Reviewer’s report

Title: Infliximab therapy together with tyrosine kinase inhibition targets leukemic stem cells in chronic myeloid leukemia

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Reviewer: Hsin-An Hou

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It is well known that CML leukemic stem cells (LSCs) persist even in patients responding well to TKI therapy. LSCs with dysregulated capacities of self-renewal and survival are thought to be the root of leukemia and responsible for the relapse. Dr Herrmann et al demonstrated that ectopic expression of BCR-ABL could induce TNFα expression and in vitro exposure to TNFα antibody (infliximab, IFX) reduced clonogenic growth of CML. IFX therapy further boosted TKI-induced therapeutic effect in serial transplantation model. The manuscript is well written and would be of interest to the readers in this field.

(A) Since TNFα is a highly pleiotropic cytokine involved in wild spectrum of physiological processes that control inflammation and oncogenic/anti-tumor responses, do you have data suggesting TNFα could activate Treg and MDSC function, creating a tumor-supportive inflammatory niche in CML. Knockdown of TNFα could suppress tumor immune invasion in in vivo model.

(B) Did the authors also perform TNFα knockdown by shRNA or siRNA?

(C) In a clinical observational study, IFX has been suspected to promote tumor development, as illustrated by occurrence of hematologic malignancies in the course of treatment with anti-TNFα (Arthritis Rheum 2002;46:3151-8). A diametrically opposed effect of IFX on the course of CML was previously reported (Ann Rheum Dis 2005;64:509-10 and Leuk Res. 2007 Mar;31(3):418-9) Do you have any comments while applying the combination therapy in clinical practice? As I am aware, there is no such ongoing clinical trial.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.
Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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