ABSTRACT

Background: To assess the identification of effective treatments for individual patients, ex vivo assays for detecting cell death induced by drugs for hematological malignancies have been developed for over 20 years. We have developed a novel approach incorporating 4 key innovations: including drugs in whole bone marrow sample without isolating leukocytes, using flow cytometry enables identification of the malignant cells selectively, an automated flow cytometry-based platform (ExTech) decreases errors and enables full pharmacological characterization, and analyzing the data using pharmacodynamic population models.

Aim: Derive the ex vivo pharmacological profiles across the AML patient population of single drugs and combination treatments at 3Ts to individualized treatment selection.

Patients and Methods: Bone-marrow samples from 160 patients diagnosed with AML were sent to Viria from 24 hospitals in Spain, within 24 h of collection. The samples were incubated with agents in triplicate for 72 h. The mortality index (MI) was computed for each drug, then the lower survival index, the more effective the drug. Dose-response curves of cytarabine, daunorubicine, etoposide, fludarabine, clofarabine, and thioguanine were measured in 160 samples. The added benefit of combining these drugs into 12 combination treatments was assessed by measuring their synergy on each individual patient. In 33 patients treated with CBT, we had clinical data of response, and then we performed a blinded interpretation of this in vivo test by an expert hematologist, to predict the clinical response based on this test result.

Results: There was a large degree of interpatient variability in the response to a single drug and even larger in the synergism between drugs. Population Pharmacological Profiles for two individual patients are shown on the figure 5. Relative drug potency in terms of percent cell death within the population is shown in the left panel from 0 (highest) to 100 (most potent). Green lines show individual patient potency relative to the population ranking, with confidence intervals (CI). 3rd column lists where a drug leaves a significant % of malignant cells alive, potential resistant clones. Synergism for an individual patient is each combination is shown in green, with CI at parallel dotted green lines. Representation of the Pharmacological Profile of an individual patient sample quickly identifies extremes, where a drug combination or single drug is very sensitive (rightward shift green lines, green boxes) or very resistant (leftward shift green lines, red boxes). These representations lead to clear guidelines in 500 samples, and based on hematologist’s interpretation of these guidelines show a clinical correlation with clinical responses to CBT/IDA of 84%.

RESULTS

CONCLUSIONS

By testing the drugs used in the treatment protocols for AML directly on patient samples, a pharmacological based model could be developed to infer drug resistance or sensitivity, patient by patient. Similarly, testing could be used as a companion diagnostic to identify subsets of patients for which specific cytotoxic drugs or targeted therapies would be effective.

The Pharmacological Profiles could be used for personalized treatment for individual patients.

Correlation of this ex vivo sensitivity with the clinical efficacy is currently being performed in a study under the supervision of the PETHMA group.

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