PERSONALIZING THERAPIES WITH EX VIVO PHARMACOLOGICAL RESPONSES MAY UNCOVER THE DIFFERENCES BETWEEN IDA-DNR-MIT AMONG EUROPEAN AML PATIENTS

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Background and objectives: Protocols for acute myeloid leukaemia (AML) frontline patients are centered on the combination of Cytarabine and an anthracycline (IDA), Daunorubicine (DNR) or Missotrubine (MIT). Patients may be treated with IDA, DNR, or MIT depending on the country of residence, because multiple national protocols have not found significant differences among them. A new Personalized Medicine (PM) tool developed by ViviaBiotech based on pharmacological responses in patient samples visibly uncovers individual responses to these treatments. Our objective is to explore whether a significant proportion 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.

Methods: Multicenter, prospective, non-interventional study of the RETEMA group for treatment of AML. Bone marrow (BM) samples were collected at diagnosis for 135 AML patients. Samples were incubated for 48 hours in 96-well plates, 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 aplastic marrow cells in each well after 48 hours incubations. Annexin-V-FTC was used to quantify the ability of the drugs to induce apoptosis. Apoptotic cells were identified with myeloperoxidase and light scatter properties. EUSL include the whole bone marrow sample, retaining the erythropoietic and immune system, undergoing the entire incubation period; and after 48h leukocytes are isolated prior to evaluation by flow cytometry. 231V6 have pioneered development of a proprietary automated flow cytometry platform called eXcela. Pharmacological responses are calculated using pharmacokinetic population models.

Results: Figure 3 shows dose responses for IDA (blue), DNR (red) and MIT (green) in 125AML patient samples. Although their average response (Figure 2) are similar, the inter-patient variability of either drug is quite large. We hypothesized that some patients could show very differential sensitivities to these drugs, as illustrated in Figure 4 (panel A) where a patient sample is resistant to IDA (right shifted dose response curve) but sensitive to DNR (left shifted dose response curve). To identify these cases, Figure 5 panel A shows a comparison of the potency (IDA vs. DNR, DNR vs. IDA). Potency is represented by their EC50 (concentration that kills 50% of the cells). Most dots tend to line up, but red dots represent patient samples with a difference in potency of between these drugs -10%. Repeating this exercise for IDA-MIT and DNR-MIT (panels B and C) to cover all alternatives among the 3 anthracyclines identifies 40% of patients samples with >30% different potency among IDA-MIT and 30% or more different potency among DNR-MIT. This showed a consistent pattern of these comparisons. The relationship of clinical responses to the individual response was performed using the Spearman-Wilcoxon test and the distribution of the compound index was calculated. More than 40% of patients showed significant differences among potency of three drugs. More than 65% of patients showed significant differences either on drug potency or synergy measurements among CYT-IDA, CYT-DNR, CYT-MIT.

Conclusions: Phantastic PCR results show that Vivia’s PM test seems to identify a subset of AML patients who’s ex vivo pharmacological response to anthracyclines drugs is significantly different. If these selective anthracycline ex vivo responses translate to clinical behavior, a fraction of this 65% population 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.

ACKNOWLEDGEMENTS


Conclusions

Figure 1. Cheemosensitivity test by dose-response modeling analysis

Figure 2. Similar sensitivity IDA DNU MIT

Figure 3. Inter-patient variability

Figure 4. Dose-response modeling analysis

Figure 5. Overall statistical differences among drugs

Figure 6. Overall statistical differences among combinations

Figure 7. Inter-patient variability on drug interaction measurements

40% of patients showed significant differences among potency of three drugs.

58% of patients showing any difference in synergy measurements among the three combinations

More than 65% of patients show differences either on drug potency or synergy measurements among CYT-IDA, CYT-DNR, CYT-MIT.

DISCUSSIONS

This preliminary results show that Vivia’s PM test seems to identify a subset of AML patients whose ex vivo pharmacological response to anthracyclines drugs is significantly different. If these selective anthracycline ex vivo responses translate to clinical behavior, a fraction of this 65% population 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.