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Treatment of relapsed/refractory chronic lymphocytic leukemia after BTK inhibitor and/or BCL-2 inhibitor failure

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Introduction

The treatment landscape for first-line and relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) has tremendously advanced with the introduction of Bruton tyrosine kinase inhibitors (BTKi) and B-cell lymphoma 2 inhibitors (BCL-2i). However, in this new era of targeted therapy for CLL, there is, unfortunately, no evidence yet to guide the optimal sequencing of these drugs. It remains unknown whether treating first-line with a BTKi and relapse with BCL-2i or BCL-2i at first-line followed by BTKi at relapse results in any difference in overall survival (OS). Ibrutinib (BTKi) was first introduced in 2014, and venetoclax (BCL-2i) in 2016, and currently, there are limited prospective data and treatment options for patients who have relapsed after one or both targeted therapies. This article will provide an overview of the approach to treatment for patients with CLL/SLL when BTKi and/or BCL-2i therapy has failed.

Before launching into the treatment of R/R CLL, it is worth noting that guidelines for risk assessment of CLL recommend determining the immunoglobulin heavy chain gene (IGHV) mutational status once, usually before the first treatment, and fluorescence *in situ* hybridization FISH for del(17p) and next-generation sequencing (NGS) before each treatment.[1] Other than *TP53*, NGS-detected mutations are not routinely considered when choosing a therapy, but they may help predict the duration of remission and may become standard of care in the future.

Treatment of R/R CLL after chemoimmunotherapy

Many of our Canadian patients with relapsed CLL have had prior treatment with

chemoimmunotherapy. The RESONATE trial was the first published trial looking at targeted therapy in relapsed disease with the entire population having received first-line chemoimmunotherapy.[2, 3] The median progression-free survival (PFS) for ibrutinib at six years of follow-up was 44.1 months. The alternate arm in this randomized study received ofatumumab, which had inferior results with a PFS of 8.1 months. Therefore, this treatment option was not brought forward for future studies in R/R CLL.

The HELIOS study randomized patients with R/R CLL to ibrutinib alone vs ibrutinib with bendamustine and rituximab.[4] The trial showed similar PFS results in both arms, suggesting there was no advantage of adding chemoimmunotherapy to the BTKi.

Acalabrutinib was the first of the second-generation BTKi's to be studied in R/R CLL. In the ASCEND trial, patients received chemoimmunotherapy as first-line treatment.[5] The median PFS was not reached at 46 months. The comparator arm was idelalisib and rituximab or bendamustine and rituximab (investigator's choice), which resulted in an inferior median PFS of 16.2 months. This study confirmed the superiority in efficacy and safety of acalabrutinib over the other treatments.

The ELEVATE-RR study was a head-to-head comparison of acalabrutinib and ibrutinib in patients who had received a median of two prior treatments.[6] The median PFS was 38.4 months for both BTKi's, at a median follow-up of 40.9 months. Adverse events, especially atrial fibrillation, hypertension, and diarrhea, were less common with the second-generation BTKi acalabrutinib.

Zanubrutinib was the next second-generation BTKi that was developed. The ALPINE study compared zanubrutinib to ibrutinib in patients with a median of one prior treatment.[7] The PFS in the zanubrutinib arm was superior at 78.4% vs. 65.9% at a median follow-up at 29.6 months and 65.8% vs. 54.3 % at a median follow-up at 36.3 months, for zanubrutinib vs. ibrutinib, respectively.[8] Again, the toxicity profile, especially atrial fibrillation, was preferable with zanubrutinib, but the rates of hypertension were similar. Since these two head-to-head comparative studies were published, second-generation BTKi's are favoured over first-generation BTKi mainly because of the superior adverse event profile.

There is no evidence that adding a CD20 monoclonal antibody to ibrutinib improves outcomes, either objective response rate (ORR) or PFS. There is, however, some evidence that adding obinutuzumab to acalabrutinib improves PFS, but this combination is not approved in most of Canada.

The next class of targeted agents studied in R/R CLL was the phosphatidylinositol 4,5-biphosphate 3-kinase catalytic subunit delta inhibitors (PI3Ki). Idelalisib was first studied in combination with rituximab compared to rituximab with placebo. The median PFS was 20.3 months in the PI3Ki arm vs. 5.5 months in the placebo arm, and the study also showed a 6-month OS advantage for the PI3Ki arm. Although the initial results were very promising, the toxicity was high. Idelalisib is available in Canada for combination treatment with rituximab but is not commonly considered an option given the adverse events and better alternatives.

Venetoclax, the first of the BCL-2i, was first studied in 2016 as a single agent given continuously, similar to BTKi. Various studies revealed an ORR of 70-79% for this treatment. With the high rates of undetectable minimal residual disease (uMRD), it was advised that venetoclax could be provided for a fixed duration, with no need for continuous treatment. The addition of rituximab was shown to reduce emerging resistant clones to venetoclax[9] and this resulted in deeper responses with higher complete remission (CR) rates.[10] The MURANO Phase 3 study compared venetoclax with rituximab (VEN-R)with a fixed duration protocol of two years to bendamustine and rituximab (BR).[11] At the 5-year follow-up, the median PFS was 53.6 months for VEN-R and 17 months for BR, confirming that this targeted combination therapy, was superior to chemoimmunotherapy for R/R CLL.[12]

Treatment of R/R CLL previously treated with BTKi

Patients who relapse on a BTKi will most often be switched to venetoclax and rituximab, or less often to venetoclax monotherapy, although published clinical trial data are limited due to small sample sizes. In four early phase studies with venetoclax in R/R CLL, approximately half of the patients receiving the standard 400 mg dose had received a BTKi previously.[13] Adverse factors for attaining a complete remission and durable responses were refractoriness to BTKi, >3 prior treatments, and bulky adenopathy. *TP53*, del(17p), and unmutated IGHV status did not affect the response, but were associated with a shorter PFS.

Switching to another BTKi is not recommended for R/R CLL since approximately 85% of patients will develop resistance by acquiring mutations, most commonly at the C481 position in the BTK kinase domain and less commonly in *PLCG2*.[14] Another option is pirtobrutinib[15], which is a highly selective noncovalent (reversible) BTK inhibitor. The ORR was similar for patients previously treated with ibrutinib, with or without the BTK C481 mutation.

If a patient has discontinued a BTKi due to toxicity, and then relapsed while off treatment, a second BTKi could be considered if the original toxicity was not generic for all BTKi, such as atrial fibrillation or bleeding.

Treatment of R/R CLL previously treated with BCL-2i

Patients previously treated with venetoclax are typically started on a BTKi for R/R disease. Four initial small case series illustrated the effectiveness of BTKi's for R/R CLL after venetoclax treatment, in which the majority of patients were on continuous venetoclax. Patients were heavily pretreated with four median prior treatments, and 76% had mutated *TP53*. Most patients obtained a partial response with the BTKi, and the median PFS was 34 months. Longer PFS was associated with a prior remission duration of >24 months and attainment of a CR.[16-19] In a larger retrospective study, 326 patients who were treated previously with venetoclax were treated with another targeted therapy, including BTKI and PI3Ki.[20] Most of these patients had received venetoclax in the R/R setting and had a median of three therapies prior to venetoclax. The ORR in BTKi-naïve patients was 84% compared to 54% in BTKi-exposed patients. The median PFS was 32 months in patients who had not received BTKi before, while it was not reached in those previously treated with BTKi but who were intolerant to it, and 4 months in those previously BTKi-treated and resistant. In a subset of patients who were BTKi-naïve and had discontinued venetoclax for progressive disease, the estimated median PFS with post-venetoclax BTKi was not reached. With post-venetoclax PI3Ki, the ORR was 46.9% with a short median PFS of 5 months.

Studies of venetoclax resistance have shown that the mechanisms do not overlap with those of BTKi, which supports the effectiveness of BTKi with R/R CLL after venetoclax. A recurrent mutation Gly101Val in BCL-2 has been identified in patients progressing on venetoclax. Resistance tends to occur late (after 19-42 months), and may, therefore, not be relevant for retreatment with venetoclax for patients with relapse after being on fixed-duration venetoclax.[21] In a small study, patients previously treated with venetoclax who acquired the Gly101Val mutation had an effective response to a BTKi at relapse, with the PFS not reached at a median follow-up of 33 months.[22]

Retreatment with venetoclax is also possible if the CLL relapse occurs after venetoclax discontinuation. A five-year follow-up of continuous or limited-duration therapy with venetoclax and rituximab included three patients previously treated with venetoclax. Of these patients, 100% had partial remissions, and the duration of responses ranged from 18.7-40.3 months.[23] The MURANO study included 18 patients who were re-treated with venetoclax, and the ORR was 72.2% with a median treatment duration of 11.4 months (range 0.7-27.6 months).[24] A retrospective study looked at 46 patients receiving a second treatment with venetoclax, which was mostly given as a monotherapy (45.7%), but was also combined with rituximab (28.2%), obinutuzumab (10.9%), and ibrutinib (4.4%) for R/R disease. In most cases, the initial venetoclax treatment was for R/R disease and the median number of prior treatments was two. There was a median of 16 months between completing the first venetoclax treatment and starting the second (range 3-52 months). The ORR was 79.5% with a CR rate of 33.3% and a median PFS of 25 months.[25] It is currently unclear whether the response to retreatment with venetoclax is affected by the duration or depth of response to the initial treatment. Reduced responses to venetoclax have been associated with ≥3 previous lines of therapy, bulky lymphadenopathy, and high-risk molecular results of del(17p), *TP53* mutation, *NOTCH1* mutations, and unmutated IGHV mutational status.[13]

Treatment for R/R CLL previously treated with both BTKi and BCL-2i

A recent review of patients who received prior BTKi and a proportion also being exposed to BCL-2i were treated with pirtobrutinib. The overall response rate for all patients was approximately 82%, similar whether or not they received a prior BCL-2i. The BCL-2i-naïve patients had a longer PFS of 23 months than those previously exposed to BCL-2i of 16 months at a median follow-up of

27.5 months. This could be explained by the more heavily pretreated status of the BCL-2i-exposed group (median prior treatments was 5 for exposed and 3 for naïve).[15,26] Pirtobrutinib was well tolerated with 3.9% of patients requiring dose reduction and 2.5% discontinuing. Some Canadian centers were involved with pirtobrutinib clinical trials; however, this treatment has not yet been approved by Health Canada for standard use.

There is limited experience in Canada with treating patients with combined ibrutinib and venetoclax as first-line therapy and likely no experience with patients who have relapsed after this protocol. This has been approved by Health Canada and is presently available with private insurance or through a clinical trial available in some centres. There is now a 5-year follow-up of the Phase 2 CAPTIVATE study for patients who received a fixed duration of 12 cycles of ibrutinib and venetoclax, which was started after three cycles of ibrutinib; 25% had progressive disease and were re-treated with ibrutinib. The overall response rate was 86%.[27]

Patients with double-refractory CLL are a growing population, and effective treatment options for this group are an unmet need. Although the prognosis of patients with double-refractory CLL who were previously treated with immunochemotherapy is poor, it remains unknown what the outcome is for patients who have only been treated with these two targeted therapies. In one small retrospective analysis of 17 patients with double-refractory progressive disease, the OS was 3.6 months.[28] These patients had high-risk features and were heavily pretreated before receiving the BTKi and BCL-2i. Another real-world study looked at a subgroup in their database who had received both BTKi and BCL-2i (most not continuous), with a small number having received prior immunochemotherapy up until 2021.[29] The majority of the 581 patients had received one of the targeted therapies in the first-line setting and in 83% of patients the BTKi was the first treatment. The most common treatment after both targeted agents contained a BCL2i with or without other treatments. The median time to treatment discontinuation or death was 5.6 months. This outlines the progressive refractoriness and poor prognosis of CLL with increasing lines of therapy and the need for effective treatments post both targeted agents.

Allogeneic stem cell transplant would be a consideration only for young and fit patients who are double-refractory. Long-lasting remissions can occur in 30-50% of transplanted CLL patients.[30] Chimeric antigen receptor (CAR) T-cell therapy[31] will likely be an upcoming option in Canadian clinical trials. Bispecific antibodies[32], bispecific T cell engagers[33], and BTK degraders[34], have also shown early favorable results and, these types of treatments will hopefully be available in clinical trials in Canada in the near future.

For patients experiencing a disease relapse who require bridging to a more definitive treatment, such as an allogeneic stem cell transplant or waiting for an imminent clinical trial, chemoimmunotherapy with bendamustine and rituximab, fludarabine, chlorambucil, or alemtuzumab could be considered as short-term treatment.

Conclusion

With the increased use of BTKi and BCL-2i in the treatment of CLL, the question arises as to what sequence of therapies is preferred, and what therapies are best to follow-up with at the R/R stage. While research remains limited, we have provided the best evidence options for treatment after first-line chemoimmunotherapy, BTKi, BCL-2i, or combined BTKi and BCL-2i. In particular for the patient population progressing to R/R disease after combined use of BTKi and BCL-2i, more research into second and later-line treatment options is warranted.

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