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Recognizing Unmet Need in the Era of Targeted Therapy for CLL/SLL: "What's Past is Prologue" (Shakespeare)

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Abstract

The management of CLL has undergone unprecedented changes over the last decade. Modern targeted therapies are incorporated into clinical practice. Unfortunately, patients have begun to develop resistance or intolerance to multiple classes. Symptomatic patients previously treated with a BTK inhibitor and venetoclax represent a new and rapidly growing unmet need in CLL. Here we define unmet needs in a modern treatment context. We also critically review the literature for PI3K inhibitors and chemoimmunotherapy and lack of data to support their utility following BTK inhibitors and venetoclax. Finally, we suggest opportunities to ensure the continued innovation for patients with CLL.

Keywords

CLL/SLL; BTK; ibrutinib; venetoclax; PI3K

Introduction: A Transformation in the treatment of CLL/SLL

The management paradigm for chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) has undergone unprecedented changes over the last decade resulting in radically improved outcomes for patients (1,2). The previous cornerstone of treatment, cytotoxic chemotherapy, resulted in remission for many patients but also short and long-term treatment-related morbidities (3). For patients with poor risk disease biology these remissions were short lived (4,5). By comparison, patients can now expect to be treated sequentially with targeted therapies that are both better tolerated, orally administered, and markedly more efficacious (6–10). Despite the dramatically improved outcomes modern targeted therapies have yielded, these agents have now been incorporated into routine clinical practice for a long enough time that patients have begun to develop resistance or intolerance to multiple classes (11–17). These patients represent a new and rapidly growing frontier of unmet medical need in CLL/SLL. Ensuring continued progress for patients with CLL/SLL will require increased focus on this emerging group of patients treated with multiple classes of targeted therapy. Here, we focus on how best to define unmet needs in a modern treatment context and suggest opportunities for key stakeholders/caregivers to ensure the continued innovation our patients deserve.

An Unprecedented Decade of Drug Development in CLL/SLL

Three new classes of targeted agents have been approved for CLL/SLL globally in the last 10 years. These include the BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib), a BCL2 inhibitor (venetoclax), and the phosphoinositide-3-kinase (PI3Ki) inhibitors (idelalisib and duvelisib) (6–8,10). Of these three classes, BTK inhibitors and venetoclax-based therapy,

sometimes combined with anti-CD20 antibodies, are supplanting chemoimmunotherapy (CIT), while PI3K inhibitors are typically reserved for later lines of treatment (1,18–20). While ibrutinib and venetoclax were initially approved in CLL/SLL based on the results from single arm studies in high-risk patients, use of these agents since then has been primarily guided by randomized Phase 3 clinical trials (7,10,11,21–24). Although these studies have provided insights into the efficacy and safety of these drugs, critical evaluation of these studies also reveals important areas of ongoing uncertainty.

Ibrutinib-based therapy has demonstrated superior outcomes (either PFS, OS or both) compared to those seen with ofatumumab, chlorambucil, fludarabine/cyclophosphamide/rituximab (FCR), bendamustine/rituximab (BR) and chlorambucil/obinutuzumab (CO) in five Phase 3 studies (22,25–28). The more selective BTK inhibitor acalabrutinib has demonstrated superior outcomes over those seen with CO and investigators choice of idelalisib/rituximab or BR in two randomized Phase 3 studies (23,29). Venetoclax-based therapy has demonstrated superior outcomes over those seen with CO and BR in 2 randomized studies (21,30). Finally, idelalisib/rituximab and duvelisib have demonstrated improvements over those seen with rituximab and ofatumumab, respectively (31,32). With the exception of the ASCEND study (acalabrutinib vs. idelalisib/rituximab) (29), common among these 11 randomized trials is a comparison of modern targeted therapy to chemotherapy, an anti-CD20 antibody, or both, as well as inclusion of patients naïve to targeted therapies.

While CIT (FCR, BR, or CO) are still acceptable options in certain patients, most patients in North America and Western Europe are initially managed with either a BTK inhibitor, utilizing a treat-to-progression strategy, or the combination of venetoclax-obinutuzumab for a fixed duration of 12 months (Figure 1, Table 1) (18,33). In the next line of therapy, patients typically are either treated with a BTK inhibitor or venetoclax (either as continuous monotherapy or as 24-month fixed duration with rituximab), typically switching to the class of agent not used in the front-line setting, depending on the efficacy and tolerability of that agent (18,33). In contemporary practice, BTK inhibitor and venetoclax-based therapy, administered in either sequence, collectively define standard first- and second-line treatment (34). Although the clinical activity of BTK inhibitors and venetoclax was established in pivotal studies that included patients naïve to the other drug class, smaller prospective Phase 2 studies and real-world data demonstrate previously unrecognized incomplete cross-resistance and intolerance between BTK inhibitors and venetoclax, allowing them to be administered in either order with sequential benefit (35–40). In addition, emerging data suggests that some patients may benefit from retreatment with a venetoclax-based regimen although large prospective cohort data supporting this practice are not yet available (41). Collectively, we estimate two classes of highly effective approved targeted therapy agents typically provide patients with 10 or more years of effective disease control. However, neither class of agent is given with curative intent and some patients will derive less profound benefit due to early progression or intolerance. Therefore, ultimately many patients treated with a BTK inhibitor and venetoclax will still require subsequent therapy. Efforts to extend clinical benefit and provide time off therapy have focused on combinations of BTK inhibitors and venetoclax, which are now currently being evaluated in multiple Phase 3 studies (NCT04608318, NCT03701282, NCT03836261, NCT03737981, NCT03462719).

Although there is optimism that patients will enjoy long remissions after combined BTK inhibitor and venetoclax therapy administered on a fixed-duration schedule, limited information exists regarding the sequencing of novel agents following such combinations or the clinical efficacy of retreatment strategies."

Marked Progress but Important Knowledge Gaps

Despite the many randomized Phase 3 trials that have led to these current treatment paradigms, significant unanswered questions remain. Head-to-head comparisons of BTK inhibitors to venetoclax-based approaches have been launched (NCT04608318, NCT05057494), although results are not available. Similarly, comparisons among BTK inhibitors have been undertaken and are recently reported as abstracts at the ASCO and EHA 2021 meetings. Importantly, the studies evaluating head-to-head comparisons of modern targeted therapies may not address key outstanding questions in terms of efficacy due to their study designs / primary endpoints which include non-inferiority for PFS in the ELEVTAE R/R and overall response rate in the ALPINE study. Additionally, in terms of safety these studies demonstrate differences in safety profiles which do not definitely favor any agent over another (acalabrutinib vs. ibrutinib, zanubrutinib vs. ibrutinib) with the notable exception of cardiovascular events. (42,43) Collectively, these data gaps mean that the optimal sequencing and selection among available BTK inhibitors and venetoclax remain undefined (44). Perhaps most importantly, we still do not understand the true efficacy of available therapies in the patient population increasingly seen in our clinics today – namely those who have been previously treated with BTK inhibitors, venetoclax, or both. Indeed, it is remarkable to note that only 9 of 921 (~1%) patients treated on 6 recent randomized studies in relapsed/refractory CLL/SLL were previously treated with at least one targeted therapy and likely none on a truly contemporary chemotherapy-free treatment (41). In short, while the randomized datasets upon which we base our current practice have yielded an impressive armamentarium of agents among which to select for our patients, these same studies have not taught us the true efficacy of these agents in the relapsed/refractory patient population that constitute the majority of patients currently seen in everyday practice.

Available therapy for patients previously exposed to both BTK inhibitors and venetoclax generally include the PI3K inhibitors, cytotoxic chemotherapy, alemtuzumab, single agent anti-CD20 antibodies and allogeneic stem cell transplantation (in highly selected patients) (45). Unfortunately, studies evaluating these agents or their combinations have been exclusively conducted in patients naïve to BTK inhibitors and venetoclax and as a result their safety and especially their efficacy in patients treated on a pathway that includes a BTK inhibitor and venetoclax remains unknown. Data from limited published anecdotal and retrospective case series suggest these available therapies have limited efficacy following treatment with BTK inhibitors, venetoclax, or both (20,38,46).

The two pivotal studies with the PI3K inhibitors, idelalisib and duvelisib, illustrate the challenge of applying data generated from these studies to a treatment context now dominated by use of BTK inhibitors and venetoclax (6,31). As mentioned, no patients in these randomized studies were previously treated with a BTK inhibitor or venetoclax. Moreover, both studies utilized single anti-CD20 antibody monotherapies as the comparator

arm, a treatment approach known to have limited efficacy in CLL/SLL. Consequently, the results of these studies cannot be utilized to guide treatment decisions in patients previously treated on a chemotherapy free paradigm (41). Additionally, several real-world data sets suggest that the PI3K inhibitor class has limited effectiveness in patients who are venetoclax naïve and previously treated with BTK inhibitors (possibly due to cross resistance) or have been treated with both a BTK inhibitor and venetoclax in earlier lines of therapy. Specifically, in 17 patients who had been exposed to a prior BTK inhibitor and venetoclax, the ORR was 47% with median PFS of only 5 months (38).

The adoption of currently approved PI3K inhibitors into contemporary treatment has also been severely limited by significant immune-mediated toxicities and infectious complications resulting in high discontinuation rates. In the Phase 3 study which compared acalabrutinib to the PI3K inhibitor idelalisib with rituximab, 47% of the 119 patients who received idelalisib plus rituximab discontinued treatment prior to disease progression due to adverse events (median time on therapy 11.5 months) (29). Consistent with these clinical trial data, real-world data similarly confirm discontinuation rates with PI3K inhibitors ranging from 40–95%, again predominantly due to AEs. While real-world data are not yet available for duvelisib, the discontinuation rate from the Phase 3 DUO trial was 77%, with 27% of patients discontinuing due to adverse events (31). Given these collective data, we do not consider PI3K inhibitors a sufficiently effective standard option for patients with disease previously treated with BTK and venetoclax. As the number of CLL patients treated with venetoclax and BTK inhibitors will continue to increase with time, novel effective therapies for this patient population are urgently needed.

Another key data gap is the lack of any studies that have evaluated CIT following progression on either BTK inhibitors or BTK inhibitors / venetoclax; neither clinical trial data nor real-world data exist to answer this question. Again, anecdotal experience and small real-world series suggest that CIT would have an extremely limited role in non-transformed patients previously treated with multiple targeted therapies in an earlier line of therapy; CIT is used with transformed disease (Richter syndrome) (47). As with patients previously treated with CIT, these patients tend to have more aggressive disease characterized by resistance mutations or *TP53* aberrancy, the latter predicts for reduced efficacy of CIT (48). Furthermore, older prospective Phase 2 trials and randomized trials of CIT in the second or later treatment line setting after prior CIT have typically shown relatively modest PFS (i.e., on the order of two years or less) (49,50). In the absence of convincing data at this time, we cannot counsel or encourage the use of chemotherapy or CIT as an established standard of care (particularly if the CLL clone has acquired poor risk molecular/genetic features) for patients treated with one or more targeted therapies as earlier lines of therapy. As efficacy of CIT following BTK inhibitors or BTK inhibitors / venetoclax is not available, prospective studies will need to be conducted to assess if CIT is a valid standard of care or as a control arm in future randomized studies in this setting.

Conclusions: Addressing the Unmet Need

After a decade of unprecedented innovation driven largely by the adoption of BTK inhibitors and venetoclax that have collectively transformed the treatment landscape and outcomes for

patients with CLL/SLL, we are now seeing a growing population of patients who are in need of new therapeutic options following treatment with both of these novel targeted agents. These patients lack therapeutic options with proven efficacy and safety following treatment with a BTK inhibitor and venetoclax and, as such, constitute the vanguard of contemporary unmet need for this disease. Achieving the next round of breakthroughs for these patients will once again require close collaboration between all key stakeholders, including the patient community, clinical investigators, the pharmaceutical industry and global regulatory bodies. This progress begins by simply acknowledging that after a decade of enormous progress, we once again have CLL/SLL patients with unmet medical need. These patients can be readily identified and should be preferentially enrolled into clinical trials. Progress will certainly require biologic insight into resistance mechanisms to BTK inhibitors and venetoclax. Equally importantly, however, progress will also require consensus on key aspects of new drug development for this patient population. Importantly, as new agents are developed in this population, we must determine what absolute effect size is meaningful, as measured using objective endpoints. The urgency is real, but so is the promise. We believe that further dramatic progress in CLL therapy is not only possible but imminent – the time for collective action is now.

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Translational relevance statement

In CLL, while outcomes for patients have been dramatically improved, patients treated with prior BTK and BCL2 inhibitor-based therapy represent a new population with significant unmet need. Despite improved outcomes, the two most common reasons for discontinuation of these agents include drug resistance or intolerance. To date, no agent has clearly demonstrated efficacy in patients with double refractory CLL (i.e. resistant to both BTKi and venetoclax). Nearly all of the CLL patients enrolled on prior randomized studies of BTK inhibitors, PI3K inhibitors and venetoclax were conducted in patients who were BTK inhibitor and BCL2 inhibitor naïve and therefore do not represent patients in clinical practice - defining the true unmet need in CLL. While randomized studies have an important role in generating evidence for CLL therapies, we also recognize that to our knowledge nearly all randomized Phase 3 studies conducted in CLL in the last 10 years have utilized chemotherapy, an anti-CD20 antibody, or the combination of these agents as the comparator arm. Here we offer our perspective on how best to define unmet needs in a modern treatment context. We review the literature with a focus on agents such as PI3K inhibitors and chemoimmunotherapy and lack of data to support their utility following BTK inhibitors and venetoclax. Finally, we suggest opportunities for key stakeholders to ensure the continued innovation our patients deserve. We believe this perspective will help to initiate a conversation among our community and key stakeholders as to how to best and most rapidly advance innovation for our patients in need.

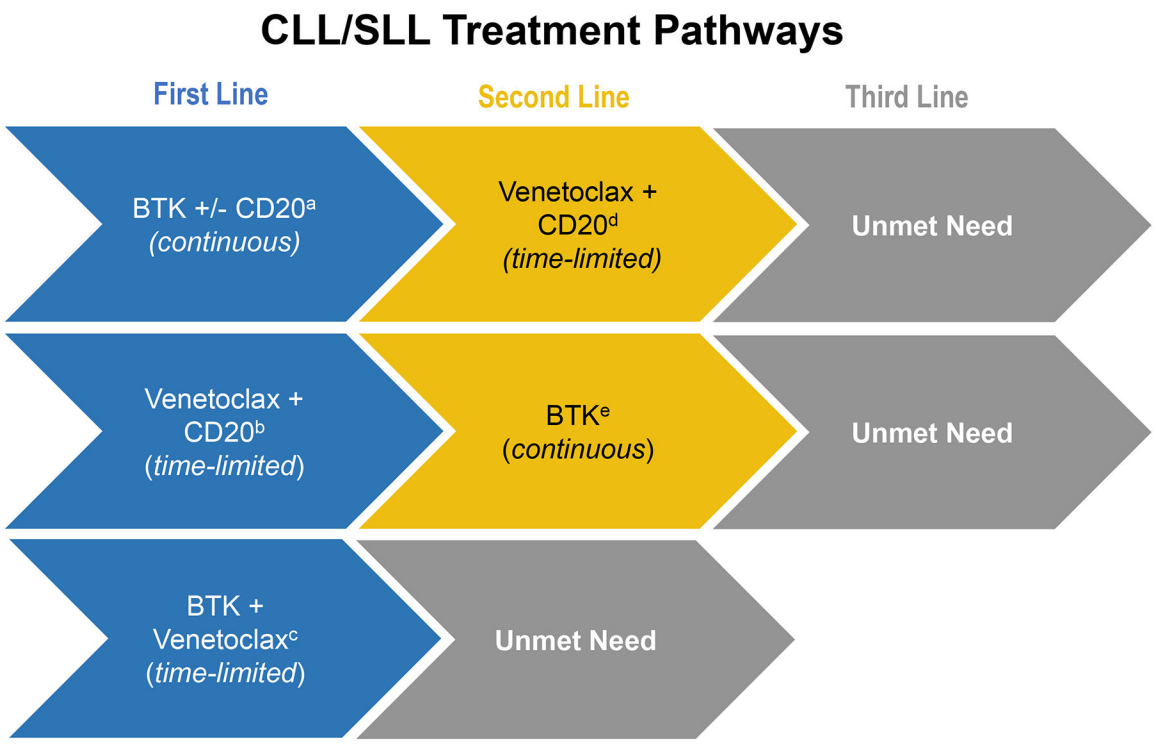

Figure 1:

Chemotherapy free sequencing algorithms for patients with CLL/SLL in modern clinical practice with current unmet needs

[a]RESONATE-2 (2016); ELEVATE TN (2019); ILLUMINATE (2019); E1912 (2020)

[b]CLL-14 (2019)

[c]GLOW; CAPTIVATE (both ongoing)

[d]MURANO (2018)

[e]RESONATE (2014); ASCEND (2019)

Table 1:

Randomized Studies of Covalent BTK Inhibitors, Venetoclax, and PI3K Inhibitors

Study Name	Disease Setting	Active arm	Comparator	Prior BTK %	Prior BCL2 %	Pts, N	Hazard Ratio
RESONATE[26]	R / R	Ibrutinib	CD20	0	0	391	0.22
RESONATE[26]	R / R (17p)	Ibrutinib	CD20	0	0	127	0.25
HELIOS[11]	R / R	Ibrutinib + Chemo + CD20	Chemo + CD20	0	0	578	0.20
RESONATE-2[25]	1L	Ibrutinib	Chemo	0	0	269	0.16
iLLUMINATE[22]	1L	Ibrutinib + CD20	Chemo + CD20	0	0	229	0.23
E1912[28]	1L	Ibrutinib + CD20	FCR	0	0	529	0.34
ASCEND[29]	R / R	Acalabrutinib	Chemo + CD20 *OR* PI3K + CD20	0	0	310	0.31
ELEVATE-TN[23]	1L	Acalabrutinib Acalabrutinib + CD20	Chemo + CD20	0	0	535	0.20 0.10
MURANO[30]	R / R	Venetoclax + CD20	Chemo + CD20	<2%	0	389	0.17
CLL-14	1L	Venetoclax + CD20	Chemo + CD20	0	0	432	0.35
NA	R/R	Idelalisib + CD20	CD20	0	0	220	0.15
DUO[31]	R/R	Duvelisib	CD20	0	0	319	0.52