Updates from the 2017 American Society of Hematology annual meeting: practice-changing studies in untreated chronic lymphocytic leukemia

C. Owen MD,* C. Toze MD MHSc,† and A. Christofides MSc RD‡

ABSTRACT

The 2017 annual meeting of the American Society of Hematology took place 9–12 December in Atlanta, Georgia. At the meeting, the oral presentations included results from key studies on the first-line treatment of chronic lymphocytic leukemia. A series of phase II studies focusing on the efficacy and safety of novel treatment strategies were especially notable. One concerned the health-related quality of life results from the GBB study, which had examined the combination of obinutuzumab and bendamustine. A second evaluated the venetoclax–ibrutinib regimen in patients with high-risk disease. The third assessed the combination of ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab in patients with mutated immunoglobulin heavy-chain variable region genes. The fourth examined the combination of ibrutinib, fludarabine, cyclophosphamide, and rituximab in younger patients. And the final study evaluated obinutuzumab–ibrutinib followed by a minimal residual disease strategy in fit patients. Our meeting report describes the foregoing studies and presents interviews with investigators and commentaries by Canadian hematologists about the potential effects on Canadian practice.

Key Words Untreated disease, first-line treatments, treatment-naïve patients, chronic lymphocytic leukemia


BACKGROUND

Chronic lymphocytic leukemia (CLL) is the most common leukemia in North American adults, with an annual incidence in Canada reported to be approximately 2500 cases.¹² Most patients with CLL are more than 65 years of age (with the median age at diagnosis being between 67 and 72 years) and have an average of 3 other health conditions.²³ Despite these patients representing an older population with comorbidities, their survival after diagnosis varies significantly, ranging from a short number of years to decades.² The identification of several negative prognostic factors—such as del(17p), TP53 mutations, and unmutated immunoglobulin heavy-chain variable (IGHV) status—might well explain some of the variation.³ Although those factors are clearly associated with lesser response rates to conventional chemoimmunotherapy (CIT), how the presence of those factors should influence treatment decisions is unclear.

Results of the CLL8 study, which demonstrated an overall survival and progression-free survival (PFS) advantage with rituximab–fludarabine–cyclophosphamide (RCh) compared with fludarabine–cyclophosphamide (FC), established RCh as the standard therapy in most Canadian provinces for patients without del(17p)²⁴. Moreover, RCh is associated with more favourable outcomes in patients with IGHV mutations, achieving 10-year PFS rates in excess of 60%, therefore making it an optimal treatment option in that subgroup.⁵⁶ However, RCh is associated with a high frequency of grades 3 and 4 toxicity and persistent cytopenias, making it unsuitable for most of this predominantly elderly population. Additional treatments that are effective but well-tolerated are therefore needed for patients who are unsuitable for or who cannot tolerate RCh.

Recent results from the CLL10 study show that, although the combination bendamustine–rituximab (BR)
is slightly less effective than FCR (median PFS: 41.7 months vs.
55.2 months; hazard ratio: 1.643; \( p = 0.0003 \)), it is better tolerated and not significantly less effective in fit elderly patients (>65 years)\(^7\). When maintaining quality of life is a key treatment goal for that population, therapeutic options might therefore present a preferred option\(^7\). Moreover, compared with rituximab–chlorambucil, a novel CD20 monoclonal antibody, obinutuzumab, combined with chlorambucil has been associated with superior PFS (hazard ratio: 0.46; \( p < 0.0001 \))\(^8\). Using obinutuzumab instead of rituximab as part of combination therapy might therefore further improve treatment outcomes. In addition, the Bruton tyrosine kinase inhibitor ibrutinib and the phosphatidylinositol-3-kinase delta isoform inhibitor idelalisib have been associated with good outcomes in high-risk disease, with overall response rates (ORRs) in the range 86%–97%\(^3\). However, it is not clear whether those agents could eventually be stopped or if they would need to be continued indefinitely, given that residual disease is common with monotherapy. Moreover, ibrutinib is relatively well-tolerated, but atrial fibrillation and bleeding are problematic adverse events in many patients. Idelalisib is also associated with important toxicities, including an increased risk of serious infections and immune complications, such that it is no longer recommended by Health Canada in the first-line setting\(^5,9\).

Finally, the novel Bcl-2 protein inhibitor venetoclax has demonstrated promising response rates of approximately 79% in patients with relapsed or refractory disease, with no difference in outcome observed for those with del(17p)\(^10,11\). However, further data are needed to determine the efficacy of venetoclax in previously untreated cll.

In an effort to improve on the efficacy and safety of currently available treatments, a number of phase II studies examining novel combinations with and without the use of standard therapies were presented at the American Society of Hematology 2017 annual meeting.

**METHODS**

The American Society of Hematology held its first official meeting in 1958. Today, it is the world’s largest professional society with a focus on hematologic malignancies. The 2017 annual meeting took place 9–12 December in Atlanta, Georgia, attracting 26,640 attendees, including 824 participants from Canada. Of 5730 abstracts accepted, 919 were chosen for oral presentation because of the high quality of their design and their potential effect on practice. To determine the most impactful abstracts in the setting of untreated cll, we searched the oral presentations using the terms “untreated,” “first-line,” and “chronic lymphocytic leukemia.” Among 54 abstracts, 12 oral presentations were identified using the criteria. Of those 12 oral presentations, only studies in phase II and beyond that focused on efficacy of treatment were included. Five oral presentations met the inclusion criteria.

The first study reported health-related quality-of-life (HRQOL) analyses from the giba trial, which examined the combination obinutuzumab–bendamustine (GB) in untreated cll. The second study examined the efficacy and safety of venetoclax–ibrutinib (VI) in previously untreated high-risk cll and in patients with relapsed or refractory disease. The third study examined the efficacy and safety of ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (IFcR) in untreated patients with IGVH-mutated cll. The fourth study examined the efficacy and safety of ibrutinib, fludarabine, cyclophosphamide, and rituximab (IFCR) in untreated fit patients with cll. The final study examined the efficacy and safety of obinutuzumab–ibrutinib (GI) followed by a minimal residual disease (MRD) strategy in fit patients with untreated cll. The next section outlines those studies and presents interviews with investigators and commentaries about the potential effects of the studies on Canadian practice.

**DISCUSSION**

**HRQOL After GB in Untreated CLL (GIBB)—Abstract 683**

**Objective**

To examine the HRQOL of patients with treatment-naïve cll treated with obinutuzumab–bendamustine in the phase II giba study\(^12\).

**Methods**

The 102 study patients 18 years of age and older with previously untreated cll received GB by intravenous infusion for 28-day cycles (Figure 1). The primary endpoint of the study was complete response (CR), with additional endpoints including ORR, PFS, overall survival, MRD, safety, and HRQOL. An earlier report from the giba study showed an ORR of 89.2%, a CR rate of 49.0%, and no unexpected safety signals (Figure 2). In addition, undetectable MRD in bone marrow was achieved in 60.8% of patients at the end of treatment. The HRQOL analysis used two questionnaires: the European Organisation for Research and Treatment of Cancer (EORTC) core 30-question Quality of Life Questionnaire, which includes a global health status measure, 5 functional scales (physical, emotional, cognitive, social, and role functioning), 8 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea), and an item about financial difficulties; and the EORTC 16-question Quality of Life Questionnaire—Chronic Lymphocytic Leukemia module, which contains 4 multi-item scales (fatigue, treatment side effects, disease symptoms, and infection) and 2 individual items (social activities and future health worries). Both questionnaires were completed by patients on day 1 of cycles 1 (baseline), 3, and 6; at the end of induction, at the response assessment, and every 3 months thereafter. A change in score of 10 points or more constituted a clinically significant improvement from baseline.

**Results**

Of 102 enrolled patients, 98 completed a questionnaire at baseline and at least 1 other questionnaire during a follow-up visit. Median age in this group was 61 years, and 68.4% of the patients were men. Based on the EORTC core Quality of Life Questionnaire, clinically meaningful improvements were observed for global health status at the response visit, and for role functioning at the end of
induction and at the response visit (Figure 3). A trend for improvement in emotional functioning was also observed. The greatest improvement in a hrqol score was observed for fatigue (mean baseline score: 37.64), with mean changes from baseline of –4.01, –5.48, –11.67, and –16.34 observed at cycles 3 and 6, at the end of induction treatment, and at the response visit respectively. Scores for insomnia also improved (mean baseline score: 33.33), with mean changes from baseline of –6.59, –9.09, –9.7, and –10.98 at the same time points. Patient-reported symptoms and functional status did not worsen over time. Based on the eortc Quality of Life Questionnaire–Chronic Lymphocytic Leukemia module, clinically meaningful improvements in symptoms were observed for fatigue, disease symptoms, and future health worries during treatment (Figure 4). A positive trend in the social activities scale was also observed.

**Author Conclusions**

Earlier data demonstrated the efficacy and safety of gb in the first-line setting. The hrqol data establish additional clinically meaningful improvements, including global health status, functioning, symptoms, and future health worries at the time of the response visit.

**Investigator Commentary by Drs. Jeffrey Sharman and Alexey Danilov**

Currently, the most commonly used crrs for the treatment of cll are fcr and br; however, the balance between selecting a crr or selecting one of the novel therapeutic agents such as ibrutinib is changing dynamically. Although fcr is very effective and could potentially lead to a cure in a small proportion of patients with mutated ighv, it is associated with high rates of toxicity and an increased risk of secondary cancers. That regimen is therefore difficult to consider in older, less fit patients, who have also been excluded from clinical trials. Given that the median age of patients with cll is approximately 72 years and that many have poorly controlled hypertension, cardiovascular concerns, and other comorbidities, most are not eligible for fcr. Compared with fcr, the br regimen is better tolerated; however, there is no expectation of cure for patients receiving br treatment, and progression after 4–5 years is likely. The cll11 trial showed that outcomes are superior for obinutuzumab–chlorambucil compared with rituximab–chlorambucil. We therefore designed the gbb trial anticipating that, compared with br, gb would produce better response rates.
The earlier efficacy results showed that gb was associated with high response rates, producing a 90%orr and a cr rate of approximately 49%. The gb regimen also proved to be well-tolerated, with neutropenia occurring in only one quarter of patients. The mrD results were comparable to those seen with fcr, with 60% of patients achieving mrD negativity in marrow. Although we do not yet have all the data in terms of response by igHv status, we would expect, given the high orr, to see responses in both mutational subgroups. Because there is no knowing upfront which patients with mutated igHv will experience long-term remissions with fcr, it is difficult to make treatment decisions based on that prognostic factor. Longer follow-up will reveal whether long-term remissions can be achieved with gb in patients with igHv mutation.

Consideration of hqol as an outcome in clinical trials is especially important in a disease such as cll, which affects mostly older patients. Patients often hold...
the misconception that chemotherapy is associated with hair loss, vomiting, diarrhea, and other side effects. They also worry that they will not recover their energy, fatigue being a key concern. In our study, we used two HRQoL questionnaires that fully encompass the HRQoL parameters specific to patients with cLl. Results showed clinically meaningful improvements in health status and role functioning, with a trend toward improvement in emotional functioning. One of the biggest improvements observed was for fatigue, which showed an incremental improvement as treatment progressed. Those results confirm what we see in practice and help to dispel the misconceptions concerning chemotherapy. For patients with previously untreated cLl, br has therefore has the potential, based on its high efficacy, favourable toxicity, and improvements in HRQoL, to be considered in place of both BR and FCR.

The availability of ibrutinib marks a movement away from chemotherapy; however, a number of concerns arise with this agent. One key issue with ibrutinib is the high cost of long-term treatment, which is likely to be unsustainable, given that patients are now living longer. A second issue with ibrutinib is that it has some unique toxicities that involve careful monitoring over time. Data have consistently shown that ibrutinib is associated with a higher risk of atrial fibrillation. In addition, because many of the patients who develop atrial fibrillation will require anticoagulation therapy, the increased risk of bleeding with ibrutinib is a concern. Hypertension is another concern that also requires careful monitoring, especially in patients with cardiac risk factors. Finally, as presented by the Ohio State University group at this 2017 American Society of Hematology meeting, infections—particularly fungal infections—are appearing in patients treated with ibrutinib. The advantage of BR over ibrutinib is that the treatment course is limited; currently, ibrutinib has to be taken until progression. Of course, in patients with del(17p) or with TP53 mutation, ibrutinib is the preferred therapy. However, those patients represent only approximately 5% of the untreated patient population. In addition, when a patient is not fit enough to receive chemotherapy, ibrutinib or obinutuzumab with or without chlorambucil might be considered.

### Combined VI for Patients with Previously Untreated High-Risk and Relapsed or Refractory cLl—Abstract 429

**Objective**
To examine the efficacy and safety of vi in patients with previously untreated high-risk disease [defined as one of del(17p) or mutated TP53, del(11q), unmutated IGHV, or age 65 years and older] and in patients with relapsed or refractory disease. The data presented here come from the untreated high-risk cohort.

**Methods**
In 77 patients (40 with untreated high-risk cLl) with an Eastern Cooperative Oncology Group performance status of 2 or greater and adequate renal and hepatic function, ibrutinib (420 mg daily) was given for the first 3 months, with venetoclax added thereafter (dose escalation to 400 mg daily, Figure 5). Venetoclax was continued for 2 years, and ibrutinib was continued until progression. Median age in the first-line cohort was 84.5 years, and 75% of the patients were men. The primary endpoint was CR or CR with incomplete bone marrow recovery.

**Results**
Median follow-up was 11.8 months, with 70 patients completing ibrutinib monotherapy. Overall, the risk category for tumour lysis syndrome (TLS) was downgraded in 54% of the patients after ibrutinib, 2 patients experienced laboratory TLS, and no patient experienced clinical TLS. In the first-line cohort, all patients responded to ibrutinib, with 3% of patients achieving a CR or a CR with incomplete bone marrow recovery (Figure 6). With the addition of venetoclax, the rate of undetectable marrow MRD increased over time, reaching 100% in 3 patients by 12 months. In 7 patients in the first-line cohort, ibrutinib monotherapy was discontinued as a result of skin rash, dizziness and hypertension, infection, and a need for prohibited concomitant medications. In addition, 8 patients in the first-line cohort discontinued therapy after the addition of venetoclax because of recurrent neutropenia, allogeneic stem-cell transplantation, and fallopian tube cancer. Dose reductions of ibrutinib and venetoclax occurred in 36% and 26% of patients respectively. In the first-line cohort, 1 death was attributed to central nervous system Cryptococcus. The overall rates of grade 3 or greater neutropenia and thrombocytopenia were 44% and 4% respectively. Atrial fibrillation occurred in 13% of the patients, and infections occurred in 14%, including 1 case of septic arthritis.

**Author Conclusions**
The vi combination is safe and active in patients with cLl, with encouraging early efficacy results. With use of ibrutinib, the TLS risk category was downgraded in more than half the patients. Moreover, data demonstrated a significant improvement in cLl infiltrate to marrow, with several patients achieving undetectable MRD status as early as 3 months after the start of combination therapy.

**Investigator Commentary by Dr. Nitin Jain**
Results of a preclinical study by our group at the MD Anderson Cancer Center in Houston, Texas, showed that venetoclax is able to augment the effect of ibrutinib in vitro, signifying a potential synergy between the two agents. Given that the two drugs also have non-overlapping mechanisms of action and different safety profiles, we felt that a test of the vi combination in clinical studies was a reasonable approach.

Our study included two cLl patient cohorts: untreated high-risk patients [del(17p), mutated TP53, del(11q), unmutated IGHV, or age 65 years and older], and relapsed or refractory patients. In both cohorts, patients were treated indefinitely with ibrutinib, unless progression occurred or the drug was discontinued based on toxicity. Venetoclax was given for 2 years in both cohorts. In future, we might modify the trial design to allow patients achieving a MRD remission to discontinue treatment. That modification would allow for a determination of whether therapy can
safely be stopped in patients achieving deep levels of remission as the results of ongoing trials suggest.

In our study, all of the 36 untreated high-risk patients responded, and 61%, 75%, and 80% achieved a complete response at 3, 6, and 9 months respectively. Moreover, by 9 months, 80% of the patients were minimal residual disease-negative in marrow, which is most likely a result of the addition of venetoclax. Those results compare favourably with outcomes after upfront fludarabine, cyclophosphamide, and rituximab treatment, which achieves complete response rates in the 40%–72% range, with 43%–58% of patients being minimal residual disease-negative in marrow4-7,15. In addition, our study included a high-risk patient group, whose members would be expected to experience outcomes inferior to those in the population studied in the fludarabine, cyclophosphamide, and rituximab trials. The advantage of venetoclax over fludarabine, cyclophosphamide, and rituximab is that it does not include chemotherapy and might therefore result in fewer long-term toxicities.

It is important to note that 15 patients discontinued treatment, mainly during the 3-month ibrutinib monotherapy phase. However, considering the safety profile of each agent, no unexpected toxicities were observed. Atrial fibrillation was seen in approximately 13% of patients (likely attributable to ibrutinib), and neutropenia was more commonly seen with the addition of venetoclax. With the use of granulocyte colony-stimulating factor (g-csf) and strategies such as dose reductions, neutropenia was easily managed.

Overall, the results are quite exciting. The efficacy looks promising, with most patients achieving complete response and minimal residual disease remissions. Outcomes with this combination appear superior to those using either agent as monotherapy, suggesting that using this combination is a good strategy in untreated patients with high-risk disease. Ongoing studies will address whether the regimen might be appropriate for untreated low-risk patients.

iFCG for First-Line IGHV-Mutated CLL Without TP53 Aberrations—Abstract 495

Objective
To examine the efficacy and safety of a short-term course of iFCG in untreated patients with IGHV-mutated CLL.

Methods
In an investigator-initiated phase II trial, 3 courses of iFCG treatment were given to 32 patients having mutated IGHV without del(17p), TP53 mutation, or complex karyotype (Figure 7). Patients achieving undetectable minimal residual disease at 1 year stopped all therapy, with minimal residual disease-positive patients continuing on ibrutinib until progression. At the start of the trial, g-csf was not mandated, but it is now required because of an increase in neutropenia. The primary endpoint was complete response or complete response with incomplete bone marrow recovery and with undetectable marrow minimal residual disease (4-color flow cytometry with a sensitivity of 10^-4) after 3 courses of iFCG.

Results
Of the 36 patients who initiated treatment, 32 completed 3 cycles of iFCG. Median age was 60 years, and 78% of the patients were men. Median follow-up was 13.6 months. After 3 cycles of iFCG, the complete response rate was 100%, and 44% of the patients achieved complete response 3 months after ibrutinib. Marrow minimal residual disease negativity was achieved in 87% of patients overall and in 100% of the patients with complete response 12 months after ibrutinib (Figure 8). Factors associated with a lower rate of undetectable marrow minimal residual disease at 3 months included β2-microglobulin, CD38, and zeta-70. The 19 patients who reached the 12-month mark...
all discontinued ibrutinib and maintained undetectable marrow MRD after a median follow-up of 5.5 months after discontinuation. Overall, 3 patients came off the study as a result of heart failure, pulmonary Mycobacterium avium complex infection, and grade 3 infusion reactions with grade 4 thrombocytopenia. One death from heart failure occurred after 9 cycles of treatment.

After 3 cycles of iFCG, grade 3 or greater neutropenia and thrombocytopenia occurred in 68% and 42% of patients respectively. Atrial fibrillation occurred in 11% of patients, and 26% experienced infection. Dose reductions of FC and ibrutinib occurred in 50% and 39% of patients respectively.

**Author Conclusions**
After 3 courses of iFCG, high rates of undetectable MRD were induced in all 19 study patients who reached the 12-month point. Those patients stopped treatment and have remained MRD-negative thus far. However, neutropenia and thrombocytopenia are common during treatment with iFCG.

**Investigator Commentary by Dr. Nitin Jain**
In young, fit patients with untreated CLL, FC is the standard treatment, reaching CR rates in the 40%–72% range, with 43%–58% of patients being MRD-negative in marrow. However, long-term toxicities are a concern, given a 5% risk of myelodysplastic syndrome or acute myeloblastic leukemia. Our goal was to build on the FC regimen by adding ibrutinib, replacing rituximab with obinutuzumab, and reducing the number of chemotherapy cycles. Ibrutinib was shown to be well-tolerated when added to bendamustine, leading to higher rates of MRD negativity. In addition, as shown in the CLL11 trial, deeper remissions were able to be achieved with obinutuzumab than with rituximab. Based on the foregoing rationale, we aimed to reduce the number of cycles of FC by using the potentially more effective iFCG regimen and by stopping treatment after 1 year in those achieving MRD negativity in marrow.

In our study, all 32 patients who completed 3 cycles of iFCG responded, with 87% of them achieving MRD negativity in marrow after 3 months. Those results appear far superior to those achieved with FC, for which we previously reported a marrow MRD negativity rate of just 26% after 3 months. All of the 19 patients who remained on study after 1 year were MRD-negative and able to stop treatment. We are now monitoring those patients, who have shown no sign of recurrence after 5.5 months—a truly remarkable observation. Although it is possible that some patients could revert to MRD positivity, a reversion of that type was not seen in an earlier study with venetoclax, in which no MRD recurrence has been seen in the 10 months since therapy stopped. Should a recurrence be observed, we would recommend resuming ibrutinib to regain response or switching to an agent with a different mechanism of action (such as venetoclax). However, within our protocol, the decision about which agent to give is left to physician discretion.

The rates of neutropenia and thrombocytopenia seen with iFCG were higher than those seen with FC alone. As a result, we have now amended the study to require G-CSF prophylaxis for the prevention of neutropenia. Since the amendment was put into effect, no further cases of neutropenia have been seen.

In general, iFCG was well-tolerated, with only 3 patients discontinuing treatment. Based on the results of our study, I would consider giving iFCG to any patient with mutated IGHV status—and without del(17p)—who would normally be considered for FC. Based on its important effect on treatment decision, IGHV status has to be determined. The necessary test is performed at our institution, but education...
of community centres at which testing is not always routine is important.

**iFCR As Frontline Therapy in Younger CLL Patients—Abstract 496**

**Objective**
To assess the efficacy and safety of iFCR in young, fit patients with untreated CLL.\(^20\)

**Methods**
In this multicentre phase II trial, CLL patients between 18 and 65 years of age with adequate renal and hepatic function and an Eastern Cooperative Oncology Group performance status of 0 or 1 were entered. Ibrutinib 420 mg daily was given for 7 days, followed by FCR for up to 6 cycles (Figure 9). Responders continued on ibritunib until progression or toxicity. The primary endpoint was CR with bone marrow MRD negativity at 2 months after FCR. An amendment to the study allowed patients to discontinue maintenance ibritunib after 2 years if marrow MRD was undetectable. The study used a 10-patient safety lead-in, which did not result in unexpected toxicities.

**Results**
The study enrolled 35 patients (median age: 55 years). All patients responded to iFCR, with 40% of patients experiencing a CR and 77% achieving marrow MRD negativity 2 months after treatment start. Response deepened over time in patients both with and without ighv mutation (Figure 10). At a median follow-up of 21 months, no patient progression events or deaths had been observed. Since the trial amendment, 5 patients have discontinued ibritunib, with no recurrences after up to 8 months off treatment. Grade 3 or greater neutropenia, thrombocytopenia, and anemia occurred in 29%, 26%, and 6% of patients respectively. In addition, nausea, bruising, and fatigue occurred in 71%, 43%, and 37% of patients respectively. Bleeding events included epistaxis (n = 2), menorrhagia (n = 1), and rectal bleeding (n = 1). Grade 3 febrile neutropenia, atrial fibrillation, transaminitis, pneumonitis intestinalis, anaplasmosis, infusion reaction, and appendicitis occurred in 1 patient each. Grade 3 or greater infection occurred in 17% of patients. Overall, 6 dose reductions were required, 5 for FCR and 1 for ibritunib.

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<td>Ibrutinib</td>
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G-CSF and PCP/HSV/VZV prophylaxis mandatory for all patients

**FIGURE 9** Design for the study of ibritunib 420 mg daily plus fludarabine, cyclophosphamide, and rituximab (FCR) administered per the standard of care. G-CSF = granulocyte colony–stimulating factor; PCP = Pneumocystis pneumonia; HSV = herpes simplex virus; VSV = varicella zoster virus.

**Author Conclusions**
In young, untreated CLL patients, iFCR induced deep responses at a rate significantly higher than the 20% seen historically with FCR alone. The low rates of hematologic and infectious toxicities could be a result of mandatory growth factor and antimicrobial prophylaxis.

**Investigator Commentary by Dr. Matthew Davids**
Recent long-term data have shown that a subset of young, fit patients with CLL and mutated ighv can be cured with FCR. We decided to build on that therapy by adding a novel agent with the aim of curing a greater number of patients. As part of an earlier trial, we had treated 3 patients with icr, and all 3 experienced deep and durable remissions. Given that experience, we designed a phase II trial in a larger number of patients to examine the efficacy and safety of icr.

We gave icr alone for the first week of treatment so as to mobilize cells out of the lymph nodes into the blood, where they can be killed more effectively. We then gave up to 6 months of icr followed by 2 years of ibritunib maintenance. With that approach, we hoped to improve on the number of patients able to achieve MRD negativity in marrow. Patients who are MRD-negative after 2 years of ibritunib maintenance can discontinue therapy. Thus far, 5 patients have discontinued icr, with the longest duration off therapy being 8 months, and no relapses have yet been observed. For any patients who relapse after discontinuation, we plan to resume icr treatment in the hope that those patients will respond to icr a second time.

In general, the safety profile of icr appears to be reasonable, with no surprising toxicities beyond those that would be expected with icr or FCR alone. To limit common infections, we mandated g-csf prophylaxis from the beginning of treatment, together with acyclovir and Pneumocystis pneumonia prophylaxis. Overall, few patients discontinued treatment, and in this select group of young and fit patients, icr was well tolerated. With respect to efficacy, the best rate of undetectable MRD in marrow was 83%, which is higher than any prior regimen used in an unselected population. Although 100% of patients with mutated ighv achieved marrow MRD negativity, what is particularly striking is that in the patients with the more aggressive unmutated ighv, the negativity rate was also high at 71%.

The icr regimen is a promising new approach for patients who are less than 65 years of age without major comorbidities. We recently expanded the study and will eventually have a total of 85 participants. If our initial results hold up, we trust that patients who desire the maximum chance of cure will have icr as an option. We hope that the regimen will be used in clinical trials as a standard comparator, and if such studies are positive, we would be able to change the standard of care.

**GI Followed by a MRD-Driven Strategy in Fit Patients With CLL—Abstract 497**

**Objective**
To assess the efficacy and safety of induction treatment with gi followed by a MRD strategy involving crr only in patients with detectable disease.\(^21\)
Methods
In this phase II trial in fit, treatment-naïve CLL patients with no del(17p) or TP53 mutation, participants were given gi for the first 9 months of treatment and then ibrutinib alone in those achieving marrow MRD negativity or CR with obinutuzumab in those with detectable disease (Figure 11). The primary endpoint was CR with undetectable marrow MRD at month 16.

Results
The study enrolled 135 patients (median age: 62 years). In 97 evaluable patients, 100% responded, and 38% experienced a CR after gi therapy. Overall, 86.6% of patients had detectable marrow MRD after treatment with gi and therefore received cit. A CR was achieved in 14 patients with IGHV mutation and in 22 with unmutated disease. The dose of ibrutinib was reduced in 4 patients, and 3
patients discontinued ibrutinib because of toxicity (atrial fibrillation, atrial flutter, and neutropenia). Grade 3 or greater toxicities were observed in 57% of the patients, with neutropenia, anemia, and thrombocytopenia occurring in 24%, 6%, and 31% respectively. Infusion reactions occurred in 69.5% of the patients. Adverse events included 5 serious cardiac events, 3 cases of serious bleeding, and 3 cases of grade 3 TLS. Two patients died during the study at the cut-off date: one of unknown causes, and one of brain hemorrhage from a fall not related to therapy.

Author Conclusions
Preliminary results indicate that 9 months of chemotherapy-free induction is associated with a high CR rate, without excess toxicity. However, most patients required subsequent CRR because of detectable marrow mrd.

Investigator Commentary by Drs. Anne-Sophie Michallet and Pierre Feugier
Improved survival has been demonstrated in patients with cll who achieve a CR with undetectable mrd after treatment. Our study examined the efficacy of an induction treatment (gi) followed by CRR only for patients who did not achieve a CR with undetectable mrd. Patients included in our trial were treatment-naïve, fit, and without del(17p) or TP53 mutation. A first assessment of response was performed at month 9, including computed tomography imaging, bone marrow biopsy, and peripheral blood and bone marrow mrd testing.

Although results are preliminary, 100% of patients had responded at the 9-month assessment, with 38% achieving a CR. Those response rates are similar to those seen with FCR. We were also able to collect marrow biopsies from all patients participating in the trial, with 13% of patients achieving a marrow mrd of less than 0.01% at the 9-month time point. Our hope is that, with additional time and intensity of treatment, more patients will reach undetectable mrd by month 16 of the trial. Our trial will aid in clarifying the ability to stop treatment with targeted agents in patients achieving undetectable mrd, potentially improving patient quality of life and cost of therapy.

Clinical Impact in Canada

Q&A with Drs. Carolyn Owen and Cynthia Toze
Q What are your thoughts about the GB regimen study (abstract 683) and the place of CRR in the first-line setting?

A (Owen) It was not surprising to see an improvement in hrqol after treatment with GB, because you would expect to see that result after any effective first-line therapy in cll. I think that the study was very well done, but I would need to see a phase iii trial of GB compared with either BR or FCR to consider using GB in this patient group. Although the data show GB to be an effective regimen, a consideration of the safety profile is also important when comparing GB with other CRR options, because the infection rate appeared to be higher than you might expect to see with BR. Based on currently available data, I would still choose to use CRR in the first-line setting for all patients with cll except those with del(17p) or TP53 mutations. Given that available data do not yet show an overall survival improvement after first-line targeted therapies, there is no reason to change the current standard of care.

A (Toze) The GB regimen appears very promising, with data showing it to be highly effective and fairly well tolerated. The study used good-quality instruments to determine hrqol, addressing the factors that are important to patients with cll. A decrease in important symptoms was documented, likely because of an improvement in the disease after treatment. Although efficacy outcomes are key, it is also important to consider measures of patient functioning. Given that some patients are unable to tolerate rituximab, and some are unable to tolerate obinutuzumab, it would be useful to have access to both the GB and the BR regimens. Barring the small subgroup of patients with del(17p) or TP53 mutations, CRR remains the appropriate standard of care. However, for patients unable to tolerate CRR, we now have targeted agents that can act as an alternative.

Q Where should targeted agents such as ibrutinib fit into the treatment algorithm?

A (Owen) Despite the potential of novel targeted agents, no current data justify the use of such regimens in the upfront setting, except in patients with del(17p) or TP53 mutations. The tolerability of ibrutinib is not as great as first thought, with a higher rate of infections than was previously shown and a lack of data about long-term toxicities. In addition, compliance is a concern given that patients must take ibrutinib until progression, and outside of clinical trials, follow-up to ensure compliance is not commonplace. Moreover, the cost implications for the upfront use of an agent such as ibrutinib cannot be ignored; clear data showing an efficacy advantage would be needed, as would further data about treatment after progression.

A (Toze) Although targeted agents such as ibrutinib are very effective, short- and long-term toxicities are of key importance. Some data show that rates of hypertension increase over time, and the associated cardiotoxicity has not been well defined. For example, a healthy patient with atrial fibrillation might be able to continue taking ibrutinib, but a less-fit patient developing cardiac toxicities might have difficulty tolerating this agent. In addition, the occasional patient taking ibrutinib will develop ventricular arrhythmia and might have to discontinue treatment. Data from ongoing studies should aid in clarifying whether ibrutinib can be used safely in this patient group.

Q What are your thoughts about the vi combination study (abstract 429)?

A (Owen) The vi combination is the most interesting regimen currently being examined for the treatment of cll. It is not surprising that deep responses occurred, and results were very impressive, with high efficacy and a good safety profile. However, the cost of these two agents could be prohibitive in Canada, and we might see good outcomes with a cheaper regimen such as venetoclax combined with a monoclonal antibody. The fact that ibrutinib is given
until progression is a key limitation. It would be interesting to examine \( \text{v1} \) against a good comparator and to include a planned treatment stop to see whether a cure can be achieved in a subset of patients. I would definitely want to use \( \text{v1} \) in the relapsed setting and would consider it upfront in higher-risk patients such as those with unmutated \( \text{igav} \), del(17p), or \( TP53 \) mutations. For those with mutated \( \text{igav} \), I would still prefer to use \( \text{fcr} \), because it is cheaper and achieves good outcomes in this population.

**A (Toze)** The \( \text{v1} \) combination is very interesting from a theoretical standpoint, as there is non-overlapping toxicity, with both agents having different mechanisms of action. Ibrutinib provides better clearance of blood and lymph nodes; venetoclax provides better clearance of marrow. Responses in the first-line setting improved over time, with the survival curve appearing promising. It was surprising that 15 patients discontinued treatment, but no safety signals appeared to stand out. The authors did report 1 case of septic arthritis and 1 death from central nervous system *Cryptococcus*. Although implicating the treatment agents is difficult, these types of infections have not been seen in the past, and careful attention should be paid to those signals.

**Q** What are your thoughts about debulking as a strategy before using venetoclax?

**A (Owen)** We know that ibrutinib works well in shrinking lymph nodes, and so it is logical to start with that agent before introducing venetoclax. This strategy is exciting, because it might reduce the risk of TLS; however, to reduce costs, it would be important to know that ibrutinib can safely be stopped.

**A (Toze)** In the \( \text{v1} \) study, patients were given 3 cycles of ibrutinib, which would be expected to be successful in debulking, although they might have lymphocytosis in blood. The regimen did manage to reduce the risk of TLS, with 54% of patients experiencing a reduction in risk category. In addition, no patients had clinical TLS, which was very interesting. However, it is still too early to draw firm conclusions; these patients will have to be closely monitored.

**Q** What are your thoughts about the \( \text{fcr} \) regimen study reported in abstract 496?

**A (Owen)** Given the toxicity of the \( \text{fcr} \) regimen, and despite \( \text{fcr} \) being the current standard of care, new studies should be looking at ways to replace chemotherapy rather than to add to it. Although data from the study showed \( \text{fcr} \) to be highly effective, it is hard to say whether the regimen is as well tolerated as \( \text{fcr} \). It is therefore hard to know whether patients would gain anything from this amount of treatment. In addition, although a discontinuation amendment was added to allow patients to stop treatment with ibrutinib after 2 years, it would have been better to measure MRD earlier so that some patients might have been able to stop treatment earlier on. Moreover, patients in the study were a highly selected group who were not representative of those in the real-world setting. Therefore, the only patients for whom I might consider using this aggressive treatment course would be those with high-risk disease, such as those with unmutated \( \text{igav} \). Even so, I would then prefer to use a regimen without fludarabine, especially in young patients, given the long-term risk of second malignancies.

**A (Toze)** I was surprised that the \( \text{fcr} \) regimen used in this study included a full dose of both ibrutinib and \( \text{fcr} \). The rate of neutropenia in the study was quite high, and g-CSF was mandated as a result. I would therefore be concerned about the future risk of myelodysplastic syndrome or acute myeloblastic leukemia in these patients. Although such an aggressive treatment course might be of value in some young patients, it would be important to work out the ideal treatment schedule when adding a targeted agent to \( \text{fcr} \). We do not have enough data, given the small number of patients, to say whether this regimen is more effective than \( \text{fcr} \), but it was interesting that more toxicity signals were not observed with such an aggressive regimen.

**Q** What are your thoughts about using MRD-based strategies to stop treatments such as ibrutinib in the first-line setting?

**A (Owen)** I think that the best way to use these novel agents upfront would be with the goal of improving survival and achieving a cure in some patients. In the relapsed setting, it does not appear that you can safely stop treatment with ibrutinib, but that observation does not mean that the same goal cannot be achieved when ibrutinib is used upfront. I agree that MRD-based strategies whose aim is to stop therapy in patients with undetectable disease are important; however, I feel that the drug most likely to meet that goal is venetoclax, given that ibrutinib has not been as successful in achieving MRD negativity. There is some question about whether MRD negativity means the same thing after the use of different classes of agents. For example, you can achieve MRD negativity in peripheral blood much faster with antibodies than with targeted therapies, but that negativity does not mean that the disease has been removed from the spleen and lymph nodes. There is the possibility that certain drugs clear the marrow better and that others work better in other compartments.

**A (Toze)** The concept of MRD negativity in the setting of CLL is something that is only just beginning to be examined. The concept is a very interesting, but it needs to be tested further in clinical trials. We are not ready to apply this concept within clinical practice, and it is not clear whether patients achieving undetectable MRD after ibrutinib will remain in remission.

**Q** What are your thoughts about the \( \text{fcr} \) regimen study reported in abstract 495?

**A (Owen)** The only patient population included in the study were those with mutated \( \text{igav} \). Given that you would expect a subset of those patients to be cured with \( \text{fcr} \) alone, the participating patients received a large amount...
of therapy despite the reduction in the number of cycles of FC. However, it is interesting to consider whether an alternative to FC in this patient group is a possibility. If an alternative therapy could lower the rate of second cancers and also improve the number of patients achieving MRD negativity, it could be an interesting treatment option. However, we would need to compare such a regimen with FC in a phase III trial, and it would make more sense to look at novel therapies such as venetoclax in preference to ibrutinib, given that venetoclax is better able to achieve deep remissions. Moreover, the FC regimen might not be less toxic than FC and would be significantly more expensive. It is therefore not a regimen I would choose to examine further in this setting.

A (Toze) It is important to examine ways to reduce the number of cycles of chemotherapy for patients with mutated IGHV. The ORR and MRD results achieved with this regimen look promising, and it is interesting that therapy was stopped to see whether patients could be cured. It is too early to know whether the patients who stopped therapy will relapse, but the trial design is fascinating. There were some concerning toxicities, such as in the patient who developed heart failure and died. In addition, a patient came off study because of a pulmonary infection. Therefore, although the regimen appears to be effective, the toxicities would need to be explored further.

Q What are your thoughts about the GI regimen study that included an MRD-driven strategy (abstract 497)?

A (Owen) The goal of stopping therapy in patients achieving MRD negativity is commendable and provides a more cost-effective approach to treatment. Patients included in the study were very young and had no high-risk factors, and so we would expect them to do well. It was therefore interesting that a number of ibrutinib discontinuations occurred. In addition, very few patients achieved MRD negativity, and so it might have been better to use an agent such as venetoclax to improve on that result. It might take longer to achieve MRD negativity with this regimen, and so it will be interesting to see the data with longer follow-up. This strategy saves 2 cycles of FC in patients not achieving MRD negativity after GI, but it is not clear that that approach is more effective and less toxic than giving standard FC.

A (Toze) Starting with a treatment that should be well tolerated is an interesting idea, although whether this dose and scheduling were the correct ones for this regimen is hard to know. No patients with del(17p) were included in the study, and so this cohort was lower-risk. Marrow MRD was positive in most patients, which is not a surprise at this early time point. In terms of safety, some toxicities of concern occurred, including atrial flutter in 2 patients, atrial fibrillation in 2 patients, and a brain hemorrhage in 1 patient. We would therefore want to look more carefully at the safety profile of this approach. It is too early to say whether MRD negativity can be achieved in these patients, given that the primary endpoint is not reached until month 16.

Q What are your thoughts about the future of CLL treatment?

A (Owen) Because we are seeing novel targeted therapies that are effective but very expensive, I could see, over time, an approach that uses a MRD strategy to eventually stop therapy in patients achieving a deep remission. The first few cycles of therapy might be given to all patients as a standard approach, and then, in those achieving MRD negativity, treatment could be stopped. In a perfect world, very effective regimens such as venetoclax which can achieve this goal would be available. It will also be important to test for IGHV status, so that we can aim for a cure in young patients with mutated IGHV.

A (Toze) In the near future, patients should be categorized as well as possible at diagnosis, including IGHV, del(17p), and TP53 status. Testing for IGHV and TP53 are not yet available throughout Canada, a situation that needs to change. Before treatment, comorbidities and disease factors have to be considered with the aim of choosing the best front-line therapy. Ongoing trials are testing various treatment strategies: reducing the cycles of CR, sequential debulking, and MRD-driven approaches. Those principles are interesting, but the best of those approaches will have to be examined in phase III trials. Although the strategies are important and theoretically interesting, it will take time to determine which ones will produce the best outcomes in the front-line treatment of CLL.

ACKNOWLEDGMENTS

This article was developed by IMPACT Medicom Inc., with sponsorship provided by Lundbeck Canada Inc.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare the following interests: CO has received speaker fees or honoraria for advisory board participation from AstraZeneca, Merck, Janssen, Roche, Gilead, AbbVie, Celgene, Novartis, and Lundbeck. Her institution has received funding from Roche, Pharmacyclics, Gilead, Celgene, Novartis, Lundbeck, and Pfizer for trials in which she is a co-investigator. CT has received honoraria for advisory board participation from AbbVie, AstraZeneca, Jazz, Gilead, Janssen, Lundbeck, and Roche. Her institution has received funding from Gilead and Janssen for investigator-initiated cll research.

AUTHOR AFFILIATIONS

1Division of Hematology and Hematological Malignancies, University of Calgary and Foothills Medical Centre, Calgary, AB; 2Leukemia/Bone Marrow Transplant Program of British Columbia; University of British Columbia; Division of Hematology, Vancouver General Hospital; and Division of Hematology, BC Cancer Agency, Vancouver, BC; 3IMPACT Medicom Inc., Toronto, ON.

REFERENCES


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