BCR inhibitor failure in CLL: an unmet need

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In this issue of Blood, Mato et al report a retrospective cohort analysis of patients with chronic lymphocytic leukemia (CLL) who discontinued a kinase inhibitor (KI).¹ Drug toxicity was the main reason for treatment discontinuation. Approximately 50% of patients who discontinued a KI responded to a subsequent salvage therapy.

Targeted therapies have revolutionized the treatment of CLL.² Several of these novel targeted agents are now approved for patients with CLL, including B-cell receptor inhibitors such as ibrutinib and idelalisib and the B-cell lymphoma 2 (BCL-2) inhibitor, venetoclax. Ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor, was originally approved for patients with relapsed CLL and/or del(17p). Maddocks et al reported outcomes of 308 patients treated on clinical trials with ibrutinib at Ohio State University, of which 76 (25%) discontinued ibrutinib.³ All patients had received ibrutinib as part of a clinical trial. The reasons for discontinuation included adverse events (42%), CLL progression (21%), and Richter transformation (RT) (18%). The median overall survival (OS) after ibrutinib discontinuation was a dismal 3.1 months (RT cohort: 2.6 months). Maddocks et al reported outcomes of 308 patients treated on clinical trials with ibrutinib at Ohio State University, of which 76 (25%) discontinued ibrutinib.³ The main reasons for discontinuation included infection and adverse events (59%), CLL progression (17%), and RT (24%). The median OS after RT was 3.5 months and after CLL progression was 17.6 months. Notably, most of the patients in both analyses were highly pretreated before receiving ibrutinib and had high-risk disease features.

Here, Mato et al report aggregate data on KI discontinuation from 10 institutions in the United States and from the Connect CLL Registry. The authors evaluated outcomes of 178 patients with CLL who had discontinued their first KI (ibrutinib, n = 143; idelalisib, n = 35). The median time on KI prior to treatment discontinuation was 5 months for ibrutinib and 5.5 months for idelalisib. Almost half of the patients who discontinued treatment did so due to toxicities. Other reasons included progressive CLL (29%) and RT (8%). The median OS after RT was ~12 months, ~29 months for those with progressive CLL, and not reached (70% at 30 months) for the KI intolerance group.

A total of 64% of the patients who discontinued KI received further salvage therapy. An alternate KI was the most common choice (39%), followed by a BCL-2 inhibitor (14%). The overall response rate for the alternate KI (ibrutinib → idelalisib and vice versa) was 50%. The median progression-free survival (PFS) from the initiation of alternate KI was 11.9 months (7 months in patients with CLL progression to first KI vs not reached in those with intolerance to first KI), and the sequencing of the KI (ibrutinib→idelalisib or vice versa) had no impact.

This study is significant for several reasons. (1) This is the largest study on KI discontinuation and clinical outcomes after discontinuation, an important issue given the increasing use of KIs in CLL. (2) It describes the outcomes of patients switching from one KI to another, whereas only anecdotal data existed previously. This study provides a retrospective look at these patients. Outcomes after discontinuation of the first KI were generally poor; in patients who progressed on ibrutinib and then received idelalisib, the median PFS was only 7 months. As with the prior 2 publications on discontinuation, most of these patients had received multiple prior regimens and had high-risk disease. This suboptimal clinical outcome underscores the need to develop better therapies for these patients. (3) The authors describe patients from several institutions, and it appears that most patients were treated outside of a clinical trial (this study did include some patients on clinical trials but the actual numbers are not provided), which may represent more of a “real world” experience.

There are also several limitations to the data. This is a retrospective analysis.

Comment on Mato et al, page 2199
with the inherent limitations of such an analysis, including lack of uniform follow-up, response assessments, and toxicity management. In addition, the unusually short duration of first KI therapy and the fact that the toxicities leading to discontinuation were often serious (atrial fibrillation) and unusually frequent (17% pneumonitis among patients with discontinued idelalisib), testify to the selective nature of the cohort. The authors describe real world experience with regard to the outcomes, but it is notable that all centers involved are university hospitals with expertise in the management of CLL and KI toxicities.

Additionally, they report that “Moreover, outcomes did not appear to differ whether ibrutinib or idelalisib was selected as the first or second KI, suggesting that either sequence is appropriate.” However, we would urge caution in this interpretation, as no data are provided on response rates and PFS for the first KI. Data were only collected on the patients who discontinued the first KI; hence, the true response rate to the first KI and median PFS was not captured.

Resistance to KI remains a major clinical concern. Many patients who fail ibrutinib have an acquired mutation of BTK C481S, or rarely, PLCγ2 mutation. resistance mechanisms to idelalisib and venetoclax remain unclear and are the subject of ongoing investigations. The current study provides valuable data on the outcomes after KI discontinuation and emphasizes the need to develop more effective therapies for KI failure.

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Comment on Richter et al, page 2206

Gene therapy simplified

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In this issue of Blood, Richter et al report their work on an in vivo gene transduction system using the adenovirus-based vector and hyperactive SB transposase (SB100×) system. Their results show that this system is effective and safe and performs without needing ex vivo expansion and transduction of hematopoietic stem cells (HSCs). This system may overcome some of the difficulties associated with cell collection and manufacturing and provide technical advances for the field of gene therapy.

Gene therapies using HSCs for the treatment of immunodeficiencies and inherited diseases have demonstrated substantial clinical benefits. Currently, most clinical gene therapies start with HSC mobilization using granulocyte colony-stimulating factor (G-CSF) alone or along with AMD3100 (Plerixafor) followed by leukapheresis collection and the enrichment of HSCs by immunoselection. The purified cells are stimulated and transduced in a cell manufacturing center located in the same institution as the collection facility or shipped to another facility for manufacture. For the safety of patients and quality of the collected and manufactured cells, all these procedures must be conducted in accredited facilities following strict standards (ie, American Association of Blood Banks Standards for Cellular Therapy Services and standards of Foundation for Accreditation Cellular Therapy in the United States). In addition, the collection and production of HSCs for gene therapies must also follow the guidance of regulatory agencies like the European Union or US Food and Drug Administration. To meet these requirements, considerable investment is needed, particularly in establishing and maintaining the cell processing center. In addition, manufacturing the gene corrected autologous HSCs can be costly. In this paper, the autologous HSCs were mobilized into peripheral blood, and the HSCs were directly transduced with a novel transduction system in vivo, resulting in functional transduced HSCs in animal models. Therefore, HSC collection and cell manufacturing were not required. These results imply that the gene therapy may be conducted in 1 facility, follow a simplified regulation pathway, and should be less costly.

This new system circumvents the technical/medical limitations of leukapheresis collection. Leukapheresis is very time consuming, and unfortunately, collection yields and efficiencies are highly variable. The efficiency of the CD34+ HSC collection may be influenced by many factors, including the volume of processed whole blood, flow rates of the blood separators, and the decision to perform single or multiple collections. Venous access is also a limiting factor of leukapheresis, especially for pediatric patients, for whom a central line may be necessary for the collection.

This system also avoids the potential concerns associated with the ex vivo expansion and transduction of CD34+ HSCs. At present, HSCs are typically stimulated and expanded using a cocktail of cytokines, such as stem cell factor, thrombopoietin, Flm-like tyrosine kinase 3 ligand, and interleukin 3 and then transduced with viral vectors. All of these steps may affect the phenotype, long-term viability, and homing and repopulation.
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