In this issue of *Blood*, Stein and colleagues provide an update of the enasidenib study of 214 R/R AML patients (median age of 68) treated at a dose of 100 mg/d. This report confirmed the high rate of complete remission (CR) in 19.6% of patients with 10.3% proceeding to an allogeneic bone marrow transplant. Thus, enasidenib monotherapy demonstrated high efficacy with an ORR of 38.8% (95% confidence interval [CI] 32.2-45.7) and a median overall survival (OS) of 8.8 months (95% CI 7.7-9.6). Notably, similar to epigenetic treatment, the best response was seen quite late (ie, by cycle 4 in 46% and by cycle 6 in 80% of responding patients). This suggests that molecular monitoring will be important in this AML subgroup, as molecular response might be detected before clinical response and can be used to better guide targeted IDH2 treatment (see figure). Reduction in *IDH2* variant allele frequency and molecular clearance with enasidenib were associated with attainment of CR. Similarly, the magnitude of 2-hydroxyglutarate reduction on-study was associated with CR in *IDH2*-R172 patients.

Although response rates were similar among patients with relapsed (37.7%) and refractory disease (37.5%), recent data presented at the 2018 Annual Meeting of the American Society of Hematology Meeting in San Diego point to an even higher effectiveness in first-line AML therapy.[7] In the current study of R/R AML, clinical activity of enasidenib was negatively affected by baseline comutations in patients with *FLT3*-ITD or -TKD as well as *NRAS* mutations. Similarly, in previously untreated cases, *RAS* or *PTPN11* were also found unfavorable.[7]

Enasidenib monotherapy is well tolerated, and the most common grade 3 to 4 treatment-related adverse events were hyperbilirubinemia in 10%, thrombocytopenia in 7%, and IDH differentiation syndrome in 6% of cases. This suggests that enasidenib might also be well tolerated in combination therapies. Initial data provide evidence for compatibility with azacitidine,[7] and with conventional chemotherapy in first-line therapy.[8]

Given that not all *IDH2* mutant patients respond to IDH2 inhibition, combination treatment with state-of-the-art conventional chemotherapy and azacitidine, as well as combined with novel AML treatment strategies, such as tyrosine kinase and BCL2 inhibitors, will be important to further improve outcome (see figure). This is of special importance because recently mechanisms of acquired resistance to targeted IDH2 therapy have been demonstrated by the detection of second-site *IDH2* mutations.[9] However, relapse can also arise by clonal evolution or selection of ancestral clones.[10] Thus, combined targeting of several potential bypass pathways in parallel could be used to increase CR and OS rates.

In summary, Stein and colleagues provide further evidence that IDH inhibition may be an important addition in the leukemia treatment armamentarium with the power to induce remissions and hematologic responses in patients with AML for whom prior treatments had failed, especially in older AML patients. In the future, individualized combination treatment strategies will include enasidenib for *IDH2* mutant patients, thereby adding more pieces to better solve the molecular puzzle of AML.

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LYMPHOID NEOPLASIA

Comment on Efentakis et al, page 710

Off-target effects of carfilzomib that cause cardiotoxicity

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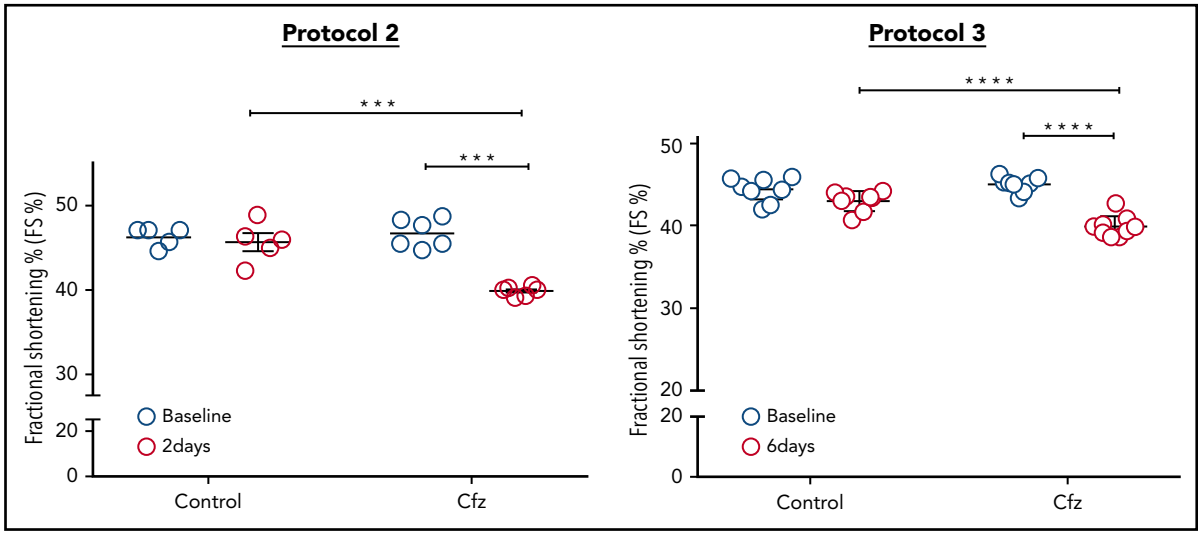
In this issue of *Blood*, Efentakis et al report using an animal model to study carfilzomib (Cfz)–induced cardiotoxicity and to demonstrate that the molecular mechanism is not related to the inhibition of the proteasome function but instead has an influence on modulation of the autophagy pathway, inactivation of AMPKα, and upregulation of PP2A phosphatase activity.[1]

For many years, cardiotoxicity in patients with cancer has been associated with cumulative doses of anthracyclines. Then different types of cardiotoxicity caused by HER2/neu inhibitors emerged, and in recent years, with the advancement of



This figure demonstrates evidence of significant fractional shortening in all mice receiving Cfz without much variability. In protocol 2, the Cfz dose was equivalent to a human dose of 14.85 mg/m^2 and was given for 2 days. In protocol 3, the Cfz dose was equivalent to a human dose of 29.65 mg/m^2 given every other day for 4 doses. ***P = .001, ****P < .001. The figure was adapted from Figure 1E-F in the article by Efentakis et al that begins on page 710.

targeted therapy in cancer, more and more agents have been reported to have cardiovascular adverse effects[2] that necessitated the establishment of a new discipline of cardio-oncology.

Carfilzomib is an irreversible proteasome inhibitor that has been shown to be effective in the treatment of relapsed multiple myeloma. However, it has been shown to have significant grade 3 to 4 cardiotoxicity in as many as 5% to 10% of patients.[3] This incidence is higher than that reported for bortezomib, although cardiotoxicity has been reported with all clinically approved proteasome inhibitors.[4] Fortunately, Cfz-induced cardiotoxicity is reversible in many patients after the drug is stopped. Several studies have tried to assess clinical predictive factors, but the occurrence of symptomatic Cfz-induced cardiotoxicity is still mostly unpredictable. Thus, it is important to study its pathogenesis, predictive biomarkers, and ways to protect patients against such toxicity.

The article by Efentakis et al focuses on establishing a clinically relevant mouse model to study the cardiotoxic effects of Cfz by echocardiography and correlating the findings with changes in molecular targets. By using C57BL/6 male mice, the authors established appropriate Cfz treatment regimens that resulted in cardiotoxicity that can be reversible upon stopping the drug but can also be prevented by cotreatment with metformin (Met). The surprising finding is the off-target effects of Cfz on autophagy proteins and activation of PPA2 (the reasons for the cardiotoxicity) and not proteasome inhibition. Thus, Met (a known activator of MAPKα and promoter of autophagy, as reported by many studies) has protective effects without interfering with proteasome inhibition. Conversely, the administration of bortezomib in this animal model did not result in cardiotoxicity or in the molecular changes observed with Cfz.

Cardiotoxicity animal models have been used to elucidate possible molecular mechanisms and demonstrate protective effects of different agents, including Met. A quick search of PubMed using the 3-word phrase "cardiotoxicity animal models" revealed 584 publications on the topic, and most dealt with anthracycline-induced cardiotoxicity. One study published in 2017[5] used a Wistar albino male rat model to study Cfz cardiotoxicity, which was measured by histopathologic changes as well as molecular and biochemical markers. In that study, rutin (a bioflavonoid) was able to reverse Cfz-induced cardiotoxicity. The molecular and biochemical studies pointed to the NF-κB pathway, the cardiac hypertrophic gene, and oxidative stress as being responsible for Cfz-induced toxicity. These findings raise a question about whether using different animal models is applicable for studying effects in humans. The real test will come when clinical trials confirm the findings of these animal studies; results and conclusions remain to be seen.

Another issue regarding whether studies in animal models are applicable to humans is related to the fact that not all patients receiving Cfz will develop cardiotoxicity, but all animals in these models will develop cardiotoxicity (see figure). Other factors such as the effects of old age and prior heart disease in patients could explain the difference. Genetic polymorphism could also be a factor that plays a role in different patients' susceptibility, and it needs to be investigated. There is a body of literature on using pharmacogenomics in anthracycline-induced cardiotoxicity[6,7] that led the Canadian Pharmacogenomics Network for Drug Safety to recommend genetic testing to reduce the incidence of anthracycline-induced cardiotoxicity.[8] Genetic risk profiling could be used to identify high-risk patients who can then be provided with safer treatment options, including cardioprotective agents.

From the literature on Met, one gets the impression that it is a wonder drug because of its potential beneficial effects in cancer treatment and its lack of significant adverse effects. The successful use of Met to protect against Cfz-induced cardiotoxicity could be a breakthrough in the field, and it will have major impact on treatment for patients with multiple myeloma. Autophagy is a complex process involved in cell homeostasis, and novel

modulators are being actively pursued.[9] Once novel modulators with a better therapeutic index are discovered, their cardioprotective effects can be tested by using the animal model presented by Efentakis et al.

Overall, the study by Efentakis et al provides new insights into the mechanism of Cfz-induced cardiotoxicity by establishing a relevant animal model and demonstrates the protective effects of Met. But a few questions remain to be answered. In addition to those raised by the authors in the "Discussion," there are other questions of interest. Because all proteasome inhibitors are reported to cause some cardiotoxicity but less cardiotoxicity than Cfz, what is the mechanism for the other proteasome inhibitor–induced cardiotoxicities and how can the higher incidence of cardiotoxicity with Cfz be explained? Are the animal data from this study or any other animal model going to be clinically applicable to human patients? Clinical trials in humans are needed to answer this question. And last, will the recently approved dose and dosing schedule for Cfz be less or more cardiotoxic?

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LYMPHOID NEOPLASIA

Comment on Qian et al, page 724

Yet another susceptibility variant for ALL: what's next?

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In this issue of *Blood*, Qian and colleagues[1] add *ERG* variants to a growing list of common host DNA polymorphisms that have been associated with an increased risk of childhood acute lymphoblastic leukemia (ALL). It has long been known that Hispanics more frequently develop childhood ALL. In addition to *GATA3*, *PIP4K2A*, and *ARID5B*, this increased risk is now also accounted for by *ERG* variants with the frequency of risk variants being positively related to the proportion of Native American Ancestry.

Susceptibility for ALL covers a wide continuum that ranges from rare, but highly penetrant, cancer prone syndromes with a 10- to 100-fold (or even more) increased risk of ALL to common germline DNA variants that mediate only a modest (1.2- to 3.0-fold) increased odds ratio.[2] The former group includes both syndromes dominated by their nonmalignant phenotype, such as Down syndrome and ataxia telangiectasia, as well as pure cancer syndromes, such as Li-Fraumeni syndrome. At the other end of the spectrum, the risk genes include *ARID5B*, *PIP4K2A*, *IKZF1*, *CDKN2A*, *CEBPE*, *GATA3*, and now also *ERG*. Many of the risk genes associated with ALL are transcription factors involved in hematopoietic development. Several of these are frequently affected by somatic mutations in ALL, such as *IKZF1*, *CDKN2A*, and *ERG*, but the common variants that associate with ALL risk in most cases reside in noncoding regions.

Adding to this, the susceptibility variants and cancer-prone syndromes are often strongly associated with certain subsets of ALL, such as *ARID5B* variants being associated with high-hyperdiploid ALL, *GATA3* variants with Philadelphia-like ALL, and Li-Fraumeni syndrome with hypodiploid ALL. Of interest, the gap between the common susceptibility variants and the rare cancer-prone syndromes is slowly closing with the demonstration that 1% to 3% of ALL patients harbor deleterious coding variants in genes previously only linked to rare cancer-prone syndromes, such as *ETV6*[3] and *TP53*.[4]

Whereas some of the common variants, like those residing in *ARID5B*, have been associated with an increased risk of ALL across multiple ethnicities, others like *ERG* seem to be more race restricted. However, it remains uncertain whether this reflects the broader, yet undefined, ethnicity-dependent genomic context within which they mediate their biological effect, or whether it reflects interactions with environmental risk factors for ALL that are influenced by certain behavioral profiles.[5]

The mapping of the natural history of ALL has mostly used the *ETV6/RUNX1* and high-hyperdiploid ALL subsets as prototypes as they are the most common ALL subsets and furthermore frequently initiated prenatally. Thus, clone-specific markers representing preleukemic cells can be detected in neonatal blood spot samples or Guthrie cards.[6] The preleukemic cell burden at birth can then taper off, or the preleukemic cells can persist and acquire the additional somatic mutations necessary for development of

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