Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients


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Background: Ibrutinib, idelalisib, and venetoclax are approved for treating CLL patients in the United States. However, there is no guidance as to their optimal sequence.

Patients and methods: We conducted a multicenter, retrospective analysis of CLL patients treated with kinase inhibitors (KIs) or venetoclax. We examined demographics, discontinuation reasons, overall response rates (ORR), survival, and post-KI salvage strategies. Primary endpoint was progression-free survival (PFS).

Results: A total of 683 patients were identified. Baseline characteristics were similar in the ibrutinib and idelalisib groups. ORR to ibrutinib and idelalisib as first KI was 69% and 81%, respectively. With a median follow-up of 17 months (range 1–60), median PFS and OS for the entire cohort were 35 months and not reached. Patients treated with ibrutinib (versus idelalisib) as first KI had a significantly better PFS in all settings; front-line [hazard ratios (HR) 2.8, CI 1.9–4.1, P < 0.001], relapsed-refractory (HR 2.8, CI 1.9–4.1, P < 0.001), del17p (HR 2.0, CI 1.2–3.4, P = 0.008), and complex karyotype (HR 2.5, CI 1.2–5.2, P = 0.02). At the time of initial KI failure, use of an alternate KI or venetoclax had a superior PFS when compared with chemoimmunotherapy. Furthermore, patients who discontinued ibrutinib due to progression or toxicity had marginally improved outcomes if they received venetoclax (ORR 79%) versus idelalisib (ORR 46%) (PFS HR .6, CI .3–1.0, P = 0.06).

Conclusions: In the largest real-world experience of novel agents in CLL, ibrutinib appears superior to idelalisib as first KI. Furthermore, in the setting of KI failure, alternate KI or venetoclax therapy appear superior to chemoimmunotherapy combinations. The use of venetoclax upon ibrutinib failure might be superior to idelalisib. These data support the need for trials testing sequencing strategies to optimize treatment algorithms.

Key words: CLL, ibrutinib, idelalisib, kinase inhibitor, venetoclax
Introduction

Ibrutinib, idelalisib, and venetoclax have all been approved for the treatment of CLL [1–5]. While ibrutinib and idelalisib are KIs targeting the Bruton’s tyrosine kinase (BTK) and phosphatidylinositol-3-kinase p110-delta (PI3Kδ), respectively, venetoclax is a BH3 mimetic targeting the BCL-2 protein, with significant apoptotic activity [6, 7]. There is limited data in the literature on how to best sequence these agents and how to manage patients who fail these therapies [8]. Furthermore, the best salvage therapy in patients who fail these agents is unknown and represents an unmet medical need.

Several studies have demonstrated that patients who discontinue either agent due to toxicity may fare better than those who discontinue due to CLL progression or transformation [9–14]. Moreover, whether chemoimmunotherapy (CIT) demonstrates efficacy following KI failure is unknown.

In order to evaluate the optimal sequence of these newer therapies, we conducted a multicenter review of 683 CLL patients treated with any of the above 3 agents across 9 United States-based cancer centers and the ConnectR CLL Registry. We aimed to identify rates and causes of discontinuation, to assess outcomes following discontinuation, and to define the best sequencing strategy utilizing KIs and venetoclax. To our knowledge, this is the largest series of patients treated with these novel therapies published to date.

Patients and methods

We conducted a multicenter, retrospective cohort study of CLL patients treated with ibrutinib, idelalisib or venetoclax-based therapies across 9 United States-based academic centers and the ConnectR CLL Registry. The study was approved by the institutional review board of each participating institution. Data collected included: patients demographics, clinical and genetic characteristics where available, initial dose, combination versus monotherapy, treatment discontinuations, treatment interruptions, best response, discontinuation rate, reasons for discontinuation, and subsequent therapies. Investigators were asked to utilize resources such as institutional clinical/pathological databases, chart review, electronic medical records at each respective institution to identify the complete cohort of CLL patients treated with KI or venetoclax.

Reasons for discontinuation were categorized as follows: toxicity/ intolerance, CLL progression, Richter’s transformation (RT), planned cellular therapy [allogeneic hematopoietic stem cell transplantation or chimeric antigen receptor genetically modified T-cell therapy], second malignancies, patient choice, death, or other. Toxicities leading to discontinuation were categorized as: hematologic toxicity, infection, atrial fibrillation, congestive heart failure, drug-induced pneumonitis, drug-induced colitis, transaminitis, bleeding, arthralgia/myalgia, dermatologic, neurotoxicity, other, and unknown.

The primary study endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), overall response rates (ORR), and reasons for novel agent discontinuation. PFS and OS were estimated using the Kaplan–Meier (KM) method [15]. For patients treated with a KI (prior to venetoclax), we stratified by first KI choice (ibrutinib versus idelalisib), line of therapy (front line versus relapsed), clinical trial participation versus commercial use, and high-risk genetic features (presence/absence del17p, presence/absence complex karyotype).

Following KI discontinuation, we further described subsequent therapies, response rates, and survival outcomes. We stratified survival outcomes by choice of subsequent therapy (KI -> alternate KI versus CIT or venetoclax). We also examined outcomes to subsequent therapies stratified by reason for discontinuation (CLL progression versus KI intolerance).

Disease progression was defined based on the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria [16, 17]. PFS was defined as the time in months from initiation of therapy to documented progression, transformation, or death. OS was defined as the time in months from initiation of KI to death from any cause. The log rank (LR) test was used to compare differences between KM curves [18]. Univariate Cox regression analyses were used to estimate hazard ratios (HR) [19]. All other analyses were descriptive. All tests were two-sided at the 5% level. Statistical analyses were performed using Stata Version 10.1.

Results

Patient population

We identified 683 CLL patients who were treated with first KI therapy [621 (91%): ibrutinib based and 62 (9%): idelalisib based]. Median number of prior therapies was 2 (range 0–10). Fourteen percent of patients received KI-based therapy in the front line setting (n=80 ibrutinib, n=14 idelalisib), and 19% of all patients were treated on a clinical trial. Approximately one-third of patients had high-risk genetic features defined as del17p, del11q, or complex karyotype, with 59% having unmutated IGHV. Baseline characteristics were similar between the ibrutinib and idelalisib groups (Table 1).

Response rate and outcomes to first KI

In the relapse setting, for patients with a reported response assessment the ORR to ibrutinib as the first KI (n=357) was 68% [complete response (CR) 11%, partial response (PR) 46%, and partial response with lymphocytosis (PR-L) 11%]. In the front line setting, the ORR to ibrutinib (n=80) was 71%. The ORR to idelalisib in the relapse setting (n=47) was 80% [CR 4%, PR 72%, PR-L 4%] and was 85% (n=14) in the front line setting. With a median follow-up from start of first KI of 17 months (range 1–60), the median PFS and OS for the entire cohort was 35 months (216 events) and not reached, respectively (107 events) (Figure 1).

We further stratified outcomes by first KI choice. Patients who received ibrutinib-based therapy (versus idelalisib-based therapy) as their first KI experienced a significantly better PFS in all settings; front-line (HR 2.8, CI 1.3–6.3, P = 0.01), relapsed-refractory (HR 2.8, CI 1.9–4.1, P < 0.001), del17p (HR 2.0, CI 1.2–3.4, P = 0.008), or complex karyotype (HR 2.5, CI 1.2–5.2, P = 0.02) (Figure 2).

Discontinuation of KI

As of the data cutoff date of 1 August 2016, 47% of patients discontinued their first KI (94% idelalisib cohort, 42% ibrutinib cohort). The reasons for discontinuation were similar between the agents (Table 2). Notably, KI toxicity was the most common reason to discontinue either agent, accounting for almost 50% of discontinuation events. The five most common toxicities leading to discontinuation of ibrutinib were atrial fibrillation (n=18), infection (n=13), pneumonitis (n=12), bleeding (n=11), and arthralgia (n=9); whereas the five most common toxicities...
leading to discontinuing idelalisib were pneumonitis (n = 7), colitis (n = 6), rash (n = 5), transaminitis (n = 4), and infection (n = 2). The median time to discontinuation of KI for toxicity was 6 months (0–28 months).

Subsequent therapies
To date, 167 patients (24%) have received another line of therapy after their first treatment with a KI containing regimen (supplementary Table S1, available at *Annals of Oncology* online). The median time to next therapy following KI discontinuation was 1 month (range 0–28 months). Subsequent regimens were grouped as KI-based therapy, venetoclax or CIT combinations. The ORRs (CR rate) to KI-based therapy, venetoclax, or CIT combinations were 58.5% (4.1%), 73.6% (31.5%), and 49.9% (2.1%), respectively.

Response data for alternate KIs and venetoclax following initial KI are included in Table 3. At the time of initial KI failure, the use of vandetanib resulted in an ORR of 21.7% (3.2%) with respective median PFS and OS of 2.6 months and 11.1 months (95% CI not reached). A retrospective analysis showed that patients with elevated LDH and complex karyotype were statistically more likely to achieve an ORR with vandetanib compared to patients with these abnormalities on treatment with subsequent KIs. The ORR with vandetanib for patients with elevated LDH and complex karyotype was 51.1% (9.4%), while the ORR for patients with either elevated LDH or complex karyotype was 42.1% (8.2%).

Table 1. Baseline characteristics at start of first KI and dose modifications

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ibrutinib as first KI</th>
<th>Idelalisib as first KI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at diagnosis</td>
<td>61 (22–95)</td>
<td>61.5 (35–80)</td>
</tr>
<tr>
<td>Number of prior therapies</td>
<td>2 (0–10)</td>
<td>2 (0–7)</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>B symptoms present</td>
<td>33%</td>
<td>32%</td>
</tr>
<tr>
<td>Median WBC</td>
<td>28.7 (0.5–562.6)</td>
<td>25.5 (2.4–549.9)</td>
</tr>
<tr>
<td>Del 17p present (FISH)</td>
<td>28%</td>
<td>31%</td>
</tr>
<tr>
<td>p53 mutation present (NGS)</td>
<td>12%</td>
<td>15%</td>
</tr>
<tr>
<td>Complex karyotype present (≥3 abnormalities)</td>
<td>35%</td>
<td>25%</td>
</tr>
<tr>
<td>IGHV unmutated</td>
<td>59%</td>
<td>63%</td>
</tr>
<tr>
<td>Median time to treatment initiation</td>
<td>73 months</td>
<td>78 months</td>
</tr>
<tr>
<td>Median starting dose</td>
<td>420 mg daily (9% started at &lt; 420 mg daily, n = 52)</td>
<td>150 mg BID (24% started at &lt; 150 mg BID, n = 15)</td>
</tr>
<tr>
<td>Administered as monotherapy</td>
<td>87%</td>
<td>42%</td>
</tr>
<tr>
<td>Required dose modification during therapy</td>
<td>19%</td>
<td>24%</td>
</tr>
<tr>
<td>Required dose interruption during therapy</td>
<td>35%</td>
<td>51%</td>
</tr>
<tr>
<td>Median time to discontinuation</td>
<td>7 months (0.1–41)</td>
<td>6 months (0.5–42)</td>
</tr>
</tbody>
</table>

Figure 1. Progression-free survival (A) and overall survival (B) of patients from start of first kinase inhibitor initiation (ibrutinib and idelalisib combined).
Figure 2. PFS (A) by first kinase inhibitor (ibrutinib versus idelalisib) in the front-line setting. PFS (B) by first kinase inhibitor (ibrutinib versus idelalisib) in the relapsed refractory setting. PFS (ibrutinib versus idelalisib) stratified by del(17p) status (C). PFS (ibrutinib versus idelalisib) stratified by complex karyotype status (D).

Table 2. Reasons for discontinuation first KI

<table>
<thead>
<tr>
<th>Reason</th>
<th>Ibrutinib (n = 258 discontinuation events)</th>
<th>Idelalisib (n = 58 discontinuation events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity</td>
<td>51.2% (n = 132)</td>
<td>44.8% (n = 26)</td>
</tr>
<tr>
<td>Progression</td>
<td>20.5% (n = 53)</td>
<td>27.6% (n = 16)</td>
</tr>
<tr>
<td>Other/death not secondary to progression</td>
<td>11% (n = 28)</td>
<td>6.9% (n = 4)</td>
</tr>
<tr>
<td>MD/patient preference</td>
<td>6.2% (n = 16)</td>
<td>17.2% (n = 10)</td>
</tr>
<tr>
<td>Richter’s transformation</td>
<td>5.0% (n = 13)</td>
<td>3.5% (n = 2)</td>
</tr>
<tr>
<td>Stem cell transplant/CAR T cells</td>
<td>3.9% (n = 10)</td>
<td>0%</td>
</tr>
<tr>
<td>Secondary malignancy</td>
<td>1.1% (n = 3)</td>
<td>0%</td>
</tr>
<tr>
<td>Cost</td>
<td>1.1% (n = 3)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 3. Response to subsequent therapy following initial kinase inhibitor therapy

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib → idelalisib</th>
<th>Idelalisib → ibrutinib</th>
<th>Kinase inhibitor → venetoclax</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>46</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>CR (%)</td>
<td>0</td>
<td>5</td>
<td>32</td>
</tr>
<tr>
<td>PR/PR with lymphocytosis (%)</td>
<td>46</td>
<td>70</td>
<td>42</td>
</tr>
<tr>
<td>Stable disease (%)</td>
<td>39</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Progressive disease (%)</td>
<td>15</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
of either an alternate KI or venetoclax was associated with superior PFS when compared with CIT/CD 20 monoclonal antibodies (Figure 3A, \( P < 0.001 \), LR test). In patients treated with an alternate KI (ibrutinib followed by idelalisib or idelalisib followed by ibrutinib), those intolerant of the initial KI had a superior PFS compared with those progressed on the initial KI (Figure 3B, \( P = 0.03 \), LR test). Furthermore, patients who discontinued ibrutinib for any reason had both a better ORR when treated with venetoclax (ORR 79%) when compared with idelalisib (ORR 46%), and a trend to improvement in PFS (Figure 3C, \( P = 0.06 \), LR test).

**Discussion**

In the largest CLL patient case series study conducted in the era of novel oral therapeutics, we demonstrate the superiority of ibrutinib to idelalisib in first-line, relapsed-refractory, and in high-risk patients, despite a higher ORR with idelalisib-rituximab. (Figure 3A, P < 0.001, LR test). In patients treated with an alternate KI (ibrutinib followed by idelalisib or idelalisib followed by ibrutinib), those intolerant of the initial KI had a superior PFS compared with those progressed on the initial KI (Figure 3B, P = 0.03, LR test). Furthermore, patients who discontinued ibrutinib for any reason had both a better ORR when treated with venetoclax (ORR 79%) when compared with idelalisib (ORR 46%), and a trend to improvement in PFS (Figure 3C, P = 0.06, LR test).

Not surprisingly, more patients were treated with ibrutinib than with idelalisib, likely due to the earlier FDA approval, ease of once daily dosing and the indication to use as monotherapy, as well as concerns regarding toxicities. As physicians become more experienced in using these novel therapies and as patients seek out more tolerable, targeted therapies, the use of these agents will likely increase. Although initially approved in limited disease settings, their indications are expanding quickly, particularly with the anticipated results of the front line studies through the Alliance (NCT01886872) and ECOG cooperative groups (NCT02048813) comparing CIT to ibrutinib-based therapy [20]. Sequencing these agents is particularly challenging as there are no comparator studies. Furthermore, choosing the appropriate agent to use first maybe critical given limited available data on how to manage KI failures.

Our 683-patient cohort was enriched with patients who were not treated on a clinical trial in an attempt to better understand outcomes in the “real world” setting. Our analysis indicated superior outcomes with idelalisib or venetoclax following ibrutinib discontinuation compared with CIT. This is not necessarily surprising as most of the patients were previously treated with chemotherapy or anti CD20 monoclonal antibody therapy. These results compare very favorably with previous studies of CIT with
bendamustine and rituximab in patients with relapsed refractory CLL [21]. Notably, we observed a marginal superiority of venetoclax versus idelalisib but the numbers are very small suggesting that further confirmation is necessary [7]. This might reflect the need to switch mechanisms of action when utilizing a salvage therapy upon progression on a KI.

Surprisingly, almost half of our patients discontinued KI therapy due to toxicity. This observation is critical as it appears to be in conflict with the clinical trial findings that led to approving ibrutinib and idelalisib, which showed progression of disease as a major reason for drug discontinuation [1, 4, 22, 23]. Furthermore, the nature of these toxicities is somewhat different to what has been previously reported. In fact, while atrial fibrillation as a toxicity reason for discontinuation was noted in 13.5% of patients in our analysis, it was not cited amongst the top adverse events in the original ibrutinib study [2]. Additionally three recent reports suggest a higher rate of atrial fibrillation than was initially reported in the initial ibrutinib studies in CLL [24–26]. Similarly, pneumonitis, which is classically associated with idelalisib, was observed in 9% of patients as a toxicity reason for discontinuation in our ibrutinib cohort as well [27].

Identifying the rates and types of toxicities with these agents in a more representative CLL population is essential as more patients are treated in the community in order to implement strategies to minimize such toxicities. These approaches might include vigilant monitoring to consideration of dose reduction to mitigate such toxicities [28, 29]. Another consideration might be treating patients for a set period of time as opposed to treatment until progression; however, data on the efficacy of this approach are limited. Second generation KIs in development may provide therapeutic alternatives of BTK and PI3K inhibition with less off target toxicities. Notably, early data suggests that acalabrutinib (ACP 196), Bgb-3111, and TGR 1202 have favorable toxicity profiles. However, long-term follow-up data comparing these agents to first generation KIs is needed before concluding definitively whether second generation KI offer favorable toxicity without compromising observed efficacy [30–32]. To that end, switching to better tolerated agents might be another strategy to consider when encountering unmanageable toxicities.

Limitations of our study lie in the retrospective nature of the analysis. First, we were unable to obtain complete data regarding patients’ risk stratification and outcomes. Second, our toxicity data were collected from chart reviews as opposed to a centralized assessment of patients’ conditions. Additionally, we only collected adverse event data leading to discontinuation, without available Common Terminology Criteria for Adverse Events (CTCAE) grading. Similarly, indications for treatment were based on treating physicians’ discretion and were not specified. Lastly, while most of the patients were treated with commercial drug and not on a clinical trial, the fact that they were largely treated in academic centers as opposed to community setting could introduce a selection bias. Despite these limitations, our data provide an insight into possible sequencing strategies for the treatment of CLL. We note that most patients in this dataset received KI and venetoclax in the relapsed setting. These data do not provide insight toward how to sequence agents in patients who initiate therapy on a KI or venetoclax as we move toward “chemotherapy free” CLL treatment paradigm. We also note that in the United States venetoclax is approved for the treatment of del(17p) CLL in the relapsed setting and therefore this sequence is based in part on off label use of this agent. In Europe, venetoclax is approved for CLL patients with a del(17p)/TP53 mutation who are unsuitable for or have failed KI therapy and those who have failed at least one CIT and KI regardless of their CLL genetic profile.

Optimization of sequencing is underscored by the increased emphasis on clinical pathways in the era of value-based medicine [33, 34]. To that end, the observation that ibrutinib might be superior to idelalisib in multiple settings could offer some guidance when building these pathways. Furthermore, recognizing the toxicities that we describe can assist in implementing monitoring guidelines as part of CLL pathway development. Finally, since our cohort is the largest published series of CLL patients treated with either KI or venetoclax it establishes expected results for sequencing of novel agents and toxicities against which future clinical trials can be compared.

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Cyclacel: research funding; Medimmune: research funding; Ambit: research funding; Astellas: research funding. PK: No conflict of interest to declare. KP: Celgene employee. JL: Celgene employee. SHB: No conflict of interest to declare. AMW: No conflict of interest to declare. A-LC: No conflict of interest to declare. CT: No conflict of interest to declare. MF: No conflict of interest to declare. KHK: No conflict of interest to declare. CD: No conflict of interest to declare. KI: No conflict of interest to declare. MY: No conflict of interest to declare. JS: Celgene: research funding; Celldex: research funding; Immunomedics: research funding; Seattle Genetics: research funding. SJS: Nordic Nanovector: Membership on an entity’s Board of Directors or advisory committees; Janssen: research funding; Novartis: research funding; Genentech: consultancy; Gilead: research funding; Hoffman-LaRoche: research funding; Celgene: consultancy, research funding; Pharmacies: consultancy, research funding. CN: Celgene Corporation: Honoraria, research funding.

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