2018

Chronic Lymphocytic Leukemia: A Review of Front-line Treatment Options, With a Focus on Elderly CLL Patients

Alma O’Reilly  
*Institute of Technology Sligo*

James Murphy  
*Institute of Technology Sligo*

Sarah Rawe  
*Dublin Institute of Technology, sarah.rawe@dit.ie*

Mary Garvey  
*Dublin Institute of Technology*

Follow this and additional works at: [https://arrow.dit.ie/scschcpsart](https://arrow.dit.ie/scschcpsart)

Part of the [Chemicals and Drugs Commons](https://arrow.dit.ie/scschcpsart)

Recommended Citation


This work is licensed under a [Creative Commons Attribution-Noncommercial-Share Alike 3.0 License](https://creativecommons.org/licenses/by-nc-sa/3.0/).
Chronic Lymphocytic Leukemia: A Review of Front-line Treatment Options, With a Focus on Elderly CLL Patients

Alma O’Reilly,1 James Murphy,1 Sarah Rawe,2 Mary Garvey1

Abstract
Chronic lymphocytic leukemia (CLL) remains the most prevalent form of leukemia in the Western world, with no cure to date. Ongoing and essential research into this heterogeneous disease has led to a number of new treatment options becoming available to CLL patients in the past decade. The present review presents the recent developments in the field of CLL treatment, with the main focus on elderly patients and CLL patients with coexisting comorbidities. The review discusses the current treatment regimens that provide the most promising outcomes for patients in this subgroup, with a number of important clinical trials summarized. These clinical trials, which have investigated promising single-agent therapies or combination therapies, are discussed, with an emphasis on the efficacy and tolerability for patients aged ≥ 65 years. Also, the misrepresentation of the true CLL population in many clinical trials and the need for better guidelines for participant inclusion criteria to provide a more realistic and accurate study population are noted.

Introduction
Approximately 10% of all cancer cases are blood cancers, with a new diagnosis every 3 minutes in the United States. In Ireland, blood cancer cases are the fourth most common cause of cancer-related deaths.1,2 Blood cancer is a broad term used to classify any cancer that affects the cells of the blood or organs where blood cells develop (ie, bone marrow and lymphatic system). Leukemia, cancer of the white blood cells, is one of the most common types of blood cancer.3 Chronic lymphocytic leukemia (CLL) is the most prevalent leukemia in adults in the Western world and accounts for 25% to 30% of all leukemia types.4 The incidence rate was 4.83/100,000 people in the United States from 1975 to 2014.5 The disease typically affects older people and is rare in those aged < 50 years.6,7 With an ever-aging population due to improved health care and better lifestyles, the average age at the diagnosis for CLL has increased by 6 years during the past decade. The median age at diagnosis was 65 years in the early 1990s,8,9 which has increased to 70 years in the present day.10 Therefore, the need to develop better tolerated treatment options for elderly CLL patients is constant and urgent.

CLL is characterized by a relentless accumulation of CD5+ B lymphocytes in the blood, bone marrow, and secondary lymphoid organs, lymph nodes, and spleen.4 This form of leukemia begins in the bone marrow and affects the lymphocytes. These cells do not mature properly and are unable to perform their immunologic function in fighting infection. The cells also survive longer than needed, eventually building up in the blood and crowding out healthy cells.11

CLL is a heterogeneous disease; thus, in some cases, the disease progresses so slowly treatment is not required, but in others, a more aggressive form of the cancer develops. In many cases, the slow progressive nature of the disease means that one third of patients with CLL never need treatment, with a “watch and wait” approach the standard management for early-stage CLL.6 Once progression has occurred, treatment is required. However, for other patients, the disease can be more aggressive, with poor prognostic factors, leading to fast progression and the need for immediate treatment. A number of genetic factors indicating a more aggressive form of CLL include, but are not limited to, deletion of the short arm of chromosome 17 [del(17p)], deletion of the long arm of chromosome 11 [del(11q)], and a mutation of the tumor suppressor gene for tumor protein
Front-line Treatment for Elderly CLL Patients

53 (TP53). TP53 mutation results in a nonfunctional p53 protein, a protein that plays a key role in signaling the cell to undergo apoptosis. In > 80% of patients presenting with del(17p), a TP53 mutation will coexist on the other allele. In the case of del(11q), the ATM gene will be mutated, another gene important for activation of the apoptosis pathway. The mutation and deletion of such genes leads to nonfunctional proteins that play an important role in inducing apoptosis in the cell, which can severely impair the efficacy of chemotherapy drugs.

Chemotherapy is now the current standard of treatment for CLL patients in general good health. FCR (fludarabine, cyclophosphamide, rituximab) is recommended for fit patients aged < 65 years as first-line treatment, and patients aged > 65 years are typically recommended to receive BR (bendamustine, rituximab). The prevalence of CLL in older people has led to a number of additional factors that should be considered when choosing a course of treatment. Also, many older patients with comorbidities are unsuitable for intense chemoimmunotherapy.

Because older CLL patients can differ dramatically in their physiologic age and pathologic conditions (eg, comorbidities and geriatric syndromes), various treatment options must be available that can cater to both patient-related and disease-related risk factors. Owing to an age-related decline in hematopoietic stem cells, which are necessary for the production of new blood cells by the body, chemotherapy-related myelotoxicities will be more frequent in older patients with CLL. This is a high-risk factor, because the resulting infections or anemia could negatively affect a patient’s current comorbidities and lead to treatment-related morbidity or mortality.

Current Front-line Treatment Options for Elderly CLL Patients

Monoclonal Antibodies

Anti-CD20 antibodies are a group of compounds that are added to chemotherapy regimens to provide a patient with chemoimmunotherapy, a treatment option that has become the reference standard treatment of CLL for fit patients.

**Rituximab.** Since the approval of rituximab in 1997, the type I monoclonal anti-CD20 antibody has been used in the treatment of numerous illnesses, including follicular B-cell lymphoma, aggressive lymphoma, and CLL. Its mode of action involves binding to the CD20 antigen on the surface of B cells. Although some studies showed it to be effective as monotherapy, other study found the antibody had a much greater effect when used in combination with other chemotherapy agents. However, the chemotherapeutic agent with which rituximab is combined must be considered carefully, because the adverse effects of some treatment options will not be tolerable by older patients or patients with comorbidities.

FCR is the reference standard treatment for CLL patients aged < 65 years with otherwise good health and low-risk prognostic factors and who have not received previous treatment. Some older patients with good health and favorable prognostic factors might be suitable for FCR. However, most patients aged > 65 years and patients with comorbidities will not tolerate FCR well. Myelosuppression, a side effect of therapy, causes a decrease in the function of the bone marrow, which leads to low counts of red blood cells, white blood cells, and platelets. It is one of the main side effects leading to the discontinuation of FCR treatment. Myelosuppression and its complications after FCR treatment are more frequent in older patients; thus, a different course of treatment with fewer side effects has been more favorable for this group.

**CLL10 Study**

Patients who are not suitable for FCR as front-line treatment because of age and/or comorbidities have other treatment options available that are better tolerated. The CLL10 study, a comparative study by Eichhorst et al, investigated FCR versus BR as a first-line treatment option for patients with advanced CLL and found BR to be a better tolerated treatment option for older CLL patients, with similar efficacy. Their study included 561 treatment-naive patients with active CLL and in good physical health. The patients were divided into 2 groups: the FCR group (282 patients) and the BR group (279 patients). The age range of the study was 33 to 81 years (median, 61.5 years), and patients with del(17p) were excluded. This trial, and all the trials discussed in this review, are summarized in Table 1. As expected, the FCR group experienced significantly longer progression-free survival (PFS), with a median of 57.6 months compared with 42.3 months for the BR group. When PFS was analyzed by dividing the population into 2 groups stratiﬁed by age (< 65 years vs. > 65 years), a difference was noted. In the younger age group, a significant difference was seen in the median PFS for the 2 treatment arms, with 38.5 months for BR and 53.6 months for FCR. However, when the older age group was analyzed, no significant difference was found. This finding, the finding that FCR treatment was more toxic in the elderly patient group (71% of patients experienced grade 4 adverse effects resulting in life-threatening consequences and/or hospitalization compared with 41% in the BR group), and the greater occurrence of therapy-related myeloid leukemia/myelodysplastic syndrome in the older patient group in the FCR arm, showed that BR is a much better front-line chemoimmunotherapy option for elderly CLL patients not suitable for FCR.

**Rituximab and Hyaluronidase Human**

A new development in the treatment of CLL with FCR has recently been approved by the Food and Drug Administration (FDA). In June 2017, rituximab and hyaluronidase human (RHH) was approved for the treatment of 3 blood cancers: follicular lymphoma, diffuse large B-cell lymphoma, and CLL. Human hyaluronidase is an endoglycosidase, an enzyme that cleaves specific internal glycosidic linkages of oligosaccharides and polysaccharides, leading to a release of oligosaccharides. It increases the rate of dispersion and absorption of drugs coadministered by subcutaneous injection. The approval of this new product has meant that rituximab can be administered in 5 to 7 minutes, a greatly reduced time compared with the standard intravenous administration, which requires several hours. Also, RHH can be used for both treatment-naive and previously treated CLL patients when combined with FC (fludarabine, cyclophosphamide). However, no clinical information is yet available on the use of bendamustine combined with RHH.

**Obinutuzumab.** Obinutuzumab, a glycoengineered type II anti-CD20 monoclonal antibody, also referred to as GA101, has shown great promise for elderly CLL patients with comorbidities...
and was approved by the FDA in November 2013 in combination with chlorambucil for the treatment of CLL. Obinutuzumab showed increased direct cytotoxicity and greater antibody-dependent cellular cytotoxicity. It was proved to have superior antitumor activity compared with rituximab in preliminary studies, resulting in complete tumor remission and increased overall survival (OS). Numerous clinical trials were conducted to determine the safety and effectiveness of obinutuzumab in recent years. Phase I and II clinical trials evaluated the effectiveness of obinutuzumab as monotherapy and showed promise for heavily pretreated CLL patients. These trials showed obinutuzumab was a more effective monotherapy than rituximab and ofatumumab, with greater efficiency of B-cell depletion.

### CLL11 Study

A phase III clinical trial, the CLL11 study, compared the treatment options of obinutuzumab combined with chlorambucil (G+CB), against chlorambucil alone (CB) and rituximab plus chlorambucil (CB+R). The CLL11 trial included 589 patients with previously untreated CLL (summarized in Table 1). For the first stage, the patients were divided into 3 groups, at a 2:2:1 ratio (238 patients in the G+CB group, 233 patients in the R+CB group, and 118 patients in the CB group). The second stage included 192 additional patients, randomly grouped into either the G+CB or R+CB arm. The median age of the trial population was 73 years, with coexisting comorbidities a part of the inclusion criteria (total Cumulative Illness Rating Scale [CIRS] score > 6 and/or creatinine clearance [CrCl] < 70 mL/min). A recent update from that study showed that G+CB almost doubled the median PFS compared with the R+CB combination, extending the PFS to 29.2 months compared with 15.4 months. According to Owen, in many parts of Canada, BR is the preferred treatment option when tolerable. However, for older patients, unfit for the more aggressive treatment of BR, the G+CB combination is now a commonly used regimen in most treatment centers. However, no clinical trial has yet compared BR and G+CB.

#### The GREEN Study

An ongoing phase IIIB clinical trial, called the GREEN study (see Table 1), is comparing the safety of obinutuzumab as monotherapy (G-Mono) or combined with different chemotherapy regimens in both untreated patients and patients with relapsed/refractory (R/R) disease (ie, patients with disease no longer responding to treatment). The combination treatment options analyzed were G+FC for fit patients only (ie, CIRS score of ≤ 6 and CrCl of ≥ 70 mL/min), G+CB for unfit patients only (CIRS score > 6 and CrCl < 70 mL/min) or G+B (obinutuzumab, bendamustine) for any patient. The study is currently active, with an estimated completion date of October 2018. However, the results of the primary analysis of the trial were presented at the 59th annual meeting and exposition of the American Society of Hematology in December 2017. The trial population is 971 patients, divided into 3 patient groups: 339 fit; 291 unfit, and 341 with R/R disease, with a median age of 66 years. The initial report concluded that toxicities were "manageable and no new safety signals were identified." The median observation time for the study to date was 24.5 months. The most frequent adverse effects reported across all treatment options were neutropenia (58.4%), pyrexia (32%), thrombocytopenia (31.2%), nausea (27.8%), and anemia (23.7%), with no significant difference in the 3 patient groups; 80.3% of the patients developed grade ≥ 3 adverse effects, with neutropenia, thrombocytopenia, anemia, and pneumonia the most frequent. A similar frequency of grade ≥ 3 adverse effects were experienced by all 3 patient groups. However, serious adverse effects (neutropenia, pneumonia, and febrile neutropenia) occurred more frequently in the unfit patient group (58.8%) than in the fit patient group (43.7%).

---

**Table 1** Summary of Important Clinical Trials for Determination of Superior Treatment Regimens for Elderly CLL Patients

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Treatment</th>
<th>Patients, n</th>
<th>Median Age, y</th>
<th>Patient Group</th>
<th>Superior Treatment for Age &gt; 65 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL11³⁵</td>
<td>FCR vs. BR</td>
<td>561</td>
<td>61.5</td>
<td>Untreated CLL; del(17p) excluded</td>
<td>BR³⁶</td>
</tr>
<tr>
<td>CLL11³⁵,²⁴</td>
<td>G+OB, CB, R+CB</td>
<td>589</td>
<td>73</td>
<td>Untreated CLL; coexisting health issues</td>
<td>G+CB</td>
</tr>
<tr>
<td>GREEN⁵⁶</td>
<td>G-Mono, G+FC, G+CB, GB</td>
<td>971</td>
<td>66</td>
<td>R/R CLL and untreated CLL</td>
<td>Ongoing³⁶</td>
</tr>
<tr>
<td>COMPLEMENT-1³⁶</td>
<td>O+CB, CB</td>
<td>447</td>
<td>69</td>
<td>Untreated CLL; not suitable for fludarabine-based treatment</td>
<td>O+CB</td>
</tr>
<tr>
<td>COMPLEMENT-2²⁷</td>
<td>O+FC, FC</td>
<td>365</td>
<td>61.5</td>
<td>R/R CLL</td>
<td>NA³⁶</td>
</tr>
<tr>
<td>RESONATE³⁷</td>
<td>I, O</td>
<td>391</td>
<td>67</td>
<td>R/R CLL</td>
<td>Ibrutinib</td>
</tr>
<tr>
<td>RESONATE-2³⁹</td>
<td>I, CB</td>
<td>269</td>
<td>73</td>
<td>Untreated CLL; 65 years &amp; older</td>
<td>Ibrutinib</td>
</tr>
<tr>
<td>HELIOS³⁰</td>
<td>I+BR, CB</td>
<td>578</td>
<td>63.5</td>
<td>R/R CLL</td>
<td>NA³⁶</td>
</tr>
<tr>
<td>CLL14³¹</td>
<td>V+G, G+CB</td>
<td>445</td>
<td>NR yet</td>
<td>Untreated CLL; coexisting health issues</td>
<td>Ongoing³⁶</td>
</tr>
</tbody>
</table>

**Abbreviations:** BR = bendamustine, rituximab; CB = chlorambucil; CLL = chronic lymphocytic leukemia; del(17p) = deletion 17p; FCR = fludarabine, cyclophosphamide, rituximab; G+CB = obinutuzumab, ofatumumab, chlorambucil; G+FC = obinutuzumab, fludarabine, cyclophosphamide; GB = obinutuzumab, bendamustine; G-Mono = obinutuzumab monotherapy; I = ibrutinib; NA = not available; NR = not reported; O = ofatumumab; R+CB = rituximab, chlorambucil; R/R = relapsed/refractory; V+G = venetoclax, obinutuzumab.

¹Although low median age, results for those aged > 65 years were analyzed.

²Estimated completion date October 2018.

³Because of low median age, trial not suitable for determining superior regimen for those aged > 65 years.

⁴Because of low median age, trial not suitable for determining superior regimen for those aged > 65 years.

⁵Estimated completion date September 2021.
A comparison of treatments showed the lowest death rate in the G+FC patient group (4.7%), followed by the GB group (7.8%), G+CB group (7.9%), and G-Mono group (8.7%). However, the G+FC patient group experienced the greatest rate of adverse effects (87.6%) compared with the other treatment groups (G-Mono, 75.4%; G+CB, 76.3%; and GB, 79.7%). The occurrence of grade ≥ 3 adverse effects was also significantly greater, with a greater incidence of infection in the G+FC group (70.5%) than in the other treatment groups (G-Mono, 49%; G+CB, 53%; GB, 52.6%).

With the initial findings of the study showing acceptable safety data in line with data for previously reported obinutuzumab-based treatments, the forthcoming results should help determine the best obinutuzumab treatment combinations for patients of different fitness groups and also for R/R patient groups.

Ofatumumab. Ofatumumab, also known as HuMax-CD20, is a fully human type I anti-CD20 monoclonal antibody that targets a distinct small-loop epitope on the CD20 molecule. Preliminary studies showed greater levels of cytotoxicity with ofatumumab compared with rituximab. Early clinical trials focused on the effectiveness of ofatumumab as a single-agent therapy for patients with R/R disease. These trials concluded that ofatumumab is a well-tolerated, effective treatment for patients with R/R CLL with a poor prognosis. After another clinical trial, by Lemery et al, which analyzed ofatumumab as a treatment of CLL refractory to fludarabine and alemtuzumab, the FDA granted accelerated approval of ofatumumab for R/R CLL.

COMPLEMENT Studies

A phase III clinical trial (COMPLEMENT-1) by Hillmen et al in 2015 studied ofatumumab combined with CB (O+Cb) versus CB alone in the treatment of treatment-naive CLL patients. The study contained 447 patients with active CLL who were unsuitable for fludarabine-based treatment; the median patient age was 69 years. The O+CB group had significantly longer PFS at 22.4 months compared with 13.1 months for the CB group. Although adverse effects were more frequent in the O+CB arm of the study (50% vs. 43% CB), the trial found that front-line treatment with O+CB for elderly patients and patients with comorbidities was an important treatment option for those not suitable for more intense regimens.

The results of another phase III clinical trial, COMPLEMENT-2, considered ofatumumab combination with FC (O+FC) versus FC alone for treatment of relapsed patients were reported by Robak et al. The study, consisting of 365 patients with a median age of 61.5 years, showed that with the O+FC arm of the study, the median PFS of patients was significantly improved at 28.9 months for O+FC versus 18.8 months for FC alone. Of the patients, 74% experienced grade ≥ 3 adverse effects in the O+FC group versus 69% for the FC group. The study concluded that O+FC combination therapy had manageable safety, with increased PFS. A reduced occurrence of thrombocytopenia and anemia was seen with in the O+FC treatment option compared with FC (grade ≥ 3 thrombocytopenia, 14% vs. 25%; and anemia, all grades, 20% vs. 30%), indicating that ofatumumab might help to prevent myelosuppression.

Although no direct comparative study is yet available of O+FC and FCR therapy, an indirect comparison of the COMPLEMENT-2 trial against another phase III trial of previously treated CLL patients who received either FCR or FC (population size, 552 patients; median age, 62.5 years) has indicated that grade ≥ 3 adverse effects were comparable with the 2 treatment options (COMPLEMENT trial: O+FC, 74%; FC, 69%; FCR vs. FC trial: FCR, 80%; FC, 74%). However, a direct comparison trial of O+FC versus FCR is needed to confirm these suggestions and to help determine which treatment option is more efficient and tolerable. If ofatumumab were found to reduce the risk of myelosuppression with FC treatment, this could give more elderly patients a chance of receiving FC-based therapy.

Small Molecules

Three novel agents have recently been approved for treatment of CLL in the United States, 2 kinase inhibitors, ibrutinib and idelalisib, and the Bcl-2 inhibitor venetoclax. No guidelines were available regarding the superiority of the 3 compounds until a recent study by Mato et al in 2017. Their study, which included 683 patients, identified ibrutinib as superior to idelalisib. Where KIs were not effective, venetoclax appeared superior to chemoimmunotherapy combinations. Also, treatment with venetoclax after ibrutinib failure was recommended as a superior treatment option to idelalisib.

Ibrutinib. Ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor, was originally approved by the FDA in 2014 for the treatment of CLL patients who had received ≥ 1 other treatment and for patients with del(17p). It was granted further approval by the FDA as a first-line treatment of CLL in March 2016. The compound, which is an effective treatment for patients with poor prognostic factors, has also shown promising results for the treatment of elderly CLL patients.

Ibrutinib acts downstream of the B-cell receptor pathway, inhibiting BTK, a critical component of the B-cell receptor signaling pathway, which is only essential for B cells; therefore, inhibition of this kinase is not fatal. Both in vitro and in vivo, this BTK inhibitor reduces the ability of microenvironment-induced survival and proliferation of CLL cells. Ibrutinib as front-line therapy for CLL patients with the unfavorable del(17p) resulted in more effective responses than those reported with FCR treatment and is now the standard front-line treatment for this patient group. It is also an alternative treatment option to chemoimmunotherapy for elderly patients.

RESONATE Study

This phase III clinical trial, investigated the use of ibrutinib or ofatumumab as a treatment option for pretreated CLL patients unsuitable for chemoimmunotherapy. The inclusion criteria for the study were patients who had received ≥ 1 previous treatment that had resulted in a short remission time because of one of the following: age > 70 years, coexisting illnesses, or del(17p) CLL. The median age was 67 years, with a study population of 391 patients. The findings of the RESONANTE study showed ibrutinib to be superior to ofatumumab in all subgroups analyzed, including R/R patients, patients with del(17p) and patients aged > 65 years. Thus, the investigators concluded that ibrutinib as a monotherapy is an excellent treatment option for CLL patients unsuitable for immunochemotherapy.
Another phase III clinical trial (RESONATE-2) by Burger et al. in 2015 showed ibrutinib to be a superior treatment regimen to CB in elderly patients. The study included 269 CLL patients aged > 65 years (median age, 73 years) and showed ibrutinib achieved significantly longer PFS than CB. At a median follow-up of 18.4 months, the median PFS had not been reached for ibrutinib versus 18.9 months for CB. The OS with ibrutinib was significantly improved compared with the OS with CB. At 24 months, the corresponding OS rates were 98% and 85%. A follow-up study of the RESONATE-2 study by Barr et al. showed increased PFS for ibrutinib compared with CB at 24 months (89% vs. 34%, respectively). It has been proved that ibrutinib as monotherapy is a treatment option without the use of traditional chemotherapy drugs that can provide a first-line treatment option for elderly patients not suitable for FCR. An indirect comparison of ibrutinib as monotherapy and BR therapy was conducted from the results of 2 phase III clinical trials, the RESONATE and HELIOS (a study of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma) trials, by Hillmen et al. in 2015. The RESONATE trial (discussed previously) had a study population of 391 patients, with a median age of 67 years. The HELIOS trial included a population of 578 patients with a median age of 63.5 years. The HELIOS trial investigated ibrutinib combined with BR (1+BR) versus BR alone as a treatment regimen for previously treated patients. Because these 2 trials had populations with different patient characteristics (eg, age) and exclusion of high-risk factor groups such as del(17p) in the HELIOS trial, the group used patient-level data from both studies to complete the cross-comparison. The results of the cross-comparison of the 2 trials suggested single-agent ibrutinib was a superior treatment option to BR treatment and that the combination regimen of 1+BR had comparable results for PFS and OS compared with ibrutinib alone. However, a direct comparison of ibrutinib monotherapy and 1+BR combination therapy is needed to determine the superiority of the 2 regimens.

In the HELIOS trial, the combination of 1+BR for patients suitable for BR therapy resulted in significantly improved outcomes with no new safety signals and a manageable safety profile. This suggests that 1+BR could be a superior treatment regimen for elderly patients eligible for BR therapy.

**Idelalisib.** Idelalisib is an orally available, highly specific, and reversible kinase inhibitor that targets the phosphatidylinositol 3 kinases (PI3Ks). PI3Ks are essential for the activation, proliferation, migration, and survival of B cells, along with their homing and retention in lymphoid tissue. Idelalisib has been shown to be an effective treatment option for patients with R/R CLL, even patients with poor prognostic factors. A phase II clinical study reported in 2014 by Zelenetz et al. of idelalisib as monotherapy for previously untreated elderly patients (age > 65 years) showed encouraging results with a manageable safety profile. Another phase II trial by O’Brien et al. in 2015 showed promising results for a combination regimen of idelalisib plus rituximab for treatment-naive elderly patients (median age, 71 years). In that trial, the overall response rate for patients with a del(17p) or TP53 mutation was 100%, and the overall response rate for unmutated immunoglobulin heavy chain variable genes, another poor progression factor, was 97%. After a 36-month period, the PFS rate was 83%. The advantage of this combination compared with either agent as monotherapy was the shortened duration of lymphocytosis (high lymphocyte count) and improved PFS times, response rates, and OS. These findings revealed the excellent potential for idelalisib as a treatment regimen for elderly patients and patients with poor prognostic factors.

However, further investigations have raised concern about idelalisib, and it is not thought to be a safe monotherapy for treatment-naive patients. Idelalisib was approved by the FDA in July 2014 for combination treatment with rituximab for R/R CLL but not for use as a first-line treatment option for CLL. However, since approval by the FDA, at least 6 clinical trials involving idelalisib were stopped because of severe adverse effects and toxicity leading to death. In March 2016, the FDA announced they were reviewing the findings of the clinical trials and alerted health care professionals of “increased rates of adverse effects” with idelalisib. At present, the FDA is reviewing the results of the clinical trials and has warned of the increased rates of adverse events, including death.

**Venetoclax.** Venetoclax, also referred to as ABT-199, is an anti-apoptotic Bcl-2 inhibitor that received accelerated US FDA accelerated approval in 2016 for the treatment of relapsed del(17p) CLL, because it was proved to be highly effective in the treatment of R/R CLL. Venetoclax has been proved to be highly active in patients with poor prognostic factors such as del(17p), with preclinical data showing the ability of the inhibitor to kill CLL cells and spare healthy T cells, granulocytes, and platelets. Bcl-2 is a prosurvival protein. Its function is to inhibit the actions of proapoptotic proteins such as BAX/BAK. When Bcl-2 is inhibited in the cell, the activation of such proapoptotic proteins is triggered. The Bcl-2 protein is known to be critical for B-cell survival, and proteins such as Bcl-xL are more important for the survival of other lymphocytes such as T cells and granulocytes. Thus, venetoclax is selective to B cells. However, the compound is as potent on non-CLL phocytes such as T cells and granulocytes. Therefore, venetoclax is selective to B cells. However, the compound is as potent on non-CLL phocytes such as T cells and granulocytes. Thus, venetoclax is selective to B cells. However, the compound is as potent on non-CLL phocytes such as T cells and granulocytes. Thus, venetoclax is selective to B cells. However, the compound is as potent on non-CLL phocytes such as T cells and granulocytes. Thus, venetoclax is selective to B cells. However, the compound is as potent on non-CLL cells as on CLL B cells. Venetoclax has been shown to produce promising results both as monotherapy and combined with rituximab.

Although venetoclax has been shown to be an efficient treatment for R/R CLL patients, the use of the Bcl-2 inhibitor in a treatment regimen for elderly CLL patients is not clear. A number of clinical trials are underway assessing the efficacy and safety of venetoclax as monotherapy and in combination therapies (V [venetoclax]+BR for R/R and previously untreated patients, G+V vs. G+CB for previously untreated patients, V+G+I in R/R and previously untreated patients, and V+I in treatment-naive patients). One such trial, the CLL14 study, focusing on treatment-naive CLL patients with coexisting medical issues, is a phase III study of the efficacy and safety of V+I combination therapy versus G+CB. The CLL14 trial is currently active and has 445 participants enrolled. Although no results have yet been reported, a run-in safety phase was conducted. That phase included 13 patients with a median age of 75 years; it found no initial safety risks, and the
Front-line Treatment for Elderly CLL Patients

CLL14 trial opened in August 2015. The anticipated results from this study, summarized in Table 1, and from the numerous other clinical trials actively investigating the safety and efficiency of venetoclax as both mono-therapy and in combination therapies will help advise health care professionals on the uses of these regimens for elderly patients with active CLL.

Upcoming Clinical Trials

According to the US National Library of Medicine, almost 200 clinical trials are currently recruiting CLL patients. These trials are investigating numerous novel treatment options and new combinations of currently approved therapies with the purpose of further improving the progress of CLL treatment. However, a common misrepresentation of the CLL population exists in a large number of clinical trials. Although the median age at diagnosis for the disease has been 70 years, with many patients not requiring immediate treatment, the average age in many clinical trials has been < 65 years, with some studies setting the age criterion at 18 to 70 years and thereby preventing patients aged > 70 years from participating in the trial. In addition to age, the exclusion criteria for many studies prohibit the recruitment of patients with common health issues, which are representative of the overall CLL population. The Eastern Cooperative Oncology Group (ECOG) performance status is a scale from 0 to 5 used to measure a patient’s level of function and ability to conduct daily tasks. For a large number of clinical trials, an ECOG level of 0 to 2 has been accepted for inclusion in the study (an ECOG performance status of 2 indicates the patient is ambulatory and capable of all self-care but unable to carry out any work activities and is up and about for > 50% of waking hours). Patients with an ECOG status of ≥ 3 (with 3 indicating the patient is capable of only limited self-care and is confined to a bed or chair for > 50% of waking hours) are often excluded from participation in clinical trials, although a high proportion of CLL patients might be at this ECOG level. A study of small-cell lung cancer, which considered the uptake and tolerance of chemotherapy for patients aged ≥ 75 years, found that 39% of patients aged 75 to 79 years were considered to be at ECOG level 3 or 4.

Conclusion

Although significant progress has been made in the field of CLL treatment in the past 2 decades, CLL remains an incurable disease. The available options for patients with poor prognostic factors and elderly patients with comorbidities are increasing rapidly, with better tolerated therapies and more effective outcomes. However, elderly patients and patients with coexisting comorbidities, which account for a high percentage of the CLL population, are still significantly underrepresented in the field of clinical research. This has led many unanswered questions and insecurities when choosing the most effective and best-tolerated regimens for patients in these categories. The overall CLL population should be better represented in clinical trials with guidelines to ensure that trial participants are chosen as a true reflection of the disease characteristics needed to provide more accurate information on the treatment regimens.

Acknowledgments

The present study was funded by Sligo Institute of Technology (Sligo, Ireland).

Disclosure

The authors have stated that they have no conflicts of interest.

References

47. Owen C. Canadian perspective by Dr. Carolyn Owen on the updated analysis of
39. Yamamoto K. Endo-enzymes. In: Stress and immunity (Ishizaka, K. and
38. Mossner E, Brunker P, Moser S, Puntener U. Increasing the ef
37. US National Library of Medicine. A study to compare the ef
36. Love N. Final Analysis of the phase III CLL10 study: FCR versus BR in physically
32. US National Library of Medicine. A study to compare the ef
29. US National Library of Medicine. A study to compare the ef
27. US Food and Drug Administration. Approved drugs: FDA approves rituximab plus
25. Food and Drug Administration. GAZYVA (obinutuzumab)—BLA approval, 2013.
21. Love N. Final Analysis of the phase III CLL10 trial: FCR versus bendamustine
20. Love N. Final Analysis of the phase III CLL10 trial: FCR versus bendamustine
1. National Cancer Institute. FDA approval for idelalisib. Available at: https://www. Clinical Lymphoma, Myeloma & Leukemia Month 2018
Front-line Treatment for Elderly CLL Patients


