Clinician Perspective on Once-Daily Zanubrutinib Dosing for B-Cell Malignancies at a Single Center

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ABSTRACT: Zanubrutinib, a next-generation, irreversible, highly potent, and selective Bruton tyrosine kinase inhibitor, is approved by the U.S. Food and Drug Administration to treat patients with B-cell malignancies in 2 dose regimens: 160 mg twice daily (BID) and 320 mg once daily (QD). Although the 160 mg BID regimen was the recommended phase 2 dose and more widely used in clinical trials, both regimens have yielded similar efficacy and safety. Currently, there is a lack of reported clinician experience on zanubrutinib QD versus BID practice patterns. This article provides perspectives on zanubrutinib dosing through interviews with 2 clinical care professionals at the Maryland Oncology Hematology Center, based on their experiences treating patients with Waldenström macroglobulinemia (WM) or chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Zanubrutinib QD is the preferred regimen for some physicians and pharmacists, as it may improve treatment adherence within weeks after initiation compared with BID dosing. According to the clinician interviews provided in this report, patients have reported positive experiences with QD dosing, including a reduced administration burden in those with complicated polypharmacy. Thus, observations from this single center indicate that the zanubrutinib QD regimen may offer benefits to both patients with WM or CLL/SLL and their clinical care teams and should be considered in patients receiving zanubrutinib.

KEYWORDS: Zanubrutinib, chronic lymphocytic leukemia, small lymphocytic lymphoma, Waldenström macroglobulinemia, real-world, dosing schedule

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Introduction

Bruton tyrosine kinase (BTK) is an important component of the B-cell receptor signaling pathway, and its targeted inhibition has led to significant improvements in the treatment of B-cell malignancies.[1] Zanubrutinib is a next-generation, irreversible, potent, and selective BTK inhibitor designed to maximize BTK occupancy and minimize off-target kinase inhibition commonly seen with other BTK inhibitors.[2,3] In the United States, zanubrutinib is approved to treat Waldenström macroglobulinemia (WM), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and mantle cell lymphoma (MCL) in patients who received ⩾1 prior therapy and to treat relapsed/refractory (R/R) marginal zone lymphoma (MZL) in patients who received ⩾1 anti–CD20-based regimen.[4] The focus of this article is on zanubrutinib use at a single center in the United States; however, zanubrutinib is also approved in the European Union to treat CLL, WM in patients who received ⩾1 prior therapy or as first-line treatment for patients unsuitable for chemo-immunotherapy, and MZL in patients who received ⩾1 prior anti–CD20-based regimen.[5] In China, zanubrutinib is approved to treat CLL.[6]

Two zanubrutinib dosage regimens are approved: 160 mg twice daily (BID) and 320 mg once daily (QD) dosing.[4,5] The QD and BID dosages were selected based on a phase 1 dose-finding study that reported >95% BTK receptor occupancy with either 160 mg BID or 320 mg QD in peripheral blood mononuclear cells 4 hours post-dose and reported 100% and 94% median lymph node BTK occupancy at the steady state trough with 160 mg BID and 320 mg QD, respectively.[7] The dose-finding study also reported >95% lymph node BTK occupancy in 50% of patients receiving 320 mg QD versus 89% of those receiving 160 mg BID.[7] Based on these findings, 160 mg BID was identified as the recommended phase 2 dose, and phase 3 clinical trials of zanubrutinib have largely utilized the 160 mg BID regimen as a result.[8-10]

Despite these slight differences in pharmacodynamics, the QD and BID zanubrutinib regimens have yielded similar efficacy and safety.[7,11] A pooled analysis of a phase 2 study (BGB-3111-206) and a phase 1/2 dose-finding study (BGB-3111-AU-003) in patients with MCL found that treatment with either zanubrutinib dosage achieved similar plasma exposure and BTK inhibition with minimal pharmacokinetic differences.[12] In a study of zanubrutinib in patients with CLL/SLL, WM, MZL, or MCL who were intolerant of the BTK inhibitors ibrutinib and/or acalabrutinib, the disease control rate (defined as stable disease or better) was 95% and 92% with 160 mg BID and 320 mg QD, respectively.[3] Another study of zanubrutinib in Chinese patients with R/R B-cell malignancies reported comparable efficacy, safety, and daily area under the curve with 160 mg BID and 320 mg QD regimens.[13] Overall response rates and complete response rates were 73% and 27% with 160 mg zanubrutinib BID and 80% and 20% with 320 mg QD, respectively.[13] The study concluded that zanubrutinib was well tolerated and clinically practical at either dosage.[13]

The option to administer zanubrutinib either QD or BID provides flexibility for patients and physicians to choose a regimen that maximizes clinical efficacy and facilitates adherence.[11,12] Currently, the perspectives of clinicians and patients on zanubrutinib QD versus BID dosage are not well documented. Through interviews with 2 clinical care professionals at the Maryland Oncology Hematology Center in Columbia, Maryland, we describe perspectives on QD zanubrutinib to treat patients with WM or CLL/SLL. Our goal is to report clinician experiences regarding zanubrutinib dosages and enhance confidence in prescribing QD zanubrutinib in the management of WM, CLL/SLL, and other B-cell malignancies.

Physician Perspective

Mohit Narang, MD, oncologist and hematologist at Maryland Oncology Hematology

To treat WM and CLL/SLL, I have prescribed QD zanubrutinib to 44 patients and my colleagues have prescribed QD zanubrutinib to an additional 30 patients. Most of these patients in my care received first-line zanubrutinib treatment, while some patients were switched from ibrutinib to zanubrutinib. Approximately 8 to 10 of the patients were switched from BID to QD zanubrutinib, while the rest were initially prescribed QD zanubrutinib. The only 2 patients under my care who receive zanubrutinib BID concurrently take other BID medications. Some of my patients began taking zanubrutinib during the clinical trials in WM, while others were prescribed zanubrutinib following U.S. Food and Drug Administration (FDA) approval in 2019. The patients at my community practice are diverse in terms of race, ethnicity, and age and would be considered representative of the general population of suburban Maryland.

My motivation to prescribe zanubrutinib QD to patients with WM or CLL/SLL is to improve treatment adherence. In my experience, patients across cancer types who are prescribed treatments more than once per day are likely to miss doses, which can lead to resistant or refractory disease. I noticed that patients receiving zanubrutinib BID have started missing doses after only weeks of treatment initiation. One contributor to treatment nonadherence is that patients with WM or CLL/SLL typically do not have obvious symptoms upon diagnosis, so it can be challenging for patients to remember to take medication regularly. As some patients may take zanubrutinib for years to decades, a QD regimen may result in more sustainable compliance long term. I believe that a QD regimen is more beneficial for my patients, and this choice is supported by clinical trial data showing that the efficacy and safety of the approved zanubrutinib QD and BID regimens are similar.

To introduce patients to the idea of switching from zanubrutinib BID to QD, I typically ask, "Why take zanubrutinib twice daily when a once-daily regimen is available?." I explain that there is no increase in monitoring with QD versus BID dosing, so patients receive the same level of clinical management regardless of dosage. Despite the potential benefits of QD zanubrutinib, some patients have expressed concerns about switching from BID. For example, patients taking zanubrutinib BID were under the impression that QD dosing would be shorter-acting and therefore not as effective. In addition to efficacy concerns, patients have asked whether side effects will increase with zanubrutinib QD versus their current BID regimen. Because of clinical trial data reporting similarities between the 2 dosage regimens, I have reassured my patients that they should expect to experience similar efficacy and no increased risk of side effects when switching to QD dosing. So far, none of my patients have reported an increased side effect burden with the switch to QD but instead report favorable tolerability. None of my patients have required long-term zanubrutinib dose reductions; 1 patient had reduced zanubrutinib dose due to a rash but returned to normal dosing after 2 weeks. In addition, none of my patients who switched to QD dosing have returned to BID dosing; 2 patients decided to switch from QD to BID but then returned to QD due to the convenience of administration.

After switching to QD dosing, patients have generally agreed that QD dosing is easier to adhere to than BID dosing. For patients previously on QD ibrutinib, switching to QD zanubrutinib is beneficial as it keeps their dosing routine consistent. Younger patients who work full-time report that it is preferable amid busy schedules to only take medication once per day. Patients who live alone and take other medications report that it is easier to administer zanubrutinib once per day when combined with other treatments. Once-daily dosing can also be beneficial for older patients because caretakers only have to administer medication once per day. In addition, I've observed that patients in my practice who take QD zanubrutinib miss fewer doses than those taking BID zanubrutinib (based on pill counts recorded at appointments). As increased numbers of physicians prescribe QD rather than BID zanubrutinib, the workload for physicians and pharmacists will likely decrease and patient care will become more cost-effective as information for only 1 dosage regimen will need to be distributed. While the QD zanubrutinib dosage requires patients to take 4 capsules of 80 mg each, patients have not expressed concern regarding pill burden but instead prefer taking QD zanubrutinib due to the favorable safety profile and ease of administration.

Overall, I recommend that healthcare providers consider primarily prescribing QD zanubrutinib and switching patients who are currently taking BID zanubrutinib to the QD regimen. The benefits of QD versus BID zanubrutinib in my experience include improved compliance with no known additional safety or efficacy concerns and a more streamlined process for pharmacies, physicians, and patients.

Pharmacist Perspective

Courtney Horn, PharmD, medically integrated dispensary manager at Maryland Oncology Hematology

I provide zanubrutinib to 20 to 25 patients monthly through the medically integrated dispensary at Maryland Oncology Hematology, which oversees in-person delivery of oral

chemotherapy treatments. Approximately 40% of patients under my care receive zanubrutinib QD.

Part of my role is working directly with physicians to ensure that patients receive the optimal regimen with the correct medications at the correct doses. For example, if a physician does not specify the dosing regimen or prescribes zanubrutinib BID then I will often suggest QD dosing, especially if the patient has complicated polypharmacy. Over the past 6 months, the trend toward zanubrutinib QD versus BID prescriptions has increased due to physician preference and because once a physician begins prescribing QD they rarely switch back to prescribing BID. The default zanubrutinib dosing schedule in our electronic system is BID unless the physician specifically elects QD dosing, so communication between our team and physicians can help to ensure that the optimal dosing regimen is prescribed.

During consultations with patients switching from BID to QD zanubrutinib, I discuss the change and confirm that the patient understands the dosage of 4 capsules at once. Taking 320 mg zanubrutinib QD as 4 capsules at once can feel burdensome and patients/caregivers sometimes express concern; however, I offer reassurance that QD zanubrutinib is not associated with additional adverse effects. Patients often have complicated polypharmacy and ask how to take zanubrutinib with their other medications. For these patients, I clarify their medication schedule and create a chart as needed to explain their medication timing. Because it can be difficult for patients to take medications around meals or other medications, taking zanubrutinib QD can eliminate some of the scheduling complications.

Patients under my care have responded well to QD zanubrutinib, which increases my confidence in suggesting QD dosing to physicians and patients. To monitor how patients respond to QD dosing, I ask open-ended questions to identify changes in side effects after switching regimens. Patients have not reported new or worsening side effects with QD versus BID dosing and I have not observed negative effects on efficacy or safety. Generally, patients report positive experiences with switching to the QD regimen because it simplifies their polypharmacy.

Currently, our medically integrated dispensary staff are preparing formal documentation to monitor treatment compliance. Our team often calls patients to remind them to refill prescriptions and will ask how many doses they have missed and how many tablets they have left. We also suggest that patients bring the pill bottles to their provider's office to monitor adherence. However, it is important to note that counting pills is not always the most reliable way to measure adherence because physicians may ask patients to hold medication due to an upcoming procedure, which can appear as low compliance. Due to this possibility, we ask patients if they have been instructed to hold therapy for any reason since their last refill. In my experience, switching patients from BID to QD zanubrutinib has largely improved treatment adherence. In addition, the improved adherence observed with QD versus BID zanubrutinib is consistent with my observations with QD dosing for other types of cancers.

There are no differences in patient monitoring or insurance coverage when switching zanubrutinib dosages. For both dosing regimens, pharmacists should communicate with the prescribing physicians to ensure that the patient's laboratory testing is up-to-date while administering medication and before any medication switch. In addition, there is no impact on cost when switching from zanubrutinib BID to QD and prior authorizations are not required.

Overall, I believe that QD zanubrutinib offers benefits to both patients and pharmacists. Once-daily zanubrutinib increases treatment adherence in patients who often have complicated polypharmacy and simplifies the administration process compared with BID dosing.

Limitations

This article reports individual clinical perspectives and from 2 professional medical opinions at a single center. In addition, quantitative data analyses were not available.

Conclusions

An important consideration of clinical care is optimizing treatment adherence so that patients can experience the greatest therapeutic benefits. Zanubrutinib is approved for BID and QD administration with similar efficacy and safety between the dosage regimens.[3,7,11,14] Medical professionals at Maryland Oncology Hematology have shared that QD zanubrutinib is preferable to BID administration for patients with WM or CLL/SLL as well as for caregivers and medical teams. Overall, perspectives from this single center indicate that QD zanubrutinib improves treatment adherence compared with BID dosing and streamlines the efforts of physicians and pharmacists to effectively treat patients with B-cell malignancies.

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