A precision medicine approach to haematological malignancies

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In *The Lancet Haematology*, Berend Snijder and colleagues[1] report interim results of their study evaluating the effect of ex-vivo drug sensitivity screening on the treatment of patients with refractory haematological malignancies. Using an automated immunofluorescence microscopy-based platform named pharmacoscopy, the authors prospectively evaluated 48 patients with various haematological malignancies, 17 of whom received treatment guided by this approach. Given the inherent heterogeneity of this cohort, the investigators opted to compare the benefit of pharmacoscopy-guided treatment to the effect of previous treatments in the same patient. They observed a marked improvement in progression-free survival with pharmacoscopy-guided intervention with almost half of the patients (eight of 17 patients) still disease free at their last follow-up visit, providing evidence for the promise of drug-response profiling in haemato-oncology.

Most precision medicine initiatives have focused on genomics, but few have included functional assays.[2] Phenotypic screening approaches could contribute important information to improve the selection of the right drug for the right patient at the right time in their treatment. First proof-of-concept data was obtained with functional screens using kinase inhibitors,[3] leading to a clinical trial for targeted therapy of relapsed acute myeloid leukaemia that is still ongoing (NCT01620216). In line with the results of Snijder and colleagues, a landmark paper[4] showed how drug profiling predicts activity and resistance to drugs in patients. Both platforms detect drug activity in cell cultures with luminescent assays. This format has the advantages of full automation and high throughput, but does not deliver functional information at the single-cell level. To address intrapatient heterogeneity of malignant and normal cells, and to take advantage of more complex coculture systems, many investigators are now turning to automated, microscopic imaging technology. Such minimally invasive protocols enable highly informative drug-response profiling in stroma coculture systems that can maintain leukaemia and multiple myeloma cells for a longer time, expanding the screening capabilities of patient samples.[5–7] Snijder and colleagues now show that it is possible to do multiparametric, image-based, immunophenotypic cytometry to reliably distinguish malignant cells from normal blood cells in a high-content screening context. In their seminal paper,[8] the investigators showed how this approach can detect phenotypes across several cellular compartments, quantifying, for example, T-cell engagement by the bispecific, CD19-directed, T-cell engager blinatumomab in patient samples.

The idea of testing cellular drug resistance to assist clinical decision making is not new. Short-term 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays to determine responses to conventional antileukaemic drugs almost three decades ago did not translate into clinical practice.[9] Why would the revival of ex-vivo drug testing make a difference today? Studies[4,5,8,10] from Snijder and colleagues and others provide strong elements of a response. Testing a sufficient number of therapeutic agents across functional classes detects highly informative, but individually heterogeneous, drug-response patterns for each disease. Valuable information can be gained with respect to sensitivity to functional classes of agents and drug resistance, which underscores the underlying complexity and the need for more personalised approaches to treatment. The approach will become more powerful as functional information is interpreted in relation to data from a growing number of patients with sufficient coverage for each disease. This principle is highlighted by a study[10] showing that drug responses can partition chronic lymphocytic leukaemia in clinically relevant subgroups according to Bruton's tyrosine kinase (BTK) and mechanistic target of rapamycin (mTOR) dependencies. Importantly, relevant phenotypes can be detected that would not have been predicted by genomic information. To build such a growing database of knowledge will require substantial efforts to harmonise output from different platforms and solve logistical bottlenecks for multicentric trials.

Finally, this study provides stimulating insights for future clinical trial design. Staber and colleagues have chosen the pragmatic single institutional approach for their interventional study of relapsed or refractory acute leukaemia (NCT03096821). Their study design

provides the highest possible flexibility for experimental treatment including combination of different modalities in the best interest of their patients. This trial pilots several relevant clinical scenarios that will have an impact on the design of future trials, for example data-guided combination of targeted agents with antibody-based therapies for lymphoid malignancies. As Snijder and colleagues point out, larger studies should focus on specific disease entities to capture the full potential of phenotypic screening. In my view, phenotypic screening should also be explored in frontline therapy with the aim to reduce unnecessary exposure to toxic agents and improve responses in selected subgroups in the future. One could envision trial designs that allow for modular substitution of treatment elements and randomisation of combination therapy including immunotherapy. The jury is still out, but systematic exploration of such functional approaches should be intensively promoted to demonstrate their potential in precision oncology.

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I declare no competing interests.

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