account for all factors biasing transplant referral.

Hematologists caring for adults with Ph+ ALL are hungry for data to guide practice. The findings of this study are significant, but the conclusions must be limited to comparable patients: those with newly diagnosed, de novo Ph+ ALL who achieve a deep remission (*BCR-ABL1* transcript level <0.01%) within 90 days of treatment being managed with an intensive induction and consolidation chemotherapy regimen. This study does not address the role of allo-HCT in patients with chronic myeloid leukemia (CML) in lymphoid blast crisis, therapy-related ALL (an increasingly recognized entity), or Ph+ ALL that responds more slowly to therapy. It also does not apply to those treated with a chemotherapy-free or chemotherapy-light approach. Indeed, a recent report from the ongoing GRAAPH 2014 study revealed inferior outcomes in patients who did not receive either intensive (cytarabine-based) consolidation or allo-HCT.[8] Finally, this study does not address the need for allo-HCT in patients treated with novel chemotherapy-free regimens such TKI plus blinatumomab.[9]

Perhaps the biggest challenge of applying the findings of this study to current practice is the rapid expansion of knowledge and improvements in clinical practice in both Ph+ ALL and allo-HCT. Thus, the risk-benefit ratio of allo-HCT overall, and particularly within specific patient subgroups, is likely to continually evolve. Will patients with additional high-risk genetic features such as *IKZF1* plus other copy number abnormalities be found to benefit from allo-HCT?[10] Will use of measurable residual disease (MRD) assays more specific for the lymphoblastic disease compartment better identify patients needing therapeutic intensification with allo-HCT? Will advances in prevention and management of graft-versus-host disease, and development of non-TBI allo-HCT conditioning decrease toxicity and treatment-related mortality after allo-HCT? Will availability of more effective salvage therapies (TKI and non-TKI based) ensure that allo-HCT in CR2 can be reliably realized so that we do not need to "get it right the first time"? Will advances in chimeric antigen receptor therapy (CAR-T) make it the preferred and definitive salvage option in relapsed or refractory disease?

The management of Ph+ ALL is evolving at lightning speed, and it is imperative that prospective, randomized trials of transplant and nontransplant approaches be conducted to obtain the necessary high-quality data to rationally advance the field. In the meantime, the study by Ghobadi et al suggests that allo-HCT may be reasonably deferred in transplant-eligible patients who respond rapidly and deeply to a TKI plus intensive chemotherapy. Still, given the complexity of the disease and treatment landscape, as recommended by the authors, "early referral to a high-volume transplant center to evaluate transplant eligibility, identify potential allogeneic donors, and discuss the risks and benefits of allogeneic transplant as a therapeutic option remains an essential component of management in Ph+ ALL." Until all the cards have been dealt, transplant colleagues: we still need you!

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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LYMPHOID NEOPLASIA

Comment on Thomalla et al, page 2113, and Thijssen et al, page 2127

Mechanisms of resistance to venetoclax

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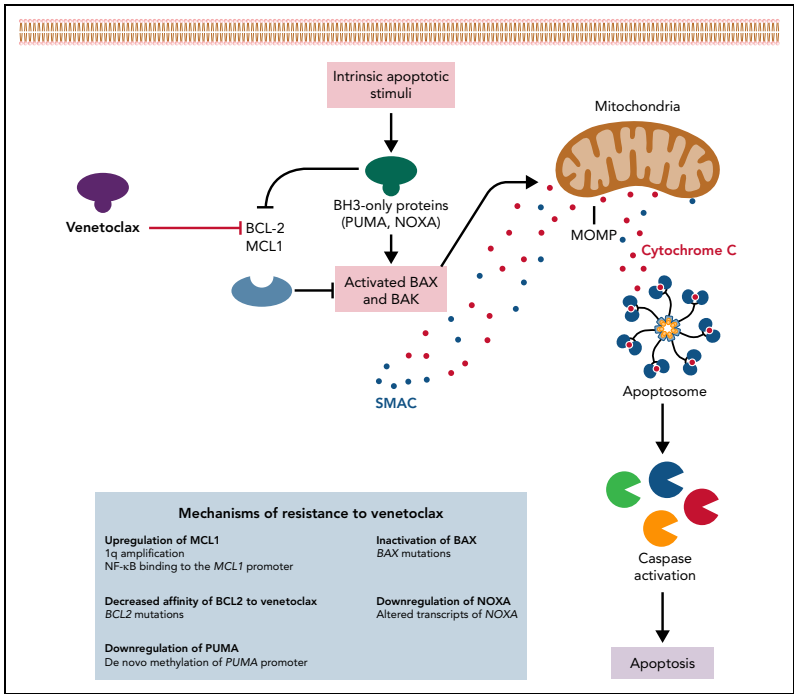
In this issue of *Blood*, complementary manuscripts by Thomalla et al[1] and Thijssen et al[2] expand our understanding of the adaptive mechanisms associated with resistance to venetoclax (see figure). Venetoclax blocks

the ability of BCL2 to inhibit proapoptotic proteins such as BAX, leading in turn to permeabilization of the mitochondrial outer membrane and committing the cell to apoptosis.[3,4] Like BCL2, the antiapoptotic protein MCL1 also interacts with proapoptotic BAX proteins to block their function, but MCL1 is not affected by venetoclax. PUMA and NOXA interact with BCL2, thus freeing BAX, which is then able to signal apoptosis to the mitochondria.[5]

The mechanisms that block or blunt the activity of venetoclax are unexpectedly heterogeneous.[6-11] Recurrent mutations in *BCL2* lead to resistance due to decreased affinity of BCL2 for venetoclax.[6-8] Upon treatment with venetoclax, *BAX* mutation can occur in the myeloid compartment.[9] *BAX* mutations abrogate the outer mitochondrial membrane localization of BAX, thus keeping it in its inactive form, and are associated with the development of lineage-specific clonal hematopoiesis. Beside mutations, upregulation of MCL1 due to amplification of chromosome 1 is associated with resistance to venetoclax.[10,11]

Using functional genomic screens followed by validation in primary tumor samples, Thomalla et al identify an epigenetic mechanism of adaptation of tumor cells to venetoclax. The authors show by multiple convincing experiments in cell lines and primary samples that resistance toward venetoclax is mediated by de novo methylation of the *PUMA* promoter and subsequent downregulation of PUMA expression.

By using single-cell approaches, Thijssen et al clearly show that *MCL1* overexpression dominates in venetoclax-resistant clones. However, *MCL1* gene amplification accounted for increased *MCL1* expression in only a limited number of tumors that became resistant to venetoclax. Conversely, Thijssen et al show that it was more common that marked NF-κB activation and NF-κB binding to the MCL1 promoter resulting in increased MCL1 expression resulted in relapses occurring on venetoclax therapy.



Mechanisms of resistance to venetoclax. The intrinsic apoptotic pathway can be engaged by stimuli that regulate BCL-2 and MCL1 interactions with BH3-only proteins (ie, PUMA and NOXA), modulating the activation of the effector proteins BAX and BAK. Once activated, BAX and BAK cause MOMP, leading to the release of proapoptotic proteins. Cytochrome C leads to apoptosome formation that recruits and activates caspase. Mechanisms of resistance to venetoclax described in the papers by Thijssen et al and Thomalla et al are shown in the blue box. MOMP, mitochondrial outer membrane permeabilization; SMAC, second mitochondria-derived activator of caspase.

The high granularity of the approach used by Thijssen et al also demonstrated large intra- and inter-patient heterogeneity. Multiple mechanisms of escape (eg, 1q24 amplification, *BCL2* mutations, *BAX* mutations, and altered transcript of proapoptotic *NOXA*) may coexist in the same tumor, usually restricted to different subclones. While some of these escape mechanisms are unique, others are found in multiple patients, indicating that tumor cells intrinsically adapt in multiple ways to selection pressure on cell survival exerted by venetoclax treatment.

The articles by Thijssen et al and Thomalla et al provide two translational implications. Epigenetic changes of resistance (ie, NF-κB–promoted upregulation of MCL1) are driven and sustained by ongoing venetoclax therapy. Indeed, they disappear once venetoclax therapy is stopped. Hence, limited duration venetoclax therapy is an appealing strategy to prevent the emergence of resistance. Mechanisms of resistance to venetoclax use the regulators of the intrinsic apoptotic pathway. Hence, therapeutic approaches that induce apoptosis through the extrinsic pathway (ie, tumor necrosis factor–related apoptosis-inducing ligand TRAIL-mediated apoptosis) can be effective in resistant cells.

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LYMPHOID NEOPLASIA

Comment on Bhat et al, page 2142

Cardiotoxicity in patients treated with acalabrutinib

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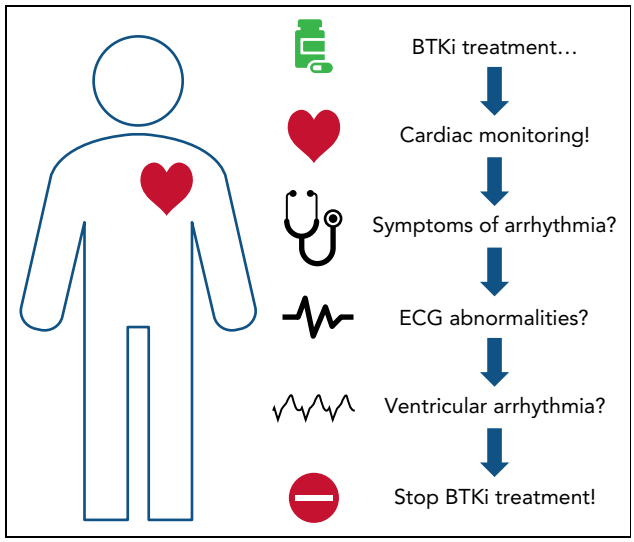
In this issue of *Blood*, Bhat et al systematically evaluated the rate of incident symptomatic ventricular arrhythmias (VAs) in a large case series of patients treated with acalabrutinib.[1] Although the observed cardiotoxic adverse events in nearly 3% of patients treated with acalabrutinib was lower than that reported in patients treated with ibrutinib, the percentage was eightfold higher than that in similar untreated control patients. These data indicate that VAs may be a class-specific effect of Bruton tyrosine kinase inhibitors (BTKi's).



Monitoring for VAs in patients treated with a BTKi.

The BTKi ibrutinib was approved by the US Food and Drug Administration for treating B-cell lymphoproliferative disorders almost 10 years ago. Just recently, the second-generation BTKi acalabrutinib was granted approval for treating chronic lymphocytic leukemia (CLL).

Cardiac toxicity is a recognized treatment-limiting adverse effect of BTKi's. The mechanism of this toxicity is hypothesized to be on-target inhibition of BTK and related kinases such as tec protein kinase, which results in reduced PI3K-Akt activity in cardiac cells thus decreasing its cardioprotective role under conditions of stress.[2]

The most common cardiac toxicity is atrial fibrillation, which might lead to subsequent use of anticoagulation therapy to reduce the risk of thromboembolism. Because BTKi's selectively also inhibit platelet signaling and function downstream of the collagen receptor glycoprotein VI,[3] their use is associated with an increased risk of bleeding, which usually manifests as minor bruising. However, concomitant use of anticoagulants significantly increases the risk for major hemorrhage.[4] In clinical practice, the onset of atrial fibrillation often mandates that treatment with BTKi's be terminated because of the increased risk of bleeding.

In clinical trials, ibrutinib (a first-generation BTKi) led to cardiac arrhythmias in up to 20% of patients,[5] including 12% of patients with atrial fibrillation, compared with 8% of patients with cardiac arrhythmias and 1.2% of patients with atrial fibrillation in the untreated population. With longer follow-up, case series of VAs and sudden cardiac deaths that have been described in patients treated with ibrutinib[6,7] further raises awareness of the potential for severe cardiotoxicity.

Second-generation BTKi's demonstrate greater BTK selectivity and less off-target inhibition compared with ibrutinib. The first direct comparison of the more selective acalabrutinib vs the less selective ibrutinib demonstrated noninferior progression-free survival with fewer cardiovascular events. The adverse event of atrial fibrillation was prospectively assessed as a secondary end point and was significantly lower in the acalabrutinib treatment arm than in the ibrutinib arm (9% vs 15.6%, respectively).[8]