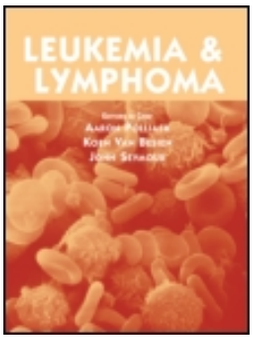

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COMMENTARY

Reversing multidrug resistance (MDR1, ABCB1) in acute myeloid leukemia: back to the ABCs

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Acute myeloid leukemia (AML) remains a devastating disease. The vast majority of patients will not achieve long-term survival. Progress has been made in understanding AML, but that has not translated fully into successful avenues of treatment. AML can now be subdivided into over 40 molecular subtypes based on cytogenetics and point mutations in genes such as FLT3, NPM1 and RAS [1]. However, although the identification of these biological aberrations has yielded much prognostic information for risk stratification, none has led to effective and specific targeted therapy. Each new discovery regarding AML biology is greeted with excitement as holding therapeutic promise, but unfortunately, many frustrations and disappointments have followed the initial enthusiasm.

An early milestone in the search for specific targets in AML was the observation that AML cells often overexpress the multidrug resistance gene MDR1 (ABCB1) [2]. Much effort was invested into trying to exploit this to enable more effective anti-leukemic therapy. Non-specific ABCB1 inhibitors led the way to second- and third-generation, more specific inhibitors; however, paradoxically, each newer generation of inhibitors seemed to be less effective than the older non-specific ones [3,4]. It is now known that there are multiple, partially redundant transporters, such that it is probably counterproductive to specifically inhibit individual ones. Furthermore, it is now understood that these transporters have important cellular functions in normal tissues, particularly in the hematopoietic stem cell but also in other organs. Therefore, it is not surprising that interfering with their function causes substantial toxicity.

With this as background, in this issue of *Leukemia and Lymphoma* a group of clinicians and scientists report a very small study in which they attempted to use a new tactic directed at circumventing drug resistance in AML [5]. Their study is notable for a number of factors that are relatively novel. First, they used a combination of two drugs which are known or purported to inhibit MDR1. The customary MDR1 antagonist is cyclosporine A, known to inhibit several transporters, including ABCB1, but is not specific for the latter transporter. The second agent is pravastatin, a lipid lowering agent which was recently discovered to exert an effect on drug resistance via its action on cholesterol biosynthesis. These two inhibitors were combined with two chemotherapeutic agents which are both substrates of drug transporters: etoposide, transported by ABCB1, and mitoxantrone, which is effluxed by ABCB1 but also by other transporters that are inhibited by cyclosporine A. Thus, they had a unique four-drug combination of two cytotoxic agents and two resistance modulators. Another notable aspect of this study is the fact that the investigators planned a small study and carefully calculated how they could determine whether or not the risk–benefit ratio warranted continuation, without exposing more patients to excessively risky or ineffective therapy. In fact, this prudence was quite important in view of the very high toxicity encountered, which would otherwise have been unpredictable using this new combination of four well-known drugs. The authors were therefore able to rapidly terminate what appeared to be a very promising study, due to unacceptable toxicity, before too many patients were enrolled.

What can be learned from the failure of this study? It has been suggested that the biology of transporters is such that any effective regimen is highly likely to be so toxic that any therapeutic benefit would be obscured [6]. Does this mean that attempts at reversing drug resistance in AML should be abandoned, as has been suggested [7]? Experts have expressed the opinion that the answer to this question is probably "no" [6]. First of all, regarding efficacy of drug reversing agents, no trial using these agents has ever been performed in patients selected for expression of drug resistance. Therefore negative or equivocal results of trials in unselected patients may indeed not be representative. Second, the reasons for failure of these agents has not been analyzed in depth. The few clinical trials done were mostly performed when it was not feasible to analyze the effects of reversing agents on multiple transporters that may work in concert, some of which may be inhibited and others up-regulated in response to inhibition. In addition, analysis of the concurrent and downstream events of transporter inhibition has not been performed.

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Before prematurely abandoning an avenue that could provide clinical benefit in this disease which is so difficult to treat, it is important to go back to the ABCs of laboratory benchwork using modern technology. Very recently, the questions that still need to be answered regarding drug resistance modulation in AML have been clearly summarized [6]. New technologies such as proteomics, metabolomics and gene expression profiling can be utilized to analyze the cellular responses, not just to cytotoxic agents, but to the combination of such drugs used together with drug resistance reversers. Such laboratory studies need to be done on primary cells isolated from patients, since cultured cell lines do not reliably reproduce the biology of patient cells. AML cells are generally easily accessible from peripheral blood, in contrast to other malignancies, such that this is indeed feasible to perform. Much basic laboratory work still needs to be done at the *in vitro* level to lay out the groundwork for clinical trials, which would then ideally be performed in patients selected for disease characteristics predicting a good clinical response. Once we better understand the "ABCs" of ABCB1 and other transporters, we may well be able to more effectively apply this knowledge to the successful use of drug resistance reversers in AML and other malignancies.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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