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CLINICAL TRIALS AND OBSERVATIONS

Comment on Castillo et al, page 582

Risk/benefit of BTK/venetoclax combos: the context matters!

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In this issue of *Blood*, Castillo et al report a combination study of ibrutinib and venetoclax in Waldenström macroglobulinemia (WM), a combination previously reported as safe and effective in >1500 patients with other lymphoproliferative diseases, yet enrollment to the study was halted prematurely after 42 patients were treated due to the relatively early development of major ventricular arrythmias between cycles 3 and 7 in 4 patients (9.5%), including 2 fatal events.[1] How did we get here, and why did this happen?

Bruton tyrosine kinase inhibitors (BTKis), such as ibrutinib, have transformed the management landscape for many indolent lymphoproliferative disorders, including WM. BTKis mediate their therapeutic effect via interruption of the B-cell receptor signaling pathway, interfering with the cellular localization, survival, and proliferation programs mediated via microenvironmental interactions.[2]

Venetoclax, a BH3-mimetic BCL2 inhibitor, is also highly active as a single agent in indolent lymphoproliferative disorders, including in WM.[3] Venetoclax exerts its therapeutic effect via direct interaction with the intrinsic apoptotic pathway negative regulatory protein BCL2, unleashing apoptotic cell death in those diseases in which the malignant cells are "primed" for apoptosis and dependent on BCL2 for its prevention.[4]

Given their complementary mechanisms of action, single-agent activity, and marked preclinical synergy, the combination of ibrutinib and venetoclax is a compelling regimen for clinical evaluation.[5]

This combination has been widely studied and shown highly promising activity in mantle cell lymphoma,[6,7] marginal zone lymphoma, and chronic lymphocytic leukemia (CLL) (reviewed by Bennett et al[8]). Doses of ibrutinib have ranged from 420 to 560 mg daily, and doses of venetoclax have ranged from 200 to 600 mg daily. No concerning cardiac safety signal was seen in these studies with some patients receiving continuous combination therapy for >7 years (Con Tam, Alfred Hospital, written communication, November 2023).

It is in that context that Castillo et al pursued the time-limited (24 months) combination of ibrutinib 420 mg daily and venetoclax 400 mg daily in patients with previously untreated WM. They targeted a "promising" very good partial remission (VGPR) rate of ≥45% as the primary efficacy end point and attained an actual VGPR rate of 42% and a major response rate of 96%. The combination unequivocally has significant activity in WM. However, the previously mentioned cardiac toxicity of ventricular arrythmias halted the trial. Atrial fibrillation (AF) was also seen in 3 patients (7.1%). This was despite the study eligibility excluding patients with "significant cardiovascular disease, or [taking] medications that could prolong the QT interval."

Although developed as a "selective" BTKi, ibrutinib binds covalently via the sulfur moiety of the cysteine 481 residue on BTK and has moderate "off-target" binding to other structurally similar kinases. This kinase binding promiscuity may contribute to the arrhythmia signal now well described with ibrutinib.[9] The vast majority of ibrutinib-related arrhythmias are atrial (predominantly AF), but there is also a less frequent, but definite and reproducible, signal of an increased relative risk of ventricular arrhythmias that may manifest as sudden unexplained cardiac death.[9] The largest cohort of patients treated with ibrutinib are those with CLL, but the same proarrhythmic phenomenon has been described with apparently similar frequency in other lymphoma types. Venetoclax as a single agent has not been associated with any direct arrhythmic effects.

Why were these serious ventricular arrhythmias seen specifically and selectively in the WM disease context? Unfortunately no definitive answer is currently available, and it remains possible that this is simply the random play of chance leading to an apparent cluster of rare events with a low background rate. Given the number of events and the close temporal relationship to treatment commencement, this is unlikely, and resorting to such an explanation is also intrinsically unsatisfying and risks patient safety given the widespread use of this combination in other contexts. Both our patients and investigators in the field deserve a better explanation to enable mitigation strategies or risk-informed patient selection.

Are there other potential explanations? These events occurred in the absence of venetoclax-mediated tumor-lysis syndrome and associated electrolyte imbalances. There were no concomitant QT-prolonging medications. Both venetoclax and ibrutinib are hepatically

metabolized by the same CYP pathway with some drug-drug interactions at higher doses, but in the doses used in this trial such effects have not been significant.

Such a magnitude of ventricular arrhythmia signal has not been seen with many hundreds of patients of similar age range and presumed background cardiovascular risk profile in identical combination trials in other diseases, suggesting that there may be a specific factor related to the WM disease context that is responsible. Although both drugs are highly protein bound in the serum, this is predominantly via albumin, but the unique scenario of the immunoglobulin M paraprotein in WM warrants consideration. However, any drug-binding effect would be postulated to reduce effective levels. Although clinically infrequent, tissue amyloid deposition occurs in WM, and when the heart is involved, it is highly proarrhythmogenic. Amyloid screening was not performed, nor are suitable samples available for retrospective testing in this study. This is a potential disease-specific factor that could explain these events. Regardless, the risk/benefit assessment strongly argues against further use of the ibrutinib/venetoclax combination in WM.

So how can the efficacy signal for the BTKi/venetoclax combination in WM be developed without knowing the mechanism of the toxicity? More selective covalent BTKis, such as acalabrutinib and zanubrutinib, have a markedly reduced rate of AF compared with ibrutinib.[10] Although data are less definitive given the markedly lower event rate, ventricular arrythmias are also rare with these agents. The newer noncovalent BTKi pirtobrutinib is similarly highly selective and also has a low arrhythmia rate. Given that mechanistically it is probable that the ibrutinib was the major factor in the arrythmias, substitution of one of these more selective BTKi is a reasonable consideration, which has been pursued by Castillo using pirtobrutinib (NCT05734495). I would argue that until the exact mechanism of the cardiac toxicity is proven, any such combination studies in WM should include careful cardiac screening prior to entry, pharmacokinetic drug monitoring, and evaluation for the potential presence of tissue, specifically cardiac, amyloid. Hopefully such approaches can maximize the benefit and minimize the risk of BTKi/venetoclax combinations in the specific WM disease context.

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REFERENCES

1. Castillo JJ, Branagan AR, Sermer D, et al. Ibrutinib and venetoclax as primary therapy in symptomatic, treatment–naïve Waldenström macroglobulinemia. *Blood*. 2024;143(7):582-591.
2. Ponader S, Burger JA. Bruton's tyrosine kinase: from X-linked agammaglobulinemia toward targeted therapy for B-cell malignancies. *J Clin Oncol*. 2014;32(17):1830-1839.
3. Davids MS, Roberts AW, Seymour JF, et al. Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. *J Clin Oncol*. 2017;35(8):826-833.
4. Valentin R, Grabow S, Davids MS. The rise of apoptosis: targeting apoptosis in hematologic malignancies. *Blood*. 2018;132(12):1248-1264.
5. Chiron D, Dousset C, Brosseau C, et al. Biological rational for sequential targeting of Bruton tyrosine kinase and Bcl-2 to overcome CD40-induced ABT-199 resistance in mantle cell lymphoma. *Oncotarget*. 2015;6(11):8750-8759.
6. Tam CS, Anderson MA, Pott C, et al. Ibrutinib plus venetoclax for the treatment of mantle-cell lymphoma. *N Engl J Med*. 2018;378(13):1211-1223.
7. Portell CA, Wages NA, Kahl BS, et al. Dose-finding study of ibrutinib and venetoclax in relapsed or refractory mantle cell lymphoma. *Blood Adv*. 2022;6(5):1490-1498.
8. Bennett R, Anderson MA, Seymour JF. Unresolved questions in selection of therapies for treatment-naïve chronic lymphocytic leukemia. *J Hematol Oncol*. 2023;16(1):72.
9. Salem JE, Manouchehri A, Bretagne M, et al. Cardiovascular toxicities associated with ibrutinib. *J Am Coll Cardiol*. 2019;74(13):1667-1678.
10. Seymour JF, Byrd JC, Ghia P, et al. Detailed safety profile of acalbrutinib vs ibrutinib in previously treated chronic lymphocytic leukemia in the ELEVATE-RR trial. *Blood*. 2023;142(8):687-699.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on D'Agostino et al, page 592, and Guerrero et al, page 597

Don't let the genie out of the bottle!

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In this issue of *Blood*, 2 companion articles from Guerrero et al[1] and D'Agostino et al[2] explore predictors of disease resurgence despite obtaining measurable residual disease negativity (MRD_{neg}) with first-line therapy in newly diagnosed multiple myeloma (MM).

It is amply evident that achieving an MRD_{neg} status is the most impactful outcome from the treatment of MM, as it is for many hematological cancers, improving progression-free survival (PFS) and, importantly, overall survival (OS).[3] Although MRD_{neg} does not translate into a cure in MM, it is likely that the profound reduction in the clone size puts a brake on the clonal evolution, leading to improved OS.[4] Notably, the therapeutics have kept pace with the increasing sensitivity of MRD detection technology, with the current treatments leading to an unprecedented MRD_{neg} rate even when defined stringently using a cutoff of 10^{-6}. In the absence of MRD_{neg} not translating to a cure, it is essential to demonstrate the value of maintaining MRD_{neg} status for considerable periods of time, the concept of sustained MRD_{neg}, which is already part of the International Myeloma Working Group response criteria.[5] In fact, many studies have examined the value of sustained MRD_{neg}, typically using 6- and 12-month intervals, and demonstrated the positive impact on PFS and OS.[6] What has become disappointingly obvious, with longer follow-up of recent studies, is that nearly all patients eventually relapse, with a substantial proportion of those with MRD_{neg} sustained for a year or more losing that status as a prelude to