COMMENTARY

blood advances

TO THE EDITOR:

The dosing of ibrutinib and related Bruton's tyrosine kinase inhibitors: eliminating the use of brute force

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The Bruton's tyrosine kinase (BTK) inhibitors are key drugs for the management of chronic lymphocytic leukemia (CLL) and related lymphoproliferative disorders,[1] and clinical trials are ongoing in various autoimmune diseases (eg, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis).[2,3] Although this article focuses on the 4 irreversible BTK inhibitors approved in the United States or Japan, there are many other BTK inhibitors in clinical development. Although most of these investigational agents (and all approved agents) are irreversible inhibitors, there are several reversible inhibitors (eg, pirtobrutinib).[4-6]

Ibrutinib was the first BTK inhibitor approved for marketing and currently has 6 indications, including multiple lymphoproliferative disorders and chronic graft-versus-host disease. Ibrutinib binds to the cysteine residue resulting from the C481S mutation in BTK.[7] The approved ibrutinib dose is 420 mg daily for most indications, but 560 mg daily for mantle-cell lymphoma (MCL) and marginal zone lymphoma. However, the initial 2013 review by the US Food and Drug Administration (FDA) noted that doses $>$2.5 mg/kg daily appeared excessive: "We recommend you evaluate lower doses of ibrutinib in future clinical development as data from the phase 1 trial PCYC-04753 showed that maximum BTK occupancy and maximum response were achieved at doses of $\geq$2.5 mg/kg."[8] Despite this FDA recommendation, all subsequent trials of ibrutinib were conducted with doses of 420 and 560 mg daily. The company that markets ibrutinib, Pharmacyclics, obtained method-of-treatment patents for its multiple indications, all of which exclude the lower dose recommended by the FDA, which has been described as "negative innovation."[9]

The dose-finding study of ibrutinib and venetoclax published in this journal by Portell and colleagues concluded that the optimal doses for MCL were ibrutinib 420 mg and venetoclax 200 mg daily.[10] This conclusion was based on a dose-limiting toxicity rate of $\leq$25% and "maximizing" the objective response rate (ORR) at 2 months. This definition is inconsistent with the principles of drug development, now embodied in the FDA's Project Optimus.[11,12] There is no evidence to support the conclusion that these doses are optimal, because the ORR was no higher than that of a lower dose. If one combines cohorts receiving different venetoclax doses, 21 patients were treated with ibrutinib 420 mg daily, and 10 patients were treated with 280 mg daily (Table 1). The small number of patients does not allow for a reliable conclusion as to the optimal ibrutinib dose, but the lower dose appears equally effective and less toxic.

Ibrutinib causes a high incidence of atrial fibrillation (AF), which is not related to inhibition of BTK. Patients with X-linked agammaglobulinemia (XLA), which is caused by inactivating mutations in *BTK*, do not experience atrial fibrillation. Xiao and colleagues[13] developed a mouse model for ibrutinib cardiotoxicity, demonstrating that inducible AF developed after 4 weeks of treatment and was associated with atrial fibrosis and dilatation. Ibrutinib, but not acalabrutinib, induces AF and affects atrial and sinoatrial node myocytes.[14] Based on comparison of the non-BTK targets of these 2 BTK inhibitors, Xiao and colleagues hypothesized that AF was related to inhibition of Fyn, mitogen-activated protein/extracellular signal regulated protein kinase 5, or C-terminal Src kinase (CSK). They demonstrated that cardiac knockout of CSK produced effects similar to those of ibrutinib. Thus, CSK inhibition by ibrutinib appears responsible for the drug's cardiotoxicity. Of particular concern is the risk of induction of AF by ibrutinib, followed by a

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Table 1. Reanalysis of data

Ibrutinib dose	ORR (%)	CR (%)	DLT (%)
280	8/10 (80)	5/10 (50)	0/10 (0)
420	18/20 (90)	8/19 (42)	3/21 (14)

Data are from Table 1 of Portell et al.[10]

stroke, which had a mortality rate of 18% in a 2019 analysis of 303 cardiovascular deaths in the World Health Organization pharmacovigilance database (VigiBase).[15]

Some patients in clinical trials of acalabrutinib have developed AF, but there is minimal evidence that it was caused directly by the drug. In a randomized controlled trial involving patients with CLL, there was a 3.6% incidence of AF, higher than in the non-BTK control arm (0.6%). However, the median duration of observation for patients randomized to acalabrutinib was approximately fivefold longer than that of the control arm, and thus the AF is not likely to be related to the antileukemia therapy. Furthermore, there have been no concerns about cardiac toxicity of BTK inhibitors being developed for nononcologic indications.[16-21]

Ibrutinib frequently causes bleeding, which is also probably not caused by BTK inhibition, given that it does not occur with all BTK inhibitors,[22] and patients with XLA do not manifest a bleeding diathesis. Many of the BTK inhibitors also inhibit Tec kinase, which regulates platelet activation in the absence of BTK activity.[23,24] Inhibition of CSK may also be responsible for ibrutinib-associated bleeding, given that CSK plays a major role in regulation of platelet homeostasis.[25-27]

We do not suggest that hematologists abandon ibrutinib, a drug that has been prescribed to many patients without mishap. However, if BTK inhibition is desirable and CSK inhibition is undesirable, the goal should be to administer a dose that adequately inhibits BTK, while minimizing inhibition of CSK. That is readily achievable, as ibrutinib's inhibitory concentration (IC_{50}) for BTK is 0.5 nM, whereas its IC_{50} for CSK is 2.3 nM, a 4.6-fold therapeutic index.[7] Lower doses of ibrutinib (eg, 140 mg daily, consistent with the 2013 FDA recommendation) would be expected to maintain BTK inhibition and efficacy, while eliminating or reducing the risks of AF (and possibly also hemorrhage).[28] A small pilot study has demonstrated that ibrutinib's BTK occupancy and pharmacodynamics are unaffected by reduction to 140 to 280 mg daily.[29]

Hematologists and oncologists should abandon the notion of using toxicity to determine the optimal dose of molecular targeted agents, particularly covalent irreversible cysteine-directed binders, as exemplified by Portell et al[10] and the development of sotorasib (approved in 2021 for KRAS G12C-mutant lung cancer).[30] The optimal dose should be reassessed for other irreversible BTK inhibitors, including acalabrutinib (approved in multiple countries since 2017), zanubrutinib (approved in multiple countries since 2019), and tirabrutinib (approved in Japan since 2020).

Acalabrutinib obtained was approved for MCL at a dose of 100 mg twice daily. Although doses up to 400 mg daily were investigated in the phase 1 trial, 100 mg twice daily appeared to yield pharmacological and clinical results superior to those obtained with daily dosing in this nonrandomized assessment.[31] However, there is no relationship between exposure and efficacy (or adverse events) of acalabrutinib (and/or its active metabolite, ACP-5862) at the approved dose, which suggests that efficacy plateaus at an exposure less than that achieved with 100 mg twice daily.[32] Lower doses of acalabrutinib would be likely to maintain efficacy, although trials evaluating lower doses are not feasible, given that the only available formulation is a 100-mg capsule.

Zanubrutinib was approved initially for MCL at a dose of either 160 mg twice daily or 320 mg daily. In the phase 1 trial, responses and complete BTK occupancy were observed at doses of 40 mg daily (the lowest dose evaluated) and higher,[33] without evidence of a dose-response relationship. Forty percent of patients receiving zanubrutinib 160 mg twice daily in a phase 3 trial comparing it to ibrutinib experienced at least 1 serious adverse event. Zanubrutinib is formulated as 80 mg capsules, and trials exploring lower dosages (eg, 80 mg daily or twice daily) should be undertaken.

Tirabrutinib is available in Japan for the treatment of primary central nervous system lymphoma, at a dose of 480 mg once daily, administered as six 80-mg tablets under fasting conditions.[33] A phase 1 study in patients with relapsed or refractory lymphoma or CLL, demonstrated that all 3 patients receiving a dose of 160 mg (the lowest dose studied) responded, with 1 patient experiencing a durable complete response.[34] A subsequent trial for patients with primary central nervous system lymphoma, at a dose of 320 and 480 mg once daily, demonstrated a 64% response rate (34% complete responses) without evidence of dose response.[35] In contrast, there was a dose-toxicity relationship. Pharmacokinetic studies demonstrated that the unbound concentration in cerebrospinal fluid was comparable to that in plasma. The dose of 480 mg appears excessive, and doses of $\leq$160 mg daily should be investigated, ideally with food (given that food increases absorption[36]).

Although the newer irreversible BTK inhibitors do not cause AF related to CSK inhibition, their development has been equally flawed and unfortunately accepted by global regulatory authorities. For example, the phase 1 study of pirtobrutinib concluded that the recommended phase 2 dose was 200 mg daily, despite clear evidence that a dose of 25 mg was active.[6]

We acknowledge that atrial fibrillation and bleeding are widely believed to be related to BTK inhibition, but we believe the preponderance of the evidence refutes this conclusion, particularly the lack of such toxicities in clinical trials of BTK inhibitors in nonmalignant diseases.[16-21] The definitive test would be to rigorously evaluate lower doses of ibrutinib and perhaps other BTK inhibitors, to assess the relationship of drug dose (and exposure) to these probable off-target toxicities, given that there does not appear to be a relationship between dose or exposure and efficacy.[8,28] Such studies are of increasing importance, given the advent of FDA's Project Optimus, because the historical paradigm of using toxicity to determine the optimal dose is no longer acceptable.[12,37] The deployment of brute force in the development of targeted agents will no longer be condoned, to the great benefit of patients with a wide variety of malignant diseases.

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