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Letter to the Editors/Reply

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Sirs,

We read with interest, the paper by Poplin et al. [1] describing the results of a phase I study of escalating doses of carboplatin when given with a fixed dose of doxorubicin (60 mg/m^2). The maximum tolerated dose of carboplatin was 400 mg/m^2. Thrombocytopenia was found to be dose-limiting. The addition of GM-CSF did not allow further escalation.

The authors employed the Egorin model [2] to estimate the predicted change in platelets (pretreatment count minus predicted nadir count) from the administered dose of carboplatin, creatinine clearance, body surface area and extent of prior therapy. They noted a strong linear correlation between the observed and predicted change in platelets (Pearson correlation coefficient $r = 0.91$). Drawing from this result, they concluded that the level of thrombocytopenia was "appropriate for the dose, BSA and renal function" and thus, was unperturbed by the addition of doxorubicin.

We feel that the authors failed to establish whether the Egorin model was valid for these data. We question their conclusion that doxorubicin did not enhance platelet toxicity. We believe that the striking linear correlation between observed and predicted change in platelets is an artifact of the measures. Observed and predicted change are absolute deviations from a common starting value (pre-treatment platelet count). As such, an interdependence is imposed between these measures, resulting in an inflated measure of linear correlation.

We re-analyzed the data displayed in Table 3 of the paper. Employing the Egorin model [2], we repeated the estimation of predicted change and regression of observed change on predicted change. As displayed in Fig. 1, most data points and the regression line (solid line) fell below the line of identity (dashed line). This indicated on average, larger observed changes in platelet count than would have been predicted from the model. The authors had failed to note that the strong linear correlation was about a regression line with an estimated intercept of 50×10^3 cells and slope of 0.70 (this was significantly different from 1.00).

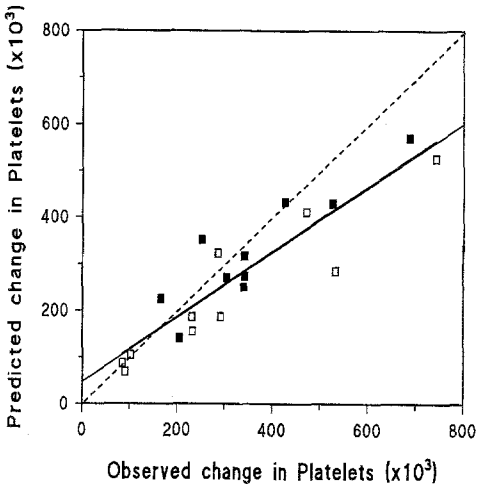

Fig. 1. Observed versus predicted change in platelet nadir (by Egorin formula). Solid squares reflect patients with extensive prior therapy. Solid line is the ordinary least squares regression line ($r = 0.91$). Dashed line is the line of identity

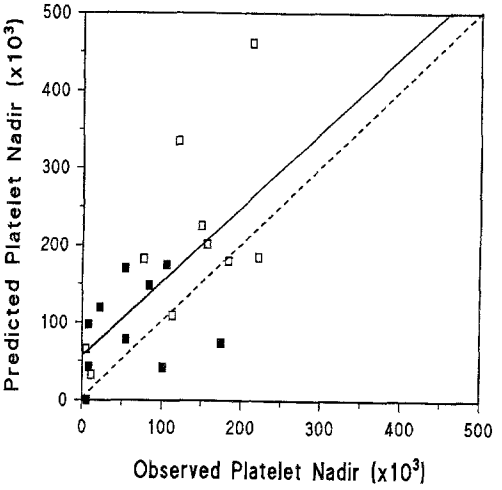

Fig. 2. Observed versus predicted platelet nadir (by Egorin formula). Solid squares reflect patients with extensive prior therapy. Solid line is the ordinary least squares regression line ($r = 0.64$). Dashed line is the line of identity

Thus, on average, the model underestimated the *change* in platelets by 70% of the observed, less 50×10^3 cells.

Examing the prediction error (observed minus predicted effect) is a superior method of model assessment [3]. The mean prediction error and standard error of the mean (MPE $\pm$ SEM) and root mean square error (RMSE) can be employed to assess model bias and precision, respectively. We noted a weaker linear association between the observed and predicted platelet nadir (r = 0.64), as noted by the scatter of data points displayed in Fig. 2. Most data points and the regression line (solid line) fell above the line of identity (dashed line). This indicated on average, lower observed platelet nadirs than would have been predicted from the model. The regression line had an estimated intercept of 55×10^3 cells and slope of 0.97 (not significantly different from 1.00), nearly parallel to the line of identity. Thus, on average, the model overestimated the platelet *nadir* by a constant value (55×10^3 cells). The bias of the model was substantiated by a MPE $\pm$ SEM of -53 ± 19 $\times10^3$ cells. The RMSE was 97×10^3 cells, that indicated a lack of precision of the model. Therefore, we feel that the Egorin model was not valid for these data. Moreover, since the observed nadir counts were on average, 55,000 less than expected, one may postulate that thrombocytopenia was enhanced by the addition of doxorubicin at 60 mg/m^2.

References

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2. Egorin MJ, Van Echo DA, Tipping SJ, Olman EA, Whitacre MY, Thompson BW, Aisner J (1984) Pharmacokinetics and dosage reduction of cis-Diammine(1,1-cyclobutanedicarboxylato)platinum in patients with impaired renal function. Cancer Res 44: 5432–5438
3. Mick R, Ratain MJ (1993) Statistical approaches to pharmacodynamic modeling: motivations, methods and misperceptions. Cancer Chemother Pharmacol 33: 1–9

Reply to the letter to the Editors

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Sirs,

We very much appreciate the thoughts of Drs. Mick and Ratain and have reviewed our data with their concerns in mind.

Since the Egorin formula predicts a change in platelet count, not absolute platelet count, we still prefer plotting expected change vs observed change. The goal of effective therapy is to maximize the dose within the limits of acceptable toxicity. Consequently, predicted and observed absolute platelet counts should cluster close to the same tolerable toxicity values, thus artificially lowering the correlation coefficient. The question of linearity in Fig. 1 is a point well taken, and in our view, suggests that the predicted change in platelet counts may only be accurate for values of 350,000 or lower.

While the Egorin formula might have its limits, it is a standard formula for this therapy. We welcome new formulas that better model the toxicities that might be predicted with these therapies, but that was not the goal of this research. Such an experiment would require varying the dosage of doxorubicin as well as carboplatin. Until that time we will make do with what we have.

We note that we had previously concluded that the contribution of doxorubicin to the development of severe myelosuppression, could not be readily determined from our study.

We thank Drs. Mick and Ratain for addressing these complex issues.