A NEW PRECISION MEDICINE TEST TO GUIDE PERSONALIZED TREATMENTS DECISION FOR ACUTE MYELOID LEUKEMIA PATIENTS

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ABSTRACT

Background and aim: Treatment of Acute Myeloid Leukemia (AML) remains a considerable therapeutic challenge. Complete remission (CR) after induction therapy is the first treatment goal in these leukemic patients. A few combinations, based mostly on empirical observations with drugs already known to be more or less effective, are frequently used in the treatment of AML. Because of this, many patients who do not respond to standard chemotherapy need to enter in clinical trials and the use of predictive assays prior to patient treatment represents the ideal scenario to guide or help in treatment decisions. We have now developed an ex vivo assay where an initial clinical validation has been achieved in an observational clinical trial in 123 AML patients on single treatment, 1st line cytarabine (81% CR) achieving 80% clinical correlation. The aim of this study is to provide accurate in vitro data to improve disease management in the context of a clinical trial, and provide key information for Precision Medicine (PM) to guide the hematologist among the different treatments to choose a CR.

Methods: AML bone marrow (BM) samples from adult patients are received at the laboratory within 24h from extraction and incubated for 48h in 96-well plates containing the single drugs or combinations pharmacologic pathway. The analysis is performed in the PharmaFlow platform and 72h after the extraction of the sample, an encoded report is sent to the hematologist before the patient begins the treatment. Pharmacodynamic scores were calculated using pharmacokinetic population models. Individual drug response was assessed according to the Cheson criteria (2003). Patients attaining a CR/CRi were classified as responders and the remaining as resistant, excluding early deaths. Final scores and treatments ranking is based on a therapeutic algorithm integrates on ex vivo activity, monotherapy dose responses quantified by the area under the curve (AUC) with brisks such as Cmax values, and synergism calculated measuring 6 concentration ratios, requiring consistency in its results in a 3D surface (so called alpha lacta synergism). The PM Test attempts to identify the best treatment for predicting sensitive for each patient.

Results: The scoring method was tested using ex vivo results from samples obtained in an observational clinical trial with 123 PETHEMA group from a cohort of 123 samples from de novo diagnosed AML patients, treated with the standard PETHEMA 1st line guideline 7/3 with CYT+IDA. The scores predicts sensitive patients with 87% accuracy. This accuracy can be compared with an independently derived clinical correlation in identifying sensitive patients, in a statistically significant clinical correlation study. The score is a simplified version of such correlation algorithm. Both methods identify a similar percentage of all clinically sensitive patients (87% vs 85%) and resistant patients (67% vs 69%). Moreover, the correlation of only valid for CYT+IDA. The PM Test can be applied to any treatment. Moreover, for CYT+IDA treatment, the PM test predicts a 3 years overall survival with 75% accuracy.

RESULTS

PM Test Predicts:

- Clinical outcome
- If it was a CDx IST:
- Patients included in trial
- Expect 82% sensitive

PM Test Predicts Clinical CR with 82% accuracy in first 24h of CYT+IDA and Overall Survival after 3 years with 75% accuracy. This test can provide more than 80% response rates for drugs as CDx under clinical trial use, impacting in RO.

RESULTS

A) CYT-IDA Methods can be Extended to Other AML Cytotoxic Combination Synergies

B) Synergism AML Treatments in more than 400 Samples

C) Capturing Interpatient Variability Leads to Alternative Treatment Options

D) Characterization of Hypomethylating agents as Antiproliferative Agents in AML Samples for PM Test

METHODS

Screening set and Workflow

RESULTS

A) CYT-IDA Methods can be Extended to Other AML Cytotoxic Combination Synergies

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CONCLUSIONS

- This novel ex vivo PM test for induction treatment in AML patients represents a valuable information to guide hematologists selecting the right treatment to achieve CR in individual patients.
- This knowledge from CYT-IDA clinical correlation algorithm have allowed us to generate an ex vivo Score for each treatment.
- Assuming a similar response rate for all these treatments, this test could estimate a net prediction for sensibility to AML treatment higher than 80% in 1 time.
- Patient that receive responders has a 3 to 7 fold increased chance of disease free survival compared to patients who do not.
- This PM test can be used in an Investigator Sponsored Trial as a Companion Diagnostic selecting sensitive patients with higher response rates and survival.

Figure 1. Panel A illustrates the average curve (gray bar) and the high variability between AML patients treated with the same drug doses. The ex vivo predicted difference in drug activity (red line) after 48h between patients that received sensitive or resistant treatments. Sensitivity is graphically observed through the shift of the surface towards the axes along sensitive or resistant outcomes in each treatment.

Figure 2. PharmaFlow PM Test predicts clinical CR with 82% accuracy in first 24h of CYT+IDA and Overall Survival after 3 years with 75% accuracy. This test can provide more than 80% response rates for drugs as CDx under clinical trial use, impacting in RO.

Figure 3. Score range from 1 to 100 in four representative patient samples (A-C). being 1 those treatments with less ex vivo efficacy and hence lower probability of response (red scale), and 100 for the highest ex vivo efficacy (green scale). The score is coded by a color gradient following traffic light colors. These treatments coded by gray are not available or tested in this high error associated. A) Sensible patient who responded to 4 different treatments. B) and C) Two resistant patients who could benefit from a treatment that includes cytarabine/docetaxel or cytarabine/idarubicin (B) and etoposide/daunorubicin (unusual) (C). Patient showing responses to all treatment could be derive to Clinical Trials of New drugs.

Figure 4. New targets and immuno-oncology (I-O) drug candidates. Figure A reflect the MDA of BAs showing both leukemic cell depletion (upper panel) and T-Cell activation (bottom panel). Figure B show the activity of engineered CAR T cells at different time points (in vivo) to deplete leukemic cells.

Figure 5. The PharmaFlow platform has the power to expand CDx PM Test to many drugs and candidates leading the infusion point towards Precision Medicine/Healthcare. Figures A to D show different samples of assays which can be performed with the PharmaFlow technology. The synergies between different drugs (A-B) can be identified obtaining high synergism between nucleosides (i.e. CYT-FLU in CYT-CHO) and low synergism between nucleoside-anticholinergine combination (i.e. CYT-IDA or CYT-DAU). The PM AML test can personalize treatments identifying different sensibilities towards very similar old cytotoxic drugs that most hematologists would consider equivalent (C). In a proliferation assay (D), the antiproliferative effect of 5-AzaCytode and Decitabine can be observed by adding specific cytokines and evaluating both the proliferative and non-proliferative subsets. Both drugs show clear selectivity, being more active in proliferative cells. 5-Aza shows also cytotoxic activity at high doses.

Table 1. Overview of several mechanisms of hypomethylating agents identified through assays performed with the PharmaFlow Platform: NE: not evaluable.

ACRESCIMENTOS DE BENS

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