ABSTRACT

Background and objectives: Protocols for acute myeloid leukemia (AML) first-line patients are centered on the combination of Cytarabine and an anthracycline (IDA), Daunorubicin (DNR), or Mitoxantrone (MIT). Patients may be treated with IDA, DNR, or MIT depending on the country of residence, because multiple clinical trials have not found significant differences among them. A new Personalized Medicine (PM) test developed by Vivia Biotech based on pharmacological responses in patient samples solely uncovering individual responses to these treatments. Our objective is to explore whether a significant % of individual patients may respond differently to IDA vs DNR or MIT treatments, in spite of their "on average" similar response shown by clinical trials.

Patients and Methods: Multi-center, prospective, non-interventional study of the PETHEMA group for treatment of AML. Bone Marrow (BM) samples were collected at diagnosis for 125 AML patients. Samples were incubated for 48 hours in 96-k Wells, each well containing different drugs or drug combinations, each at 8 different concentrations, enabling calculation of dose response curves for each single drug (CYT, IDA, DNR, MIT) and combination used in treatments (CYT-IDA, CYT-DNR, CYT-MIT). Drug response was evaluated as depletion of AML malignant cells in each well after 48 hours incubation. Annexin-V FITC was used to quantify the ability of the drugs to induce apoptosis. Malignant cells were identified with monoclonal antibodies and light scatter properties. 2D/3D were used to evaluate the ability of the drugs to induce apoptosis. Malignant cells were identified with monoclonal antibodies and light scatter properties. IHC was used to evaluate the ability of the drugs to induce apoptosis. Malignant cells were identified with monoclonal antibodies and light scatter properties. IHC was used to evaluate the ability of the drugs to induce apoptosis.

Results: Figure 3 shows dose responses for IDA (blue), DNR (red) and MIT (green) in 125AML patient samples. Although their average potency (CDEFGH) is similar, the individual dose response for each sample shows large variability (Figure 4). In Figure 5, combination treatments are showed to have a significantly different response from single drugs, with different synergy measurements for each drug combination (Figure 6).

PLATE SETUP

Eight different concentrations of each drug or drug combination is run for the used treatment protocols. The max concentration used is listed (Table 1).

WHOLE SAMPLE vs. ISOLATED LYMPHOCYTES

A. Dose response curves for IDA and DNR in isolated leukocytes and whole sample. Data from sample 6 below describe drug differences in the EC50 for IDA, but equal results for DNR.

B. The EC50 (red) of the whole sample and the isolated leukocytes fraction from 9 patient samples. With CYT, IDA, MIT, the same samples to IDA.

CONCLUSIONS

This preliminary results show that Vivia’s PM test seems to identify a subset of AML patients who’s ex vivo pharmacological response to anthracycline drugs is significantly different. If these selective anthracycline ex vivo responses translate to clinical responses, a fraction of this 65% subdivision could benefit significantly from receiving 1st or 2nd line treatments based on either IDA, DNR, MIT, and their combinations.

This approach stands for European integration of treatment protocols, based on ex vivo individual responses data rather than nationality.