Collectively Answering The Venetoclax BTK Inhibitor Sequencing Question in CLL

Kerry A. Rogers, MD
Division of Hematology, The Ohio State University, Columbus, OH

Running title: Answering The Venetoclax Sequencing Question in CLL

Disclosures: KAR receives research funding from Genentech, AbbVie, and Janssen, has consulted for Acerta Pharma, AstraZeneca, and Pharmacyclics, and received travel funding from AstraZeneca.

Funding: KAR is a Scholar in Clinical Research of the Leukemia & Lymphoma Society (CDP 2331-20).

Correspondence:
Kerry A. Rogers, MD
410 W. 12th Ave Rm 458
Columbus, OH 43210
Phone: 614-366-9338
Fax: 614-293-7526
E-mail: kerry.rogers@osumc.edu
Summary

Whether BTK inhibitors are effective when used after venetoclax in CLL patients is an important unanswered question. In a large retrospective cohort study examining outcomes for next line treatment after venetoclax, BTK inhibitors were found to result in durable responses in patients who were not previously BTK inhibitor resistant.

Main Text

In this issue of Clinical Cancer Research, Mato and colleagues report the results of a large, multi-center, international, retrospective cohort study determining the efficacy of the next treatment after venetoclax in chronic lymphocytic leukemia (CLL) patients.(1) They demonstrate that BTK inhibitors result in high response rates and durable disease control in patients who were not resistant to them prior to taking venetoclax. This addresses a key question in the field of CLL medicine as prior to their report, data on sequencing of BTK inhibitors after venetoclax were sorely lacking.

Targeted agents have completely changed the way CLL is treated by offering safer more effective treatment compared to the prior standard of chemoimmunotherapy. The two most frequently prescribed classes of drug in routine clinical practice are BTK inhibitors, ibrutinib and acalabrutinib, and the BCL2 antagonist, venetoclax. Both BTK inhibitors and venetoclax are approved in previously untreated and relapsed/refractory CLL and both have high response rates even in cytogenetically high-risk groups. While BTK inhibitor and venetoclax regimens have not been directly compared, they have a similar 24-month progression-free survival (PFS) in large randomized phase 3 trials and one is not clearly more effective than the other.(2,3)

There are key differences in the toxicity profile between these agents with BTK inhibitors increasing risk for bleeding and atrial arrhythmias and venetoclax being a difficult option for those with renal impairment due to the risk for tumor lysis syndrome. Therefore an individual patient’s comorbid medical conditions may be a deciding factor in therapy selection. Similarly, patients or physicians may have a strong preference for a particular administration schedule. Venetoclax is now generally given for a fixed-duration in combination with an anti-CD20 monoclonal antibody and requires frequent visits for tumor lysis syndrome monitoring and antibody infusions while BTK inhibitors avoid these visits, but are given indefinitely. While this is an excellent opportunity for patient and physician shared decision making, information on efficacy of BTK inhibitors after choosing to use venetoclax has been missing from the conversation.
There are prospective data on use of single-agent venetoclax after ibrutinib from a dedicated phase 2 study. That trial included 91 patients who had taken the BTK inhibitor ibrutinib as the most recent treatment prior to venetoclax with 55% of these patients having discontinued ibrutinib due to progressive disease. The overall response rate (ORR) to venetoclax was 65% with a median PFS of 24.7 months. While that may not seem like outstanding efficacy compared to other studies with venetoclax, given that patients in that study had a median number of 4 prior treatments and 47% had del(17)(p13.1), these results are good. This study established venetoclax as the most effective known CLL treatment after ibrutinib, excluding cellular therapies. However, no such data existed for BTK inhibitors after venetoclax.

In an impressive collaborative effort, Mato et al. combined retrospective data from 31 academic and community sites to determine the outcomes of treatments subsequent to venetoclax. They included a total of 326 CLL patients who were treated with venetoclax. The majority (73%) received continuous venetoclax monotherapy which was the standard for the timeframe in which they were treated. This was also a relatively high-risk cohort with a median of 3 treatments prior to venetoclax and 53% having TP53 disruption. The median time to venetoclax discontinuation was a short 9 months. This is unsurprising as this study only included patients who discontinued venetoclax, selecting for those who did not derive prolonged benefit from the drug. In their cohort 58% (n=188) went on to receive treatment subsequent to venetoclax. BTK inhibitors were the most common treatment (39%, n=74) and this experience is of the most interest.

The majority of these patients received ibrutinib or acalabrutinib with a handful (n=6) of previously BTK inhibitor exposed patients receiving an investigational non-covalent BTK inhibitor. The ORR to a BTK inhibitor after venetoclax was higher in patients who were BTK inhibitor naïve compared to those with prior BTK inhibitor exposure (84% and 54% respectively, p<0.001). However, this is not the whole story, as when patients who were exposed to a BTK inhibitor prior to venetoclax were further divided into those who discontinued due to an adverse event (BTK inhibitor intolerant) and those who discontinued due to progressive disease (BTK inhibitor resistant), patients who were BTK inhibitor intolerant had a higher response rate (70% vs 50%) and longer progression-free survival (not reached vs 4 months) compared to those who were resistant (Figure 1). These results have to be interpreted with some caution as the sample size is small and the median follow-up is only 7.7 months (range 1-48). Nevertheless, this is sufficient to demonstrate that patients who were not resistant to BTK inhibitors prior to venetoclax have good outcomes with BTK inhibitor treatment after venetoclax and that venetoclax is not ruining the success of BTK inhibitors if used first.
The short progression-free survival with BTK inhibitors after venetoclax in previously BTK inhibitor resistant patients is not unanticipated. This suggests that treatment with venetoclax does not eliminate BTK inhibitor resistance to the degree that long-term disease control is achieved with BTK inhibitor monotherapy. Further supporting this are findings from a series of previously ibrutinib-treated patients where mutations in BTK or PLCG2 associated with resistance to ibrutinib were persistent at CLL relapse on venetoclax. Different strategies such as agents with a novel mechanism, non-covalent BTK inhibitors, or cellular therapies should be pursued in this patient population.

This answer to the question regarding sequencing of venetoclax and BTK inhibitors is much needed data for the CLL community suggesting that either can be used first. This puts CLL patients in the fortunate position of continuing to let patient factors and preferences drive decision making as to which therapy to select first and allows for more individualized care for each specific CLL patient.

While this study has the same limitations as all retrospective research, prospective data answering this question are unlikely to be available anytime soon. A randomized trial comparing initial BTK inhibitor treatment followed by venetoclax at progression to a venetoclax fixed-duration regimen with BTK inhibitor at progression is impractical. The length of time required to perform such a study is prohibitive given the long PFS with these agents and our efforts should be directed elsewhere. In the absence of such a study the collective experience of Mato et al. is adequate to demonstrate that BTK inhibitors can be successfully used after venetoclax. These authors should be commended for their ability to collaborate to answer this important question so that we can focus our main efforts on tackling the next big questions in CLL such as how BTK inhibitor and venetoclax combination regimens compare to sequential monotherapy.
References


Figure 1: Treatment Outcomes with BTK Inhibitors After Venetoclax by Prior BTK Inhibitor Exposure

Outcomes of BTK inhibitor treatment after venetoclax in CLL patients are shown by prior BTK inhibitor status. While the sample size is small, these data demonstrate that patients who were not resistant to BTK inhibitors prior to venetoclax are expected to benefit from BTK inhibitor treatment with durable disease control. The short PFS in patients who were previously BTK inhibitor resistant supports that venetoclax does not restore disease sensitivity to BTK inhibitors and other therapeutic strategies should be use for these patients. ORR = overall response rate, PFS = progression free survival.
BTK inhibitor status prior to venetoclax

- No prior BTK inhibitor ($n=44$)
- BTK inhibitor intolerant ($n=10$)
- BTK inhibitor resistant ($n=20$)

Post-venetoclax BTK inhibitor outcomes

- ORR 84%
  - PFS 32 months
- ORR 70%
  - PFS not reached
- ORR 50%
  - PFS 4 months
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Clin Cancer Res Published OnlineFirst May 4, 2020.

Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-20-1035

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