence that cannot be based on a single case-report.’

We are unsure of the reviewers point here. We report a single case report of fatal hepatotoxicity in a patient with no other risk factors or drug exposures who had been taking sorafenib. It is evident from trial data that the occurrence of fatal-hepatotoxicity whilst undergoing sorafenib treatment is rare and it is clear that we believe sorafenib is the most likely cause. This case adds to those in the literature supporting the potential for hepatotoxicity with sorafenib. The point we are trying to raise in this section of the manuscript (which is an introductory background for the layman) is that in future we may be exposing a subset of individuals, a large proportion of which may be cancer free, to an unpredictable adverse consequence to which clinicians should be alert to.
3.5  Point 5

5. The report is badly written. Matters of typography or style Prefer ‘adverse drug reaction’ or ‘adverse drug effect’ to ‘side effect’ throughout. 3/16: ‘He was commenced on study medication’ means ‘He started taking...’ or ‘We gave him’ [also 5/16] 3/16: ‘he had symptom progression’ means ‘his symptoms had become worse.’ 4/16: ‘he had taken no other medications including over the counter analgesics, antibiotics or statins’ means ‘he had not take over-the-counter analgesics, antibiotics, statins, or any other medicine.’ 4/16: ‘Admission bloods revealed an acute hepatitis’ means ‘results of blood tests taken on admission showed acute hepatitis’ 4/16: ‘normal hepatic echogenicity texture’ for ‘normal hepatic echogenicity’ 4/16: ‘a septic source was not discerned’ for ‘we found [identified; discovered] no septic source’ 5/16: Units for ammonia concentration not given, neither are reference ranges. 5/16: the reviewer gave up when confronted with ‘Further radiology revealed mild peri-hepatic ascites only which was found to be transudative.’ If this is to be published, it should be translated into readable English.

We have added the units for ammonium ion concentration and the normal range. We have substituted ‘adverse effect’ or ‘adverse drug effect’ for ‘side effect’ throughout. We have altered the text to take into account the reviewer’s stylistic concerns for each of the above points.

References


