ABSTRACT

The aim is to determine the ability of the novel ex vivo drug sensitivity platform EBIasis analysing leukemic cell death to predict the CR rates after induction chemotherapy treatments with idarubicin (Ida) and daunorubicin (DA) in de novo AML. Induction response was assessed according to the Chevoss criterion (2002). Patients achieving a CR/CRi were classified as responders. The remaining patients were considered as resistant. Patients dying during induction response assessment were non-evaluable. The correlation was modeled using a generalized additive model with a log link and a binomial distribution for residuals. Kernel density estimates were then used to plot empirical probability density functions for both groups. Their separation was quantified as the area under the ROC curve and a cut point was selected using the Youden's criterion to optimize the classification probabilities (sensitivity, specificity). 95% confidence intervals for sampling errors were calculated for all these quantities.

RESULTS

127 patient samples were used to calculate the dose response curves for AML alone, Idarubicin alone, and synergy of the AML plus Idarubicin combination. For formal correlation we used 64 patients with a median age of 55 years (range 31-72). Dose responses for AML alone are shown in Figure 1A. A note for nearly satisfies the assumptions for a linear resistant curve (95% CI). This is a strong clinic predictor of resistance because in the patients the drug will never be at these high-doses for IdR. The second variable that is a good predictor of response is the synergy between these two drugs. The generalized additive model identified an algebraic combination of these 2 variables that yielded the best separation between the two groups. The probability density functions and the diagnostic plot for both the area under the corresponding ROC curve was 0.965 (0.935-0.993) and the classification probabilities for the optimal cut point (set at 0.64 for the variable expressed as percentages, were 85% (65.2-93.6%) and 86.4% (72.6-94.9%) for sensitivity and specificity, respectively. Results are shown in Figure 2B. Seventeen of the 20 (85%) patients that failed to achieve CR were predicted as resistant in the ex vivo assay. Thirty-eight of the 40 patients (95%) who achieved CR showed good positive predictive value to IdA-C, predicted for the ex vivo test predicted a patient as sensitive it was correct in 38/40 cases (95%) and when it predicted resistant it was correct 11/17 cases (65%). Overall, 45 patients (90%) had an accurate prediction of their response to treatment.

CONCLUSIONS

This novel ex vivo pharmaceutical profiling test is able to predict the clinical response to Ida-Ara-C induction. We are increasing the number of patients in this ongoing study, and we are planning a Phase 1 trial adapted Clinical Trial.