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Significance of ABC Transporters in the Treatment of Intrinsically Resistant Acute Myeloid Leukemia

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Commentary

Resistance to chemotherapy remains a major challenge to treating acute myeloid leukemia (AML) patients. One suggested mechanism of this resistance is the efflux of chemotherapy drugs by the ATP-binding cassette (ABC) transporter P-glycoprotein (also called P-gp, MDR1, or *ABCB1*, encoded by the *ABCB1* gene) [1]. Several studies have shown a positive correlation between P-gp expression and poor clinical outcome including a now classical study by the Southwest Oncology Group (SWOG) in which cyclosporin A was shown to improve overall survival in high risk AML [2-4]. Thus, other clinical trials have been conducted to target P-gp, with the goal of improving the overall survival of AML patients [5-10].

One of these was a randomized placebo-controlled double blinded study of elderly AML patients by the Eastern Cooperative Oncology Group 3999 (E3999) [10]. They tested whether inhibition of P-gp by zosuquidar, a potent third generation P-gp inhibitor, improved the response of AML patients to cytarabine and daunorubicin treatments. Disappointingly, this trial failed to demonstrate the efficacy of zosuquidar in improving the overall survival of AML patients, and it has been suggested that it is time to stop targeting P-gp to improve therapy of AML [11]. However, the failure of this trial was possibly due to short infusion time of zosuquidar, the failure to specifically target AML patients overexpressing P-gp, or the failure to take into consideration the effect of other ABC transporters. It is quite possible that ABC transporters other than P-gp may cause resistance to chemotherapy.

A recent study by the Beat AML program performed whole-exome and RNA-sequencing and examined *ex vivo* drug sensitivity on AML tumor specimens [12]. This multi-institute collaborative effort made it possible to examine the transcriptomic profiles of treatment-naïve samples from newly diagnosed untreated AML patients and to stratify those profiles based on patient responses to induction therapy (cytarabine and anthracycline-based cytotoxic therapy). We have shown that intrinsically resistant AML can be clustered into three refractory sub-populations and that only one of the refractory sub-populations overexpresses ABC transporters [13]. Thus, ideally future studies testing the role of transporters in drug resistance will focus on this sub-population, which is also the group with the poorest survival probability. Interestingly, it is not P-gp but other ABC transporters, including *ABCG2*, *ABCA2*, *ABCA9*, and *ABCA6*, that are overexpressed in this sub-population.

ABCG2 (also called breast cancer resistance protein (BCRP), encoded by the *ABCG2* gene) is another extensively studied major transporter that can efflux drugs and reduce drug accumulation, resulting in drug resistance. Because other ABC transporters such as *ABCA2* are also able to efflux chemotherapeutic drugs, it is clear that simply targeting one transporter, or targeting the wrong transporter, is not enough to reverse drug resistance in AML [14]. This may explain why the E3999 trial failed because zosuquidar is a P-gp-specific inhibitor and does not inhibit other ABC transporters, whereas as in the SWOG trial, cyclosporin A, an inhibitor of *ABCB1* and *ABCG2* and possibly other ABC transporters, was shown to be effective [4].

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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