To the editor:

Apoptotic synergism between STI571 and the farnesyl transferase inhibitor SCH66336 on an imatinib-sensitive cell line

I have read the very interesting and informative article of Hoover et al., which may open new avenues in treating imatinib-refractory and imatinib-sensitive chronic myeloid leukemia (CML). However, when testing the synergic potential of STI farnesyl transferase inhibitor (FTI) combination on the STI571-sensitive Baf BCR-ABL-s cell line, a deficient statistical proof is shown.

In their Figure 2A, an analysis of variance result is provided with a P = .019 at 24 hours of treatment. The comparison, although, was made between 4 experimental conditions (dimethyl sulfoxide [DMSO], STI571, FTI, and combination), and no post hoc tests (as the Bonferroni one) are reported to compare the most relevant treatments, STI571, and the combination with FTI. So, with the kinetic cell-death data the paper shows, no additive or synergistic interaction can be stated.

Both assays, measuring the annexin V and caspase 3 levels, also suggest an increased apoptosis with the combination, but again a lack of adequate statistic analysis hampers any estimation of increased therapeutic effect. A clear-cut evidence of a faster BCR-ABL+, STI571-sensitive cell apoptosis is a desirable goal, if the combined therapy is to be tested in vivo to treat imatinib-sensitive CML.

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References


Response:

SCH66336/ionafarnib together with STI571/imatinib shows synergistic killing of BCR/ABL transformed leukemia cells

In our recent Blood manuscript we conclude that a combination of the farnesyl protein transferase inhibitor (FTI) SCH66336/lonafarnib together with the BCR/ABL kinase inhibitor STI571/imatinib shows synergistic killing of BCR/ABL–transformed leukemia cells. The combination would thus be useful for treating patients with chronic myeloid leukemia (CML). In his letter, Dr Brodsky argues that we use a deficient statistical proof to reach this conclusion. The statistical analysis in question relates to Figure 2A. In our paper we carefully avoided describing the results in this figure as showing a synergistic effect, but rather that “the drug combination showed enhanced killing of STI571-sensitive (s) cells relative to either drug alone.” We believe this conclusion is adequately supported by the analysis of variance (ANOVA) performed between 2 groups of data: percent viabilities of cells treated with STI571 alone and percent viabilities of cells treated with the STI571/SCH66336 combination. Our conclusion that the drug combination shows synergistic killing is based on our consistent observation that SCH66336/ionafarnib alone has little effect on apoptosis (as measured by annexin V staining), while when given in combination with STI571/imatinib, SCH66336/ionafarnib typically doubles the cytocidal effect (Figure 2F).

We agree that a more rigorous statistical demonstration of drug synergy is a desirable goal. We and our collaborators have now performed a suitable analysis of the effects on cell viability for combinations of the 2 compounds across a wide range of drug concentrations for K562 and MEG-1 cells, 2 different Philadelphia chromosome–positive cell lines from CML patients (Figure 1). Using an appropriate algorithm for isobologram analysis (G. Hajian, L. Hothorn, manuscript submitted; O’Connell and Wolfinger as described previously), Data (day 3) reflect a left-shifted isobologram for both cell lines, consistent with a synergistic combination effect on cell viability.

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Figure 1. Representative isoboles for the Philadelphia chromosome–positive K562 and MEG-1 tumor cells treated with various concentrations of SCH66336/lonafarnib and STI571/imatinib. Ten concentrations of FTI SCH66336 ranging from 20 μM to 0.03 μM and 6 concentrations of STI571 ranging from 2 μM to 0.05 μM were tested. Cell proliferation was quantified on days 2, 3, and 4 after compound addition by methyl-thiazol tetrazolium (MTT) assay. Cell proliferation data from drug interaction studies were analyzed using the Thin Plate Spline methodology (G. Hajian, L. Hothorn, manuscript submitted; O’Connell and Wolfinger as described previously). Data (day 3) reflect a left-shifted isobologram for both cell lines, consistent with a synergistic combination effect on cell viability.
To the editor:

Acidic and neutral sialidase in the erythrocytes of patients with type 2 diabetes: an answer to comments by Richard et al

In a recent letter to the editor by Richard et al,1 the letter authors made some comments about our work published early this year.2 In our study we observed a sharp decrease of neutral sialidase activity on the surface of erythrocytes of diabetic patients, which accounts at the same time for the significant increase (40%) of sialic acid content. At the end of our discussion, we hypothesized that the higher negative charge at the erythrocyte surface due to this increase results in a premature sequestration of diabetic red cells by macrophages, in accordance with the data reported by Mazzanti et al3 and Jain et al.4 Our hypothesis has been criticized by Richard and coworkers because it conflicts with the notion that a reduction of total sialic acid content is responsible for phagocytosis of senescent red cells.

Our thoughts on this matter are as follows: (1) The hypothesis reported by Richard et al has been extensively debated over the years,5 and contrary to what the authors hint, it is not the only one known nor the most accepted, nonetheless it was not in our intentions to discredit it. (2) We believe in the importance of sialic acid in the process of recognition of senescent red cells, but as part of a more complex process, where other molecules are involved, as suggested in other hypotheses.6 Indeed, according to Beppu et al7 and Kannan et al,8 the molecular consequences of the oxidative damage occurring in senescent erythrocytes are likely responsible for their clearance. We think that the reduction of sialic acid content in specific domains of the surface, and not its overall decrease, may trigger the macrophage recognition.9,10 (3) The theory reported by Richard et al is eventually unsuitable to explain our experimental results. In fact, if the overall sialic acid decrease was responsible for senescent erythrocytes recognition, we should have observed an increase in life span of erythrocytes in diabetes mellitus, yet we observed the opposite phenomenon.

In conclusion we would like to emphasize once again that it was not in our intentions to invalidate the role of sialic acid decrease in erythrocyte removal, even though we do believe in a different hypothesis on erythrocytes senescence, at least in diabetic patients.

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References

To the editor:

Increased CMV infection following nonmyeloablative allogeneic stem cell transplantation: a search for the guilty

I read with interest the brief report by Bainton et al on cytomegalovirus (CMV) reactivation following the use of Campath-based nonmyeloablative conditioning regimens.1 The authors found a high incidence of CMV infection, similar to that reported by us.2 However, they suggest that fludarabine rather than Campath was responsible for this, but the existing literature on nonmyeloablative transplants does not seem to support the idea. A recent study reported CMV reactivation in 87% with and only 25% without the addition of alemtuzumab (Campath-1H) (P < .001) to fludarabine-melphalan regimen.3 The Seattle group did not find a difference in the incidence of CMV infection or disease with the addition of fludarabine to the low-dose radiation regimen.4 Similar low

References