ABSTRACT

Background and objective: Complete remission (CR) after induction therapy is the first treatment goal in acute myeloid leukemia (AML) patients. The aim of this study is to determine the efficacy of a triple drug sensitizing platform Exvivo analyzing leukemic cell death to predict the CR rates after induction chemotherapy with cytarabine (Ara-C) and idarubicin (Ida) in 1-1-line AML.

Patients and Methods: This retrospective and prospective study included samples from patients over 10 years of age diagnosed with de novo AML in 8 Spanish centers from the PETHEMA group. Morro samples were collected at diagnosis, sent to the Vivitiv laboratory, and incubated for 48 hours in small plates in a cell incubator. For each concentration Ara-C + Ida, each at 8 different concentrations to calculate inhibition data. Annexin V (A+V) was used to quantify the drug-induced apoptosis. Pharmacological responses were calculated using the logistic regression model. Induction response was assessed by the Chisen criteria (1982). Patients obtaining a CR(II) were classified as responders. The remaining patients were classified as nonresponders. Patients dying during induction response assessment were non-evaluated. The combination of pharmacological responses and the clinical response was modeled using a generalized additive model with a log link and a binomial distribution for residual density. Kernel density estimates were then used to plot empirical probability density functions of the model fitted values in the response scale for both groups. Their separation was quantified as the area under the ROC curve and a cut-off value was selected using the Youden’s index to optimize the classification (sensitivity, specificity). 95% confidence intervals for sampling errors were calculated for all these quantities.

Results: 109 patient samples were used to dose the response curves for Ara-C alone, Ida alone, and synergism of the Ara-C plus Ida combination. For clinical correlation, 105 patient samples were included. After an age median of 12 years (range 15 to 85), Dose 100% correlated clinical response shown in Figure 3-A, note that for many samples there is a significant number (x%3) of resistant cells to Ara-C (badred). It is a strong clinical predictor of resistance because in the patient the drug may never be present at these high doses for 48h. The second variable that is a good predictor of response is the synergism between these 2 drugs. The generalised additive model identified an algebraic combination of these variables that included also the maximum percentage of cells depleted by Ara-C that yielded the best fit to separate responders from non-responders (CR vs 0% CR after induction). The overlap between the probability density functions of the fitted value was small (area under the ROC curve 0.801 (9 3,943), and the classification probabilities for the optimal cut-point expressed as percentage, were 90% (95% CI: 0.800–0.880) for specificity and sensitivity, respectively. Results are shown in Figure 3-B. These results indicate that the accuracy of this model is over 90%.

Conclusions: This study shows that this novel in-vivo pharmacological profile is able to predict the clinical response to Ida + Ara-C induction. Further efforts are in progress to refine the predictive model to remove as much random variability as possible and to identify other sources of variability. A PMI test adapted Clinical Trial is planned to evaluate the impact of the PM test over clinical outcomes.

RESULTS

Figure 1- Objectives & Study Design

Figure 2- Pharmacological ex vivo Data: Single drugs & Synergies

Figure 3- Individual Dose Response Curves

Figure 4- Distribution of Cytarabine (A) and Idarubicin (I) in AML patients.

Figure 5- Pharmacological Population Parameters

Figure 6- Polynomial function of Cytarabine (EC50) & Synergism Cytarabine-Idarubicin

Figure 7- 90% Prediction ex vivo Personalized Medicine Test

Figure 8- Key clinical indicators overall prediction 95% & NPI 96%