

Ex-Vivo Drug Response Profiling for Tailoring Treatment in Hematologic Malignancies: The Prospective Non-Interventional SMART-Trial

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Introduction

Ex-vivo drug response profiling (DRP) represents a promising strategy to better understand the tumor's pathway dependencies, genotype-phenotype associations and the underlying molecular networks. However, little is known about the predictive value of drug response profiling and its utility for individualized treatment recommendations.

Methods

We report the first analysis of our ongoing prospective non-interventional SMARTrial (Systematic and Mechanism-based Approach to Rational Treatment Trial of Blood Cancer; ClinicalTrials.gov: NCT03488641). This trial aims to demonstrate the feasibility of high-throughput DRP in the clinical routine setting and the ability to predict *in-vivo* outcome by DRP. *Ex-vivo* responses to 107 different drugs including chemotherapeutic agents and FDA-approved or clinically investigated small molecules were assessed by an ATP-based assay after 48 hours of incubation. Results were processed by our customized analysis pipeline, enabling immediate reporting of DRP results. Patients with hematological

malignancies and scheduled treatment were eligible if sufficient tumor cells were available from either lymph node biopsies, the bone marrow or peripheral blood.

Results

58 patients out of the target study population of 80 patients have been recruited (AML, $n = 24$; B-cell lymphomas, $n = 28$; T-cell-lymphoma, $n = 5$; ALL, $n = 1$) as of July 24th, 2019. The median follow-up was 6 months. The primary endpoint, defined as proportion of successfully completed DRP tests within 7 days, is used to evaluate the feasibility of DRP in the clinical routine. In our study cohort, 93% of all recruited patients met this primary endpoint. We will describe our optimized workflow for drug testing and data analysis, which enables us to provide DRP reports in the clinical routine.

First, we analyzed if the DRP reflected expected genotype-drug response associations and systematically regressed mutational data on DRP phenotypes. This analysis exemplarily revealed that FLT3-ITD-mutated AML cells with a mutation ratio > 0.8 respond significantly stronger to FLT3 inhibitors than FLT3-ITD-mutated AML cells with a mutation ratio < 0.8 or wildtype AML cells (Quizartinib, *t-test*, $p = 0.022$; Gilteritinib, *t-test*, $p < 0.001$), confirming that the assay can uncover clinically meaningful vulnerabilities of cancer cells.

89.3% of all evaluable patients received treatments covered by our *ex-vivo* DRP assay, which facilitates the correlation of *in-vivo* and *ex-vivo* drug response. The majority of patients were scheduled for chemotherapy treatment (65%) or had received chemotherapy before (32%). *In-vivo* responses after scheduled treatment were categorized as response (Resp), incomplete response (IResp) or progressive disease (PD). We compared *ex-vivo* drug responses between these different *in-vivo* response categories. Cancer cells of patients with PD were significantly less sensitive to *ex-vivo* treatment with chemotherapy (mean of all *ex-vivo* tested chemotherapeutics) than patients with Resp (*t-test*, PD vs. Resp, $p = 0.007$; PD vs. IResp, $p = 0.054$). While the anthracycline daunorubicin (*t-test*, $p = 0.034$) and the purin analogon fludarabine (*t-test*, $p = 0.004$) were significantly more active in samples from patients with a clinical Resp than in samples from patients with PD, we did not observe this trend for vinca alkaloids (e.g. vincristine, vindesine) or antifolates (e.g. pralatrexate). Interestingly, individual patients exhibited an exceptional *ex-vivo* sensitivity to anti-folates, despite an almost complete insensitivity to all other chemotherapeutic drugs. For a patient with refractory Burkitt Lymphoma, we observed such a strong *ex-vivo* sensitivity to pralatrexate despite a general *ex-vivo* insensitivity to most drugs. This patient had progressed on treatment with DA-EPOCH and DHAP, but responded well to methotrexate, enabling him to undergo consolidating allogeneic stem cell transplantation.

Conclusion

Ex-vivo drug response profiling prior to treatment can be successfully implemented in the clinical routine. Our preliminary results suggest that DRP can predict *in-vivo* treatment resistance and support treatment guidance for individualized treatment.

Disclosures

Dreger: *AbbVie, Gilead, Novartis, Riemser, Roche:* Speakers Bureau; *Neovii, Riemser:* Research Funding; *MSD:* Membership on an entity's Board of Directors or advisory committees, *Other:* Sponsoring of Symposia; *AbbVie, AstraZeneca, Gilead, Janssen, Novartis, Riemser, Roche:* Consultancy.

Author notes

*Asterisk with author names denotes non-ASH members.