Optimization of a Drug Screening Platform in Acute Myeloid Leukemia

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Background

- Acute myeloid leukemia (AML) : group of hematological diseases with a poor prognosis.
- Precision medicine in AML : Delay treatment to propose a personalized approach → improve OS [1]
- Functional *ex-vivo* drug screening of primary AML cells could identify patient-specific vulnerabilities and improve the treatment of AML patients.
- To determine the chemosensitivity of primary cells from AML patients, we previously developed a multiparametric niche-like drug screening platform (NEXT platform)[2]. This platform is limited with low throughput (96 plate well, 6 colors cytometer)

Objective

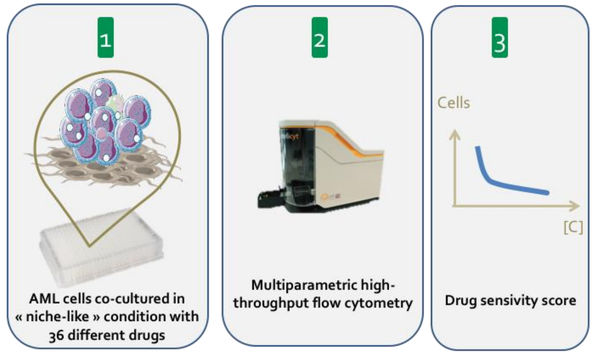
Optimization of an *ex-vivo* niche-like drug screening platform on primary AML samples to prospectively recommend second-line treatment for AML patients.

Materials & Methods

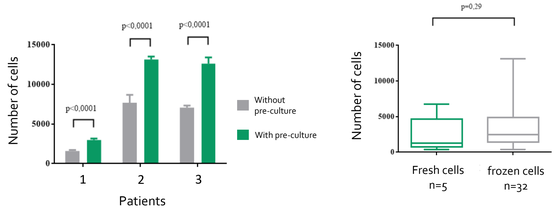
1 Primary cells from 49 consecutive patients with newly diagnosed AML were cultured for 72 hours in niche-like conditions (conditioned media, mesenchymal stroma, hypoxia) and exposed to 36 molecules at 8 concentrations.

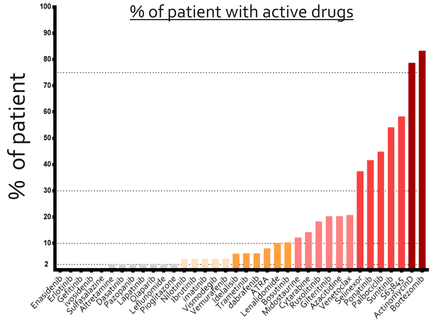
2 Total leukemic cells, blasts, lymphocytes, differentiated cells, and leukemic stem cell counts were assessed using multiparametric high-throughput flow cytometry (iQue3 Intellycyt).

3 Drug activity was assessed using a drug sensitivity score after normalization to DMSO controls[3].
A drug was considered : inactive (DSS=0), moderately effective (0<DSS<50), or very effective (DSS≥50).



Results





- Additional pre-culture step increase significantly number of gated cells
- Fresh or frozen cell lead to a number of gated cell not different significantly. Use of frozen cells improve the feasibility in a prospective application study.
- Actinomycin D and Bortezomib are active on > 75% of AML cases cells : Positive controls
- Selinexor, Ponatinib, Palbociclib, Sunitinib and S63845 are active on > 30% of AML cases cells .
- Median number of drugs with very effective or moderately effective per patient was 4 (range 0 to 13).
- In 42 (86%) AML cases, at least one drug was moderately effective and 22 (49%) was very effective.

Discussion / Conclusion

- During this study, we validated and upscaled our NEXT platform on 49 patients.
- The prospective application of our niche-like drug screening platform is now being investigated in relapsed/refractory AML patients accrued to the multicenter study ALFA-PPP (NCT04777916).

References

[1] A Burd *et* al, Nature medicine, 2020

[2] R Dal Bello *et* al Blood cancer journal, 2022

[3] Yadov *et*. al, Scientific Reports, 2014

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