Reviewer's report

Title: KIT exon 10 variant (c.1621 A>C) single nucleotide polymorphism as predictor of GIST patient outcome.

Version: 3  Date: 8 August 2015

Reviewer: Sabrina Angelini

Reviewer's report:

This is a nice work on GIST and KIT polymorphisms.

Major Compulsory Revisions

1. The major concern is about the choice of the cell line. Why authors did not ask for GIST cell line, rendering the results more specific to GIST. I understood that GIST cell lines are not commercially available, but they can be obtained for scientific purposes. The use of different cell line make translation of the results to GIST a bit ambiguous.

2. Ref 2 is out of date. I think there are many updated review to be cited in its place (example are Cioffi and Maki JCO 2015; Angelini, et al., Pharmacogenomics 2013). In any case cite a ref published in the last 5 years. Additionally in the 1990 GIST were still misclassified with leiomyosarcomas

3. There is no mention regarding Hardy Weinberg equilibrium. Authors should calculate it, as a situation of non-equilibrium would make results ambiguous.

4. As the authors stated in the abstract, “Tumor genotype plays a crucial role in clinical management of GIST, Whether inherited genetic polymorphism of KIT influences GIST patient outcome is not known” this aspects should be re-considered and deepened in the discussion, as other SNPs besides the one in kit may have influence, as well epigenetic factors, including methylation, and microRNA (the reviews Sioulas et al., Dig Dis Sci 2013; Ravegnini et al., Int J Mol Sci 2015 may be of interest).

Minor Essential Revisions

5. Background can be shortened; for example the sentence “About 10-15% of GIST do not harbor any mutations in the KIT or PDGFRA genes. Previously refered to as “wild-type” (WT), these GIST are now known to present with mutations on SDHA/B/C/D (6,7), BRAF (8–10), NF1 (11). These mutations are also associated with specific clinical presentations and clinical behaviour” is out of the aim of the paper and can be avoided.

6. The sentence “In the literature, variants have been found associated with soft tissue sarcoma incidence (12) and higher risk of relapse in different malignancies (13)” delete or make it more specific to GIST. For example, besides O’Brien et al., authors should cite: Kwon et a., J Korean Surg Soc 2012; Angelini et al., Pharmacological Research 2013; Kang et al., Asia Pac J Clin Oncol. 2014; Angelini et al., Eur J Hum Genet. 2015;
7. In material and methods: “of 109 patients with GIST” change to “of 109 GIST patients”

8. In results: The heading “Clinical and biological characteristics of the series” change “of the series” to “of the two GIST patients series”

9. Discussion should put less emphasis on the results regarding kit SNPs, unlike mutations (that usually have a drastic/dramatic effects) the influence of a single SNP can be rarely the solely responsible of important effects. Besides this, are other KIT SNPs be involved in cancer susceptibility and/or prognosis? In other words why limiting the work to just one SNP?

Level of interest: An article of outstanding merit and interest 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 declare that I have no competing interests