Signaling the End of Chronic Lymphocytic Leukemia:

New Frontline Treatment Strategies

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Abstract

The management of chronic lymphocytic leukemia (CLL) is undergoing profound changes. Several new drugs have been approved for CLL treatment (fludarabine, bendamustine and the monoclonal antibodies, alemtuzumab, rituximab, and ofatumumab) and many more drugs are in advanced clinical development to be approved for the treatment of CLL. In addition, the extreme heterogeneity of the clinical course as well as our improved ability for foreseeing the prognosis of this leukemia by the use of clinical, biological and genetic parameters now allow us to characterize patients with a very mild onset and course, an intermediate prognosis and a very aggressive course with high risk leukemia. On this background it becomes increasingly challenging to select the right treatment strategy for each condition. This paper summarizes the currently available diagnostic and therapeutic tools and gives an integrated recommendation of how to manage CLL in 2013. Moreover, it tries to give a perspective how we might integrate the novel agents for CLL therapy into sequential treatment approaches in the near future.

Overview

With an age-adjusted incidence of 4.3/100,000 inhabitants in the United States, chronic lymphocytic leukemia (CLL) is the most common type of leukemia in western countries. More than 15,000 newly diagnosed cases and approximately 4,500 deaths are currently estimated. The median age at diagnosis lies between 67 and 72 years. More male than female patients are affected by this disease.

CLL is characterized by the clonal proliferation and accumulation of mature, typically CD5-positive B-cells within the blood, bone marrow, lymph nodes and spleen. The leukemic transformation is initiated by specific genomic alterations, in particular deletions on the long arm of chromosome 13 (del(13q14)). Some of these aberrations cause the deletion of specific micro-RNA genes and increasing the resistance of B cells towards apoptosis. Additional aberrations of the long arm of chromosome 11 (del(11q)), of the short arm of chromosome 17 (del(17p)) and trisomy 12 seem to occur later in the course of the disease and predict a worse outcome. In addition, whole genome sequencing has uncovered recurrent somatic gene mutations that occur in CLL cells in parallel to the above-mentioned structural genomic aberrations. Of these, mutations affecting the genes NOTCH1, MYD88, TP53, ATM and SF3B1 seem to be more common and to have prognostic impact.

It has become increasingly clear that survival of CLL cells is not a cell-autonomous, genetically determined process. Instead, survival of CLL cells strictly depends on a permissive microenvironment composed of cellular components like macrophages, T-cells, or stromal follicular dendritic cells, which provide essential proteins (chemokines, cytokines, and angiogenic factors) for activation of crucial survival and pro-proliferative signaling pathways of transformed cells. In addition, stimulation of the B-cell receptor (BCR) also drives the activation of different tyrosine kinases, such as Bruton’s tyrosine kinase (BTK), Spleen tyrosine kinase (Syk), ZAP70, Src family kinases (in particular Lyn kinase) as well as phosphatidylinositol 3-kinase (PI3K) that stimulate malignant B-cell survival in part via activa-
tion of transcription factors such as NF-κB. The importance of BCR signaling is underscored by the fact that different features of the BCR have been recognized as a prognostic marker in CLL, such as the degree of immunoglobulin heavy chain variable gene (IGHV) mutations or IGHV stereotypy (reviewed in ). These pathways have recently gained in importance, since they can be inhibited by specific small molecule inhibitors that show clinical efficacy in lymphoid malignancies. Excellent reviews have recently summarized these BCR-mediated pathways and the corresponding therapeutic inhibitors. In some contrast, this review intends to provide an up date of the current state-of-the-art of CLL therapy and to propose strategies on how to integrate these novel inhibitors into future CLL thera-

**Standard of care using the currently approved agents**

**Cyto static agents**

Monotherapy with alkylating agents has served as initial, front-line therapy for CLL, and chlorambucil was the “gold standard” of CLL therapy for several decades. Even today, this drug remains an appropriate option for frail elderly or unfit patients. The advantages of chlorambucil are its moderate toxicity, low cost and convenience as an oral drug; the major disadvantages are its low to non-existent complete remission (CR) rate and some side effects that occur after extended use (prolonged cytopenia, myelodysplasia and secondary acute leukemia). Novel results indicate that chlorambucil monotherapy may be used less frequently, since the combination with anti-CD20 antibodies has proven more effective (see below).

Three purine analogues are currently used in CLL: fludarabine, pentostatin, and cladribine (2-CdA). Fludarabine remains by far the best-studied compound of the three in CLL. Fludarabine induced more remissions and more CR (7%-40%) than other conventional chemotherapy, like CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CAP (cyclophosphamide, doxorubicin, prednisone), or chlorambucil, but did not improve overall survival (OS) when used as single agent. Similarly, cladribine monotherapy was shown to produce a higher CR rate than chlorambucil plus prednisone (47% versus 12%) without resulting in a longer survival. More recently, bendamustine was compared to chlorambucil in a randomized trial. Bendamustine produced improved responses but greater toxicity and no OS benefit. The OR rate and median progression free survival (PFS) were 67% and 22 months respectively for bendamustine versus 30% and 8 months for chlorambucil (both p<0.0001).

**Antibodies**

Rituximab. In CLL, the anti-CD20 antibody rituximab is less active as a single agent than in follicular lymphoma, unless very high doses are used. In contrast, combinations of rituximab with chemotherapy have proven to be very efficacious therapies for CLL (see below). Some newer CD20-antibodies challenge rituximab.

Ofatumumab is a fully humanized antibody targeting a unique epitope on the CD20 molecule expressed on human B-cells, resulting in increased binding affinity to CD20, prolonged dissociation rate and increased cell kill due to greater complement-dependent cytotoxicity (CDC) and similar antibody-dependent cellular cytotoxicity (ADCC) activ-
ity compared to rituximab, especially in cells expressing low levels of CD20. Ofatumumab has shown some efficacy in patients that are fludarabine and alemtuzumab-refractory or have bulky disease (> 5 cm). The overall response rate was 58% in the FA-refractory group and 47% in the bulky disease group. However, there has been no formal comparative trial of rituximab versus ofatumumab. Therefore, value of ofatumumab for the treatment of B-cell lymphoma and CLL remains unclear.

**Alemtuzumab** is a recombinant, fully humanized, monoclonal antibody against the CD52 antigen. Monotherapy with alemtuzumab has produced response rates of 33% to 53%, with a median duration of response ranging from 8.7 to 15.4 months, in patients with advanced CLL who were previously treated with alkylating agents and had failed or relapsed after second-line fludarabine therapy. In addition, alemtuzumab has proven effective in patients with high-risk genetic markers such as deletions of chromosome 11 or 17 (del(11q) and del(17p)) and TP53 mutations. Therefore, alemtuzumab is a reasonable therapeutic option for patients with these poor prognostic features. In a prospective randomized study alemtuzumab was tested against chlorambucil. Alemtuzumab led to a greater OR and CR (p<0.0001), superior PFS with a 42% reduction in risk of progression or death (p<0.0001) and significantly longer median time to progression (TTP) (p=0.0001). Therefore, the drug remains a valuable treatment option for high-risk patients. Unfortunately, the drug is no longer licensed, but remains available in some countries on a compassionate use basis.

**Combination chemotherapy**

A major advance in CLL treatment was achieved by the combined use of different treatment modalities. Since purine analogs and alkylating agents have different mechanisms of action and partially non-overlapping toxicity profiles, they were combined both in pre-clinical and clinical studies. The most thoroughly studied combination chemotherapy for CLL is fludarabine plus cyclophosphamide (FC) given as oral drugs or intravenous infusions. In non-comparative trials, the overall response rates did not appear to be better than with fludarabine alone, but the addition of cyclophosphamide appeared to improve the CR rate up to 50%. Three randomized trials have shown that FC combination chemotherapy improves the CR and OR rate and PFS as compared to fludarabine monotherapy. The rate of severe infections was not significantly increased by the FC combination despite a higher frequency of neutropenias. An updated analysis of the CLL4 trial of the German CLL Study Group (GCLLSG) suggested that the first-line treatment of CLL patients with FC combination might improve the OS of the non-high risk CLL patients (all patients not exhibiting a del(17p) or TP53 mutation).

The Polish Adult Leukemia Group (PALG) compared 2-CdA alone to 2-CdA combined with cyclophosphamide (CC) or to cyclophosphamide and mitoxantrone (CMC) in 479 cases with untreated progressive CLL. Surprisingly, the CC combination therapy did not produce any benefit in terms of progression free survival or response rates when compared to 2-CdA alone.
**Chemoimmunotherapy**

**Combinations using rituximab.** Phase II studies suggested that rituximab combinations with fludarabine or fludarabine-based regimens would produce significant improvements in all major outcome parameters such as CR rates, PFS and overall survival (for a review see 36). The largest of these trials conducted on 300 patients with previously untreated CLL showed that rituximab plus fludarabine/cyclophosphamide (FCR) achieved an overall response rate of 95%, with CR in 72%.37 Six-year overall and failure-free survival was 77% and 51%, respectively and median time to progression was 80 months.

These results led the GCLLSG to conduct a randomized trial, the CLL8 protocol, on 817 patients, median age 61 years, with good physical fitness who received 6 courses of FC (n= 409) or FCR (n=408).38 FCR treatment was more frequently associated with CTC grade 3 and 4 neutropenia (FCR 34%; FC 21%), without any formal recommendation to use growth factor support. Other grade 3 or 4 side effects including infections were not increased. FCR induced a higher OR rate than FC (92.8% versus 85.4%) and more CR (44.5% versus 22.9%) (p<0.001). Most importantly, this trial was the first to show that the choice of a first-line therapy has an impact on overall survival of CLL patients. In an updated analysis of at a median follow up of 5.9 years, 38.0% of the patients in the FCR group were free of disease progression compared with 27.4% in the FC group (hazard ratio, 0.6 (CI 95%, 0.5 – 0.7), p<0.0001).39 At the same time-point, 69.4% of the patients were alive in the FCR group versus 62.3% in the FC group (hazard ratio, 0.7 (95% CI, 0.5 – 0.9), p=0.001). Median OS was not reached for patients in the FCR group, while median OS was 86.0 months (95% CI, 78.7 – 93.2 months) for the FC group (p = 0.001).39 FCR did not improve the survival of patients with a del(17p). Similar results were obtained in a trial comparing FCR to FC in relapsed CLL, without demonstrating a benefit for OS.40

Since CLL often occurs in elderly patients with relevant comorbidities, a dose-modified FCR-Lite regimen was designed to maintain the efficacy but decrease the toxicity of the FCR regimen.41 This regimen reduced the dose of fludarabine and cyclophosphamide and increased the dose of rituximab and used a maintenance regimen for rituximab given every 3 months until progression. The CR rate was 77% for 50 previously untreated CLL patients with an OR rate of 100%. Grade 3/4 neutropenia was documented in only 13% of cycles, which is lower than observed with the usual FCR regimen.

Following a similar concept, the CLL11 protocol of the GCLLSG was designed to test chemoimmunotherapies with anti-CD20 antibodies combined with a milder chemotherapeutic component, chlorambucil (CLB), in previously untreated CLL patients with comorbidities.42 The rationale of this study was based on encouraging results obtained in phase II trials using CLB in combination with rituximab (RCLB).43,44 The CLL11 trial compared CLB alone versus a new anti-CD20 antibody, obinutuzumab (GA101; see below), plus CLB (GCLB) versus rituximab (R) plus CLB (RCLB). The study included treatment-naïve CLL patients with a Cumulative Illness Rating Scale (CIRS) total score >6 and/or an estimated creatinine clearance (CrCl) <70 mL/min. Treatment consisted of CLB alone (0.5 mg/kg p.o. d1, d15 q28 days, 6 cycles), GCLB (100 mg iv d1, 900 mg d2, 1000 mg d8, d15 of cycle 1, 1000 mg d1 cycles 2-6), or RCLB (375 mg/m2 iv d1 cycle 1, 500 mg/m2 d1 cycles 2-6).42 The median age of patients was 73 years, the median CIRS score
was 8. So far, the results obtained allow to conclude that chemoimmunotherapy with one of the two anti-CD20 antibodies increases the ORR, allows to achieve complete remissions (22% vs. 8% vs. 0%; GCLB vs. RCLB vs. CLB) and seems to prolong PFS from 11 months (CLB) to 16 or 23 months (RCLB or GCLB), respectively. The major pronounced side effects were grade 3-4 infusion-related reactions with GCLB at the first infusion. Taken together, chemoimmunotherapy with anti-CD20 antibodies is a potent treatment concept in CLL patients with comorbidity as well.

Other variations have been tested to further improve the efficacy of the FCR regimen: Alemtuzumab (A) was added to FCR (CFAR) in a phase II trial on 60 high-risk untreated patients < 70 years with serum beta-2-microglobulin ≥ 4 mg/L. CR was achieved in 70%, PR in 18%, nodular PR in 3%, for an overall response of 92%. Of 14 patients with 17p deletion, eight (57%) achieved a CR. Grade 3/4 neutropenia and thrombocytopenia occurred with 33% and 13% courses, respectively. The median progression-free survival was 38 months and median OS was not reached. Therefore, CFAR might be helpful in cases of high-risk CLL where an effective cytoreductive therapy is desired before an allogeneic stem cell transplant. In another study on seventy-two untreated CLL patients </= 70 years, mitoxantrone was combined at 6 mg/m² on day 1 of each cycle with FCR. The overall response, minimal residual disease (MRD)-negative complete response (CR), MRD-positive CR, and PR rates were 93%, 46%, 36%, and 11%, respectively. Severe neutropenia developed in 13% of patients. These results do not justify the broad use of this regimen outside of clinical trials.

An alternative idea was to replace fludarabine in the FCR regimen with pentostatin (PCR) in order to reduce myelotoxicity. In a phase III randomized trial comparing FCR to PCR in previously untreated or minimally treated CLL patients, there were no statistical differences between treatments in OS or response rates. Moreover, this trial did not demonstrate a lower infection rate with PCR.

**Bendamustine** has been also combined with **rituximab** (BR) in 81 patients with relapsed CLL. Patients received 70 mg/m² of bendamustine on days 1 and 2 and 375 mg/m² of rituximab on day 0 of the first cycle and 500 mg/m² on day 1 of subsequent cycles administered every 28 days for up to 6 cycles. On the basis of intent-to-treat analysis, the overall response rate was 59.0% (95% CI, 47.3% to 70.0%). Complete response, partial response, and nodular partial response were achieved in 9.0%, 47.4%, and 2.6% of patients, respectively. Overall response rate was 45.5% in fludarabine-refractory patients and 60.5% in fludarabine-sensitive patients. Among genetic subgroups, 92.3% of patients with del(11q), 100% with trisomy 12, 7.1% with del(17p), and 58.7% with unmutated IGHV status responded to treatment. After a median follow-up time of 24 months, the median event-free survival was 14.7 months. Severe infections occurred in 12.8% of patients. Grade 3 or 4 neutropenia, thrombocytopenia, and anemia were documented in 23.1%, 28.2%, and 16.6% of patients, respectively.

The BR regimen was also investigated as first-line therapy in 117 CLL patients (age 34 to 78 years). Bendamustine was administered at a dose of 90 mg/m² on day 1 and 2 combined with 375 mg/m² rituximab on day 0 of the first course and 500 mg/m² on day 1 during subsequent courses for up to six courses. Overall response rate was 88.0% (95% CI, 80.7% to 100.0%) with a complete response rate of 23.1% and a partial response rate of 64.9%. Ninety percent of patients with del(11q), 94.7% with trisomy 12, 37.5% with del(17p), and 89.4% with unmutated IGHV status
responded to treatment. After a median observation time of 27.0 months, median event-free survival was 33.9 months, and 90.5% of patients were alive. Grade 3 or 4 severe infections occurred in 7.7% of patients. Grade 3 or 4 adverse events for neutropenia, thrombocytopenia, and anemia were documented in 19.7%, 22.2%, and 19.7% of patients, respectively. Overall, these results suggest that when compared to FCR, BR is somewhat less active, yielding lower CR rates, but is also less myelotoxic. The CLLSG currently compares BR to FCR in a randomized phase III trial, the CLL10 protocol.

Several other combinations have been investigated, like cladribine with rituximab, methylprednisolone plus rituximab followed by alemtuzumab or rituximab plus alemtuzumab. Their detailed description is beyond the scope of this paper, since none of them has been proven to result in higher efficacy when compared to FCR.

**Combinations using alemtuzumab.** The synergistic activity of fludarabine and alemtuzumab was initially suggested by the induction of responses, including one CR, in 5 of 6 patients who were refractory to each agent alone. The combination of fludarabine and alemtuzumab (FA) was investigated in a Phase II trial enrolling patients with relapsed CLL using a four-weekly dosing protocol. This combination has proven feasible, safe, and effective. Among the 36 patients, the ORR was 83% (30/36 patients), which included 11 CRs (30%) and 19 PRs (53%); there was one stable disease (SD). Sixteen of 31 evaluated patients (53%) achieved MRD negativity in the peripheral blood by 3 months’ follow-up. Resolution of disease was observed in all disease sites, particularly in the blood, bone marrow and spleen. The FA therapy was well tolerated. Infusion reactions (fever, chills and skin reactions) occurred primarily during the first infusions of alemtuzumab, and were mild in the majority of patients. While 80% of patients were cytomegalovirus immunoglobulin G (CMV IgG)-positive before treatment, there were only two subclinical CMV reactivations. The primary grade 3/4 hematological events were transient, including leukocytopenia (44%) and thrombocytopenia (30%). Stable CD4+ T-cell counts (> 200/µl) were seen after 1 year.

Two phase III trials tested alemtuzumab in combination with FC (FCA) or fludarabine (FA). One trial comparing FCA to FCR in first-line therapy was closed prematurely due to the higher toxicity and treatment-related mortality observed in the FCA arm. The therapeutic efficacy of FCR was clearly superior to FCA. In this trial, alemtuzumab was given subcutaneously. A second randomized trial compared FA to fludarabine monotherapy in previously treated patients with relapsed or refractory CLL. In this trial, alemtuzumab was given intravenously. FA (n=168) resulted in better PFS than fludarabine monotherapy (n=167; median 23.7 months vs. 16.5 months; hazard ratio 0.61; p=0.0003) and overall survival (median not reached vs. 52.9 months; HR 0.65; p=0.021) compared with fludarabine alone. Adverse events occurred in 161 (98%) of 164 patients in the FA group and 149 (90%) of 165 in the fludarabine alone group. Patients in the FA group had more CMV events (14% vs. <1%) and grade 1 or 2 infusion-related adverse reactions (62% vs. 13%). Major grade 3 or 4 toxicities in the FA and monotherapy groups were leucopenia (74% vs. 34%), lymphopenia (94% vs. 33%), neutropenia (59% vs. 68%), thrombocytopenia (11% vs. 17%), and anemia (9% vs. 17%). The incidence of serious adverse events was higher in the FA group (33% vs. 25%); deaths due to adverse events were similar between the two groups (6% vs. 12%).
Two phase II trials investigated alemtuzumab in combination with high dose corticosteroids, which seem to be a good therapeutic option, in particular for patients with del(17p). The combination of alemtuzumab and methylprednisolone was tested in the UK CLL206 trial on 17 untreated and 22 previously treated patients with del(17p). The ORR and CR rate were 85% and 36% in the whole cohort, and 88% and 65% in treatment naïve patient group.\textsuperscript{54} In the CLL20 trial of the GCLLSG the combination of alemtuzumab and high dose dexamethasone resulted in an ORR above 90% in treatment naive high-risk patients.\textsuperscript{55}

### Selecting the right treatment: how to treat CLL with the currently approved agents?

Given the impressive number of novel drugs, the right choice of treatment for a given CLL patient has become a task that requires experience, a good clinical assessment of the patient and an appropriate use of diagnostic tools. The following parameters should be considered before recommending a treatment for CLL:\textsuperscript{56} 1. The clinical stage of disease; 2. the fitness of the patient; 3. the genetic risk of the leukemia. 4. The treatment situation (first versus second-line, response versus non-response of the last treatment). With the use of these four parameters, the following recommendations can be given (Figures 1a and 1b):

#### First-line treatment

(Figure 1a). In a patient with advanced (Binet C, Rai III-IV) or active, symptomatic disease, treatment should be initiated. In this situation, patients need to be evaluated for their physical condition (or comorbidity). For patients in good physical condition (“go go”) as defined by a normal creatinine clearance and a low score at the “cumulative illness rating scale” (CIRS),\textsuperscript{57} patients should be offered chemoimmunotherapies such as FCR or FR in order to achieve sustained remissions.

Patients with a somewhat impaired physical condition (“slow go”) may be offered either chlorambucil in combination with an anti-CD20 antibody\textsuperscript{42} or a dose-reduced fludarabine-containing regimen with a CD20 antibody. The aim of therapy in this situation is symptom control.

Patients with symptomatic disease and with del(17p) or TP53 mutations may receive FCR or BR or an alemtuzumab-containing regimen as first-line treatment. In general, these regimen all yield response rates above 50%, but the time to progression tends to be shorter than 2 years. The recent results obtained with single-agent ibrutinib in refractory or relapsed patients with a del(17p) showed an overall response rate of 68%, with a progression-free survival at 26 months of 57% and an overall survival of 70%.\textsuperscript{58} While these results appear very encouraging, none of these therapies promises long-lasting remissions. Therefore, an allogeneic stem cell transplantation should still be offered and discussed in patients with sufficient physical fitness.

#### Second-line treatment

(Figure 1b). As a general rule, the first-line treatment may be repeated, if the duration of the first remission exceeds 24 months provided that the first-line therapy was well tolerated.

The choice becomes more difficult and limited in treatment-refractory CLL, in patients relapsing within 24 months post treatment or in cases with the chromosomal aberration del(17p). In principle, the initial regimen should be changed. The following options exist as a relapse therapy for patients no longer responding to
chemoimmunotherapy with rituximab: 1. Alemtuzumab alone or in combinations, in particular with high dose steroids; \textsuperscript{26,5,154} 2. combinations of antibodies with lenalidomide (see below); 3. BTK inhibitors such as ibrutinib,\textsuperscript{58} where available, or experimental protocols using novel agents (Table 1 and Figure 2). 4. Allogeneic stem cell transplantation with curative intent.\textsuperscript{59}

The choice of one of these options depends on the fitness of the patient, the availability of some drugs and the prognostic risk of the leukemia as defined by molecular cytogenetics. According to recommendations of an EBMT consensus group, physically fit patients with refractory CLL or with a \textit{del(17p)} should be offered an allogeneic transplantation, since their prognosis so far has remained extremely poor with conventional therapies.\textsuperscript{59} Finally, it is important to emphasize that patients with refractory disease should be treated within clinical trials whenever possible. Some of the new drugs, in particular ibrutinib or ABT-199 show good responses in these risk patients and could become an additional option in the very near future.

New drugs targeting pathogenic pathways of CLL cells

There are an increasing number of interesting new compounds in clinical development (for reviews see \textsuperscript{10,60}). The common denominator of these compounds is that their mechanism of action targets a relatively specific signaling abnormality or redirects the immune system against CLL cells. A detailed description of these fascinating agents is beyond the scope of this paper. Therefore, Table 1 lists the some of the most promising agents and their stage of clinical development. Table 1 also illustrates that these agents may yield high response rates above 50\% even in relapsed and refractory CLL patients. Some of these agents (e.g. obinutuzumab, CART19, ABT-199, Idelalisib and Ibrutinib) currently elicit the greatest enthusiasm and hope both amongst CLL patients and their treating physicians.

New anti-CD20 antibodies

\textbf{Obinutuzumab (GA101).} The humanized and glyco-engineered monoclonal antibody obinutuzumab showed impressive results \textit{in vitro} with higher rates of apoptosis in malignant B-cells in comparison with rituximab.\textsuperscript{61} The humanization of the parental B-Ly1 mouse antibody and subsequent glyco-engineering lead to higher affinity binding to CD20 type II epitope, increased antibody-dependent cellular cytotoxicity (ADCC), low complement-dependent cytotoxicity (CDC) activity, and increased direct cell death induction.\textsuperscript{62} A phase-I study with obinutuzumab showed promising results in 13 CLL patients.\textsuperscript{63} Major side effects included infections, neutropenia, thrombocytopenia and tumor lysis syndrome, which all resolved. There were no dose-limiting toxicities. Encouraging results were reported in the run-in phase of the CLL11 trial on CLL patients with increased comorbidity.\textsuperscript{64} Six subjects older than 70 years (median age 76 years; median cumulative illness rating score of 8) received 6 x 28-day cycles of obinutuzumab (1000 mg on day 1, 8 and 15 of cycle 1 and day 1 of cycles 2-6) plus chlorambucil (0.5 mg/kg on day 1 and 15 of each cycle). Infusion-related reactions occurred in 5 patients, but were mild. Grade 3/4 neutropenia were seen in 5 patients. No febrile neutropenia’s or grade 3/4 infections were observed. All subjects completed therapy. Complete responses were documented in 2 patients while 4 responded partially. After a median follow-up of 23 months from start of treat-
ment, none of the patients had progressed with CLL or died. Results of a planned interim analysis of the CLL11 trial have been recently reported and confirmed the very promising activity of obinutuzumab in CLL.\textsuperscript{42}

**Agents targeting B-cell receptor signaling**

The following section will describe selected kinase inhibitors, which have entered testing in phase III trials for CLL patients (Table 1).

**Idelalisib (CAL-101).** Class I phosphatidylinositol 3-kinases (PI3Ks) regulate cellular functions relevant to oncogenesis.\textsuperscript{65} Expression of the PI3K p110δ isoform (PI3Kδ) is restricted to cells of hematopoietic origin where it plays a key role in B-cell proliferation and survival. In CLL the PI3K pathway is constitutively activated and dependent on PI3Kδ.\textsuperscript{66} CAL-101 is an oral PI3Kδ-isoform-selective inhibitor, which promotes apoptosis in primary CLL cells in a time- and dose-dependent manner without inducing apoptosis in normal T-cells or natural killer cells and without diminishing antibody-dependent cellular cytotoxicity. CAL-101 inhibits CLL cell chemotaxis toward CXCL12 and CXCL13 and migration beneath stromal cells (pseudoemperiploesis). CAL-101 also down-regulates secretion of chemokines in stromal cocultures and after BCR triggering.\textsuperscript{66} CAL-101 reduces survival signals derived from the BCR or from nurse-like cells, and inhibits BCR- and chemokine-receptor-induced AKT and MAP kinase (ERK) activation.\textsuperscript{66}

In a phase I clinical trial in 54 heavily pre-treated and high-risk CLL patients, idelalisib showed acceptable toxicity, positive pharmacodynamic effects and favorable clinical activity (high level of lymph node regression and prolonged duration of symptomatic tumor control).\textsuperscript{67} An ORR of 56% was achieved with 2 CR and 28 PR. Of the 28 patients with PR, 6 showed persistent lymphocytosis. The majority of patients (81%) showed a lymph node response (≥50% reduction in the nodal SPD). Median PFS was 17 months. Side effects were mild, with fatigue, diarrhea, pyrexia, rash and upper respiratory tract infections being the most frequent. More importantly, there were no dose-limiting toxicities. Results on idelalisib in combination with rituximab, ofatumumab, or bendamustine/rituximab were presented in preliminary form and showed encouraging results. For example, a trial using a combination of idelalisib and rituximab as a first line therapy in 64 patients yielded a ORR of 97% with 19% CR.\textsuperscript{68} Side effects were mild, with 23% diarrhea as the only relevant CTC grade 3 toxicity.

**Ibrutinib** (formerly called PCI-32765). Bruton tyrosine kinase (BTK) leads to downstream activation of cell survival pathways such as NF-κB and MAP kinases via Src family kinases.\textsuperscript{69} Ibrutinib is an orally active small molecule inhibiting BTK that plays a role in the signal transduction of the B-cell receptor (BCR). Inhibition of BTK might induce apoptosis in B-cell lymphomas and CLL cells.\textsuperscript{69} Ibrutinib showed significant activity in patients with relapsed or refractory B-cell malignancies including CLL.\textsuperscript{70} Data of a phase 1b-2 multicenter study with single agent ibrutinib on 85 patients with relapsed or refractory CLL or small lymphocytic lymphoma, the majority of whom had high-risk disease, were published recently.\textsuperscript{58} Patients received ibrutinib once daily (51 at a dose of 420 mg, 34 of 840 mg). Side effects were mild (predominantly grade 1 or 2) and included transient diarrhea, fatigue, and upper respiratory tract infection. The ORR was 71%, the majority being partial remissions (68%). Most interestingly, the response was independent of clinical and genomic risk factors, including advanced-stage disease, the number of previous therapies, and del(17p). At
26 months, the estimated PFS rate was 75% and OS rate was 83%. This study illustrates that ibrutinib may soon become an additional treatment option for CLL patients with high-risk genetic lesions.

**Bcl-2 inhibitors**

Proteins in the B-cell CLL/lymphoma 2 (Bcl-2) family are key regulators of the apoptotic process.\(^7\) The Bcl-2 family comprises proapoptotic and prosurvival proteins. Shifting the balance toward the latter is an established mechanism whereby cancer cells evade apoptosis. Bcl-2, the founding member of this protein family, is encoded by the BCL2 gene, which was initially described in follicular lymphoma as a protein in translocations involving chromosomes 14 and 18.\(^7\)\(^2\)

**Bcl-2 inhibitors ABT-263 (Navitoclax) and ABT-199.** ABT-263 is a small molecule Bcl-2 family protein inhibitor that binds with high affinity (Ki ≤ 1 nM) to multiple anti-apoptotic Bcl-2 family proteins including Bcl-XL, Bcl-2, Bcl-w, as well as Bcl-B and has a high oral bioavailability. Initial studies showed very promising results for this drug as a single agent.\(^7\) However, its therapeutic use seemed somewhat limited by severe thrombocytopenias being a prominent side effect. Therefore, the compound was re-engineered to create a highly potent, orally bioavailable and Bcl-2-selective inhibitor, ABT-199.\(^7\)\(^4\) This compound inhibits the growth of Bcl-2 dependent tumors in vivo and spares human platelets. A single dose of ABT-199 in three patients with refractory chronic lymphocytic leukemia resulted in tumor lysis within 24 h.\(^7\)\(^4\) In a recent update on a phase I study data of 56 patients have been reported of whom 16 (29%) had a del(17p) and 18 (32%) had F-refractory CLL.\(^7\)\(^5\) Major side effects were tumor lysis syndrome and neutropenia. ABT-199 yielded an ORR of 85%, with 13% CR and 72% PR. Interestingly, 88% and 75% of patients with a del(17p) and F-refractory CLL, respectively, achieved at least a PR. Together, these data indicate that selective pharmacological inhibition of Bcl-2 hold great promise for the treatment of CLL.

**Immunomodulatory drugs**

**Lenalidomide** has shown encouraging results in the treatment of high-risk patients including carriers of a del(17p).\(^7\)\(^6\) In 58% of the patients lenalidomide causes a tumor flare reaction characterized by a marked and painful increase in lymph nodes size, malaise and fever.\(^7\)\(^7\)\(^8\) This tumor flare reaction may be life-threatening and is more common in CLL than in other lymphoid malignancies. Lenalidomide may also cause relevant myelosuppression.\(^7\)\(^9\) The overall response rate of lenalidomide monotherapy varied between 32% and 54% in different clinical trials.\(^7\)\(^8\)-\(^8\)\(^0\) Most importantly, it seems to have activity as a single agent in fludarabine refractory CLL.\(^7\)\(^8\)-\(^8\)\(^0\)

The combination of lenalidomide and rituximab seems to increase the response rate without a higher risk of toxicity, even in patients with del(17p) and/or unmutated IGHV-status. In a phase II trial, fifty-nine patients with relapsed or refractory CLL received a combination of lenalidomide and rituximab.\(^8\)\(^1\) Lenalidomide was started on day 9 of cycle one at 10 mg orally and administered daily continuously. Each cycle was 28 days. Rituximab was administered for 12 cycles; lenalidomide could be continued if patients benefitted clinically. The overall response rate was 66%, including 12% complete responses and 12% nodular partial remissions. The median time to treatment failure was 17.4 months. The most common grade 3 or 4 toxicity was neutropenia (73% of patients). Fourteen patients (24%) experi-
enced a grade 3 to 4 infection or febrile episode. In essence, this combination seems a helpful alternative for patients with refractory CLL and warrants further investigation.

In some contrast, the combination of lenalidomide, rituximab and fludarabine may induce severe side effects (myelosuppression), if all drugs are started simultaneously on day 1.\textsuperscript{82,83} Using combinations starting with lenalidomide on day 8 of the first cycle, the treatment is usually better tolerated.\textsuperscript{83,84} The GCLLSG currently investigates the combination of bendamustine, rituximab and lenalidomide (BR\textsuperscript{2}) in physically fit patients (CLL2P protocol). Additional combinations currently studied are flavopiridol plus lenalidomide which lead to a response in 7 of 15 patients (among them 4 with a del(17p) and 3 with a del(11q))\textsuperscript{85} or lenalidomide plus ofatumumab.\textsuperscript{86}

**Everolimus (RAD001).** Everolimus has shown good efficacy in some hematological malignancies\textsuperscript{87} but the results in CLL have so far been disappointing with low response rates and relatively severe infectious complications.\textsuperscript{88,89}

**Chimeric antigen receptors**

Chimeric antigen receptors (CARS) combine the antigen recognition domain of an antibody with intracellular signaling domains into a single chimeric protein. CD19 is an ideal target for CARS since expression is restricted to normal and malignant B-cells. Inclusion of the CD137 (4-1BB) signaling domain resulted in potent antitumor activity and in vivo persistence of anti-CD19 CARS in mice. The group of Carl June has recently shown that anti-tumor activity of CAR-modified autologous T cells targeted to CD19 (CART19 cells) yielded sustained responses even in high-risk CLL patients.\textsuperscript{90} Recently, the outcome and longer follow up from 10 patients treated with CART19 cells was reported.\textsuperscript{91} Autologous T cells collected by leukapheresis were transduced with a lentivirus encoding anti-CD19 scFv linked to 4-1BB and CD3-z signaling domains. Gene-modified T cells were expanded and activated ex-vivo by exposure to anti-CD3/CD28 beads. 10 patients have received CART19 cells; 9 adults median age 65 years (range 51-78) were treated for relapsed, refractory CLL and one 7 year old was treated for relapsed refractory ALL. 3/9 CLL patients had a deletion of the p53 gene. All CLL patients received lymphodepleting chemotherapy 4-6 days before infusions (FC, PC or bendamustine, while the ALL patient had an ALC <10 after prior chemotherapy and did not require further lymphodepletion). CART19 homed to the marrow in the CLL patients and marrow and cerebrospinal fluid for the ALL patient with detectable CART19 cells in the CSF (21 lymphocytes/µL, 78% CAR+) day 23 after infusion. 4/9 evaluable patients achieved a CR (3 CLL, 1 ALL). 2 CLL patients had a PR lasting 3 and 5 months, and 3 patients did not respond. In the 4 patients who achieved CR, maximal expanded cells in the blood were detected at an average of 27fold higher than the infused dose (range 21-40fold) with maximal in-vivo expansion between day 10 and 31 post infusion. No patient with CR has relapsed. All patients who responded developed a cytokine release syndrome (CRS) manifested by fever, and variable degrees of nausea, anorexia, and transient hypotension and hypoxia. In responding CLL patients, cytokine levels were increased. 5 patients with cytokine release required treatment. In summary, CART19 cells can induce potent and sustained responses for patients with advanced, refractory and high risk CLL. However, the long term toxicity and efficacy of this approach needs to be further studied.
Outlook – signaling the end of CLL?

The above described, novel therapies all target relatively specific signaling proteins of CLL cells and their microenvironment. Therefore, their overall toxicity often is moderate and does not involve myelosuppression. Moreover, complete remissions have not occurred frequently so far with any of these newer agents, except CART19.91 In addition, unlike chronic myeloid leukemia that is initiated by a single oncogene (BCR/ABL), CLL appears to be a genetically heterogeneous leukemia. It seems that CLL may be caused by a complex array of genetic events and as a consequence is a biologically complex disease. Finally, somatic mutations in the kinase genome are very rare events in CLL,92 unlike in other malignancies. For these reasons, it is very likely that the currently available therapeutic agents will be combined to yield optimal results. The current challenge is to identify the best combination and sequence of treatments in order to achieve the long-term control of CLL with optimal quality of life. Finally, it is important to keep in mind that like in other hematological malignancies, the currently available data strongly suggest that achieving a very good disease control (using MRD negativity as a surrogate parameter) prolongs survival of CLL patients.38,93

How can these goals be achieved with the current treatment modalities? In principle there are at least three options.

1. **Combining the best agents** (three, four or more) in a *simultaneous* short term treatment (up to 6 months) aimed at minimal residual disease (MRD) negative CRs93 that would last longer than the remissions achieved so far. For example, such an approach would be combining the best currently available chemotherapies (fludarabine, cyclophosphamide alone or in combination; bendamustine) with antibodies and with kinase inhibitors or Bcl-2 antagonists. However, these combinations will have to be compared against the current standard, FCR, and results will be available in a few years only. Moreover, such a treatment strategy will not be without toxicity and therefore be tolerated only by patients with good physical fitness.

2. A second possibility would be to use **sequential monotherapies** of now or old agents. Each agent would be given until maximal response was achieved. After a long-lasting response, treatment could be repeated with the same agent, whereas alternative agents would be used in case of short remissions. This strategy might be applied in elderly or non-fit patients (“slow go”), where the goal of treatment is symptom control rather than disease control.

3. A third strategy would combine the best agents in a sequence that tailors the treatment according to the initial tumor load and the response to therapy (CR versus PR; MRD positive versus MRD negative).93 This strategy would have the goal to prevent the outgrowth of adverse leukemic subclones94 and to minimize the use of chemotherapy thereby reducing the risk for secondary mutations of the CLL clone(s) and for secondary malignancies that are frequent and prognostically unfavorable events in CLL. For this treatment approach, I propose the term “**sequential TTT (triple T)**” (tailored, targeted, total eradication of MRD) (Figure 3). This sequential triple T approach will make use of all the currently available options in a non-aggressive, non-toxic way and will aim at the complete elimination or control of the malignant clone. The advantage of such an approach would consist of the following points: 1. It would be available for most (fit as well as non-fit) CLL patients due to its limited toxicity. 2. It could be given in an outpatient setting. 3. It would use the current treatment options in a tailored and response-adjusted manner and therefore use the drugs in a cost-
effective, resource saving way (Figure 3). It might also be used to monitor the evolution of new genetic subclones in CLL that may have clinical and prognostic impact.\textsuperscript{96}

The proposed \textit{sequential triple T strategy} might consist of the following three steps (Figure 3):

1. \textbf{Debulking}. Since most of the new agents either induce a compartment shift of malignant lymphocytes (e.g. ibrutinib, idelalisib) they transiently increase peripheral blood lymphocyte counts. This often causes irritations of patients and physicians and prevents combination with some other drugs. Other agents (ABT-199, obinutuzumab, lenalidomide) often cause severe reactions during the first treatment phase (cytokine release syndrome, tumor lysis syndrome). Therefore in cases with elevated lymphocyte counts (above 30,000/µl) or large lymph nodes, a short debulking therapy, e.g. with one or two courses of bendamustine or fludarabine, might be an optional first treatment element. Alternatively, non-chemotherapeutic drugs could be used as well. This step would be performed to rapidly clear the peripheral blood of CLL cells in the majority of patients. This treatment period would last 1-2 months.

2. \textbf{Induction}. After reducing peripheral blood lymphocytes to levels below a certain threshold (e.g. below 30,000 peripheral blood lymphocytes/µl), induction therapies could be initiated. These therapies would contain non-chemotherapy combinations of drugs. In order to avoid infusion related reactions, antibodies such as obinutuzumab would be given first followed a few days later by a third class of drugs, a tyrosine kinase inhibitor or Bcl-2 inhibitor (or both). This treatment period would typically last 4-6 months and be monitored at the end by MRD assessment three months after a complete remission is achieved. In general, this combination treatment during induction would last as long as the remission continues to improve and until a complete remission is achieved.

3. \textbf{Maintenance}. At the end of this induction period, the third sequential element of the triple T strategy will ensure that a very good remission is maintained. This could be achieved by giving single agents, either oral drugs (such as kinase inhibitors or Bcl-2 inhibitors or lenalidomide) or repetitive infusions of antibodies (e.g. obinutuzumab, in intervals of 2-6 months) for a prolonged period. This therapeutic approach would be monitored by MRD assessment and treatment could be stopped three months after an MRD negative remission has been achieved and restarted in case of MRD positivity. This treatment phase would last at least one year, typically two years.

While I am fully aware that the proposed sequential triple T strategy needs to be validated by clinical research, it may help to design the appropriate clinical trials for the optimal use of currently available drugs. Finally, at a time, where new and exciting therapeutic options are likely to change the management and outcome of CLL, hematologists and oncologists have the obligation to include their patients in clinical trials to ensure that maximal progress is achieved in the shortest possible time. By doing so, we will actively contribute to the historically unique chance to gain control over a so far incurable disease such as CLL.
Acknowledgement:

The author wishes to thank Drs. Anja Engelke, Gabor Kovacs, and Paula Cramer for carefully reading the manuscript and the team of the GCLLSG study office for giving important suggestions. I thank Dr. Günter Krause for generating Figure 2. Moreover, I thank all patients and physicians participating in the studies of the German CLL Study Group for their continuing support and excellent cooperation. This work is supported by the Deutsche Krebshilfe (German Cancer Aid), the Kompetenznetz Maligne Lymphome (Competence Network Malignant Lymphoma) and the Deutsche Forschungsgemeinschaft (KFO 286, SFB 832 and Center of Excellence on “Cellular Stress Responses in Aging-Associated Diseases”).

Authorship Contributions:

Michael Hallek wrote the paper.

Conflict of Interest Disclosure:

Michael Hallek has received research funding from Mundipharma, Roche, Celgene and was paid consultant for Mundipharma, Roche, Celgene, Gilead, Janssen, GSK.
References


<table>
<thead>
<tr>
<th>Class</th>
<th>Agent (References)</th>
<th>Target</th>
<th>Route</th>
<th>Current Stage of Clinical Development</th>
<th>Comments, Specific Side Effects</th>
<th>Response Rate in Relapsed, Refractory CLL as a Single Agent (CR [%]</th>
<th>PR [%]</th>
<th>ORR [%]</th>
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<td>Dacetuzumab</td>
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<td>Bcl-2  and Bcl-X</td>
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<td>Olabicax</td>
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<td>Ibrutinib (PCI-32765)</td>
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<td>85 2 68 71</td>
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<td>Dasatinib</td>
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<td>Dinaciclib</td>
<td>CDK 1,2,5,9</td>
<td>i.v.</td>
<td>Phase I</td>
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<td>SNS-032</td>
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<td></td>
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<td>mTOR</td>
<td>p.o.</td>
<td>Phase I/II</td>
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</table>

* Analysis included only fludarabine refractory patients; **60% showed nodal responses without a 50% reduction of lymphocyte counts.
Figures 1a and 1b. Treatment algorithm for CLL patients, in first and second line indications.


Figure 2

Targeting of BCR signaling as a therapeutic strategy in CLL. Red symbols and letters indicate new therapeutics as discussed in the text.

Figure 3: Future treatment concept with novel agents. For this treatment approach, I propose the term “sequential triple T” to illustrate that this future approach should be a sequence of tailored measures (according to the risk of the leukemia, the tumor burden, the fitness of the patients), should use targeted agents (i.e. using the novel non-chemotherapeutic agents whose mechanism of action is targeting pathogenic signaling events of CLL cells and their microenvironment), and aim at the total of the leukemic clone (as assessed by MRD negativity as a clinical endpoint). Please note that the drugs or classes of drugs in this Figure are shown as examples. Similar agents of the same class or additional classes of drugs (see Table 1) may be used as well.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Fitness</th>
<th>del(17p) / p53 mutation</th>
<th>Therapy</th>
<th>Alternatives</th>
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<td>irrelevant</td>
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<td></td>
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<td>Slow go</td>
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<table>
<thead>
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<th>Response to first-line therapy</th>
<th>Fitness</th>
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<th>Alternatives</th>
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<td>Refractory or progress within 2 years</td>
<td>Go go</td>
<td>Change therapy to: FA, AlDex, AlPred, Allo-SCT</td>
<td>BR, Lenalidomide, kinase inhibitors, high dose steroids</td>
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<tr>
<td>Slow go</td>
<td></td>
<td>Change therapy to: Al for del(17p), BR, R-CHOP</td>
<td>Lenalidomide, kinase inhibitors, high dose steroids</td>
</tr>
<tr>
<td>Progress after 2 years</td>
<td>All</td>
<td>Repeat first line therapy</td>
<td>trials</td>
</tr>
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*Figure 1a and b*
Potential future strategies to achieve long-term control of CLL

Debulking
- Mild chemotherapy with agents like bendamustine or fludarabine

Induction (combination therapy)
- Kinase inhibitor(s)
- Antibody
- Bcl2 antagonist

MRD tailored maintenance (single agents)
- Antibody
- Lenalidomide
- Kinase inhibitor
- Bd2 antagonist

1-2 months (1–2 courses)
6-12 months
1 year - ∞
Signaling the end of chronic lymphocytic leukemia: new frontline treatment strategies

Michael Hallek