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T-CELL AND OTHER LYMPHOPROLIFERATIVE MALIGNANCIES (J ZAIN, SECTION EDITOR)

The Evolution of Targeted Therapies in Chronic Lymphocytic Leukaemia

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Abstract

Purpose of Review The treatment landscape for chronic lymphocytic leukaemia (CLL) is rapidly evolving, with several targeted agents recently approved. These compounds have dramatically changed the natural history of the disease.

Recent Findings However, with the array of effective therapies commercially available, the challenge is to define tailored treatment strategies able to realize a balance between treatment efficacy and toxicity or tolerance. New algorithms of treatment are being developed, and it appears that minimal residual disease (MRD) directed therapy will become the norm in the future.

Summary Clinical trials are looking at various combinations of novel therapies given with a defined, fixed-period of treatment based on MRD analysis. This approach enables patients to have a period of treatment-free remission instead of continuous therapy. In this review, we summarize this evolution of targeted therapies in CLL.

Keywords Chronic lymphocytic leukaemia · B cell receptor inhibitors · Venetoclax · Combination strategies · Indefinite treatment · Time-fixed therapy

Introduction

Over the last few years, amazing progresses have been made in the therapy of patients with chronic lymphocytic leukaemia (CLL). At the beginning, chemoimmunotherapy (CIT) led to the identification of increasingly effective combinations, even though the price of these successes translated into a prolonged myelosuppression and long-term bone marrow damage [1••, 2]. More recently, targeted therapy for CLL has radically modified the paradigm of treatment (Fig. 1). Clinical trials of Bruton tyrosine kinase (BTK) inhibitor-based therapies, mainly ibrutinib, have demonstrated that these compounds are highly effective in the disease control, shrinking bulk of disease, especially nodal disease [3, 4••]. However, deep remissions are uncommon with ibrutinib and treatment is given usually continuously, until progression or unacceptable toxicity [5••]. Venetoclax, an oral BCL2 inhibitor, with high capability to induce apoptosis in CLL cells by a p53-independent mechanism [6], has been initially approved for treatment of relapsed/refractory (R/R) patients including patients with del(17p) [7••, 8••]. Of note the efficacy of venetoclax is high in patients progressing after B cell receptor (BCR) inhibitors' failure [9, 10•].

All these targeted agents, initially tested in patients with R/R disease, have been subsequently shown to be effective for previously untreated patients, and in this setting, combinations with monoclonal antibodies have been studied [11••, 12, 13••, 14, 15••].

Targeted agents are now being extensively studied in fixed time-duration regimes, which have the benefit of potentially reduced toxicity, resistance, and cost. The challenge is to use agents which deepen response for a fixed duration time mimicking the schedule of CIT (Table 1). A key question with this approach is whether a fixed duration treatment would be used for all patients or whether the duration of treatment should be defined on an individual patient basis, depending on their response. To this end, the assessment of minimal residual disease (MRD) in CLL is increasingly being used to assess response and even to provide a tailored individual patient's treatment.

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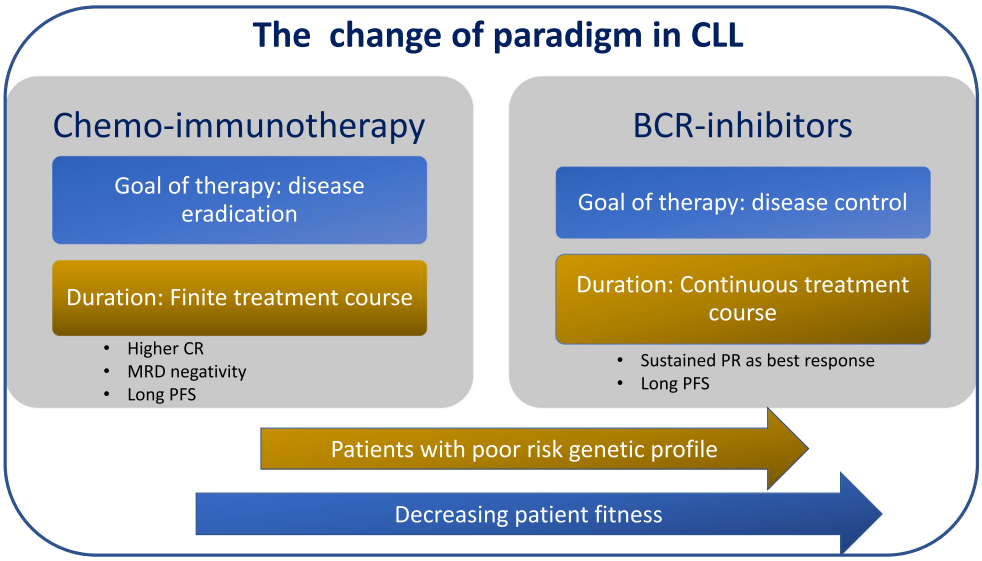

Fig. 1 Changes of paradigm in chronic lymphocytic leukaemia (CLL)

The Lesson of Clinical Trials of Ibrutinib

Ibrutinib was initially studied in the setting of R/R, heavily pre-treated, high-risk patients who experienced with chemotherapy a dismal clinical outcome [3]. Results of RESONATE phase 3 clinical trial [16••] enabled the Food and Drug Administration (FDA), in February 2014, to approve ibrutinib for the treatment of patients with CLL who had received at least one prior therapy. A few months later, ibrutinib also received breakthrough therapy designation for its use in CLL patients with del 17p. Results of RESONATE trial have been recently updated [5••] providing the longest follow-up analysis never reported with an oral target inhibitor in CLL. With up to 6 years of follow-up, extended ibrutinib treatment yielded sustained efficacy in patients with R/R CLL and small lymphocytic lymphoma (SLL) when compared with ofatumumab. Also safety remained acceptable, with low rates of treatment discontinuation due to adverse events, thus establishing long-term benefit and tolerability of ibrutinib in the treatment of R/R CLL [5••, 17].

After multiple studies in relapsed CLL [18–20], in 2016, ibrutinib was approved as a single agent given continuously for first-line treatment in older patients with CLL. According to extended follow-up results of a phase 3 trial, ibrutinib resulted in a long-term progression-free survival (PFS) benefit versus chemotherapy [21•]. The quality of response to ibrutinib continued to improve over time in the study, including a substantial increase in the proportion of patients achieving complete response (CR).

Until very recently, however, we did not have convincing evidence supporting a shift from chemotherapy to ibrutinib in upfront. Data from RESONATE-2 [11••, 21•], showing the superiority of ibrutinib as a monotherapy over chlorambucil, were not conclusive because chlorambucil as a single agent is a very uncommonly treatment for CLL nowadays. Only recently, we have had data that inform decision for this patient subset. The ALLIANCE A041202 [13••] is a phase 3 trial which randomized previously untreated older patients with CLL to either ibrutinib, ibrutinib with rituximab, or bendamustine/rituximab (BR). The study showed that there was a significant improvement of PFS in both ibrutinib arms over BR arm. Of note, rituximab did not add any significant benefit to ibrutinib, single agent. Looking at different subsets of patients on this trial, those patients who achieved greater benefit were patients with unmutated IgHV. The ibrutinib-based regimens did not lead to an overall survival (OS) gain over BR. This is most likely due to the fact that the study allowed for a crossover and most of the patients who progressed after BR were suitable to then go on to receive ibrutinib.

The iLLUMINATE is an industry-sponsored study comparing ibrutinib *plus* obinutuzumab to chlorambucil *plus* obinutuzumab in untreated CLL/SLL patients ≥ 65 or younger patients with comorbidities [14]. PFS at 30 months in the ibrutinib *plus* obinutuzumab group was significantly longer than that in chlorambucil *plus* obinutuzumab group (79% vs 31%). In this study, however, the benefit of adding obinutuzumab is not clear because a third arm with ibrutinib monotherapy was missed.

The real question is whether the results of these trials are practice-changing. For elderly untreated patients with TP53 mutation or del(17p), ibrutinib is the mandatory regimen. The improved PFS observed with ibrutinib-containing regimens in patients with unmutated IgHV suggests that such an approach is a reasonable choice in this setting. However, when selecting the best treatment strategies for patients without TP53 mutation or del(17p), several variables should be considered commencing with patients' preferences for different treatment features and ending with benefit–risk trade-offs and out-of-pocket cost. Without evidence of a survival benefit

Table 1 Ongoing phase 3 clinical trials in chronic lymphocytic leukaemia

Trial*	Subgroup	Status	Time-fixet	MRD	Treatment Arms			
ECOG-E1912 (NCT02048813)	< 70 years No del(17p)	Enrolled	No	No	Ibrutinib + rituximab			FCR
GLOW (NCT03462719)	≥ 65 years or unfit pts. No del(17p)/TP53 mut	Enrolled	Yes	Secondary endpoint	Ibrutinib + venetoclax			Chlorambucil + obinutuzumab
GAIA/CLL13 (NCT02950051)	Fit patients No del(17p)/TP53 mut	Recruiting	Yes	Primary endpoint	Ibrutinib + venetoclax + obinutuzumab	Venetoclax + obinutuzumab	Venetoclax+ Rituximab	FCR/BR
EA9161 (NCT03701282)	< 70 years, fit patients No del(17p)	Recruiting	Yes	Secondary endpoint	Ibrutinib + venetoclax + obinutuzumab	Ibrutinib + obinutuzumab		
A041702 (NCT03737981)	≥ 70 years	Recruiting	Yes	Secondary endpoint	Ibrutinib + venetoclax + obinutuzumab	Ibrutinib + obinutuzumab		
GLLC-EARLY (NCT04178798)	High-risk patients	Recruiting	No	No	Acalabrutinib	Watch and wait		
ELEVATE-TN (NCT02475681)	≥ 65 years orunfit patients	Enrolled	No	Secondary endpoint	Acalabrutinib + obinutuzumab	Acalabrutinib		Chlorambucil + obinutuzumab
ACE-CL-311 (NCT03836261)	> 18 years No del(17p)/TP53 mut	Recruiting	No	Secondary endpoint	Acalabrutinib + venetoclax + obinutuzumab	Acalabrutinib + venetoclax		FCR/BR
M16-788 (NCT03406156)	18–99 years, No del(17p)	Enrolled	Yes	Secondary endpoint	Bendamustine + obinutuzumab + venetoclax	Obinutuzumab + venetoclax		
EVOLVE (NCT04269902)	Symptomatic vs asymptomatic high-risk patients	Not yet Recruiting	Yes	No	Early treatment Obinutuzumab + venetoclax	Delayed treatment Obinutuzumab + venetoclax		
CRISTALLO (NCT04285567)	Fit patients No del(17p)	Recruiting	Yes	Primary endpoint	Obinutuzumab+ venetoclax			FCR/BR
SEQUOIA (NCT03336333)	All patients	Recruiting	No	Secondary endpoint	Zanubrutinib	Zanubrutinib+ venetoclax		BR
ELEVATE-RR (NCT02477696)	High-risk patients with R/R disease	Enrolled	No	No	Ibrutinib	Acalabrutinib		
ALPINE (NCT03734016)	R/R patients	Recruiting	No	No	Ibrutinib	Zanubrutinib		
UTX-IB-301 (NCT02301156)	High-risk patients with R/R disease	Enrolled	No	No	Ibrutinib + ublituximab	Ibrutinib		
ASSURE (NCT04008706)	All patients	Recruiting	No	No	Acalabrutinib			
ACE-CL-309 (NCT02970318)	R/R patients	Enrolled	No	No	Acalabrutinib	Idelalisib + rituximab		BR
VENICE (NCT02756611)	18–99 years R/R patients	Enrolled	Yes	Secondary endpoint	Venetoclax			

*www.clinicaltrials.gov. Last update: March2020

MRD, minimal residual disease; R/R, refractory/relapsed; FCR, fludarabine, cyclophosphamide, and rituximab; BR, bendamustine and rituximab

with ibrutinib in elderly CLL patients, CIT (i.e. BR or chlorambucil *plus* obinutuzumab) might also be a reasonable option in some patients. In the ALLIANCE study [13••], the median PFS is 41 months with BR. This regimen provides approximately 3 and a half years until disease progression and possibly even more time until the next therapy is needed. Since ibrutinib is a great salvage regimen associated with long remissions (i.e. median PFS 44 months), the chance for patients treated with a sequencing of BR and ibrutinib is to reach a PFS of 85 months.

With respect to dilemma of upfront therapy in young, fit CLL patients without significant medical problems, relevant information for clinical practice comes from ECOG-ACRIN trial [15••]. In the ECOG study, there was a significant PFS benefit for the ibrutinib-rituximab regimen over fludarabine, cyclophosphamide, and rituximab (FCR). Interestingly, the advantage of ibrutinib-rituximab involved also OS. However, when focusing on the IgHV-mutated group, no difference in terms of PFS or OS was found between ibrutinib and FCR. Given the fact that we have long-term data with FCR suggesting a plateau with a functional cure for about half of patients with mutated IgHV, FCR should be still the preferred therapy in this setting. In contrast, ECOG study provides a strong evidence in favour of ibrutinib-rituximab for patients with unmutated IgHV, even in the younger population.

The Challenge of Chemo-Free Time-Limited Therapy

Although ibrutinib has been established as a reliable and convenient orally administered agent in the frontline setting for patients with treatment-naïve CLL, the indefinite course of therapy can pose a challenge. In a real-world analysis, intolerance (particularly cardiac dysrhythmias and increased risk of bleeding) was shown to be the main reason for discontinuation [18–20]. It is also important to be aware of the "financial toxicities" associated with a recommended "life-long" treatment. Another relevant problem with ibrutinib is the development of ibrutinib-resistant CLL clones which occurs in about 20% of patients [22, 23, 24••, 25]. In the majority of patients progressing on ibrutinib, BTK or phospholipase Cg2 (PLCG2) resistance mutations predate clinical progression by up to 15 months. Resistance to ibrutinib generally correlates with progressive CLL or Richter transformation (RT). Early progression (i.e. < 12 months) being generally related to development of RT while progression occurring beyond 12 months is more likely to be determined by BTK or PLCG2 mutations [24••, 25].

In this context, it is important to identify novel patient-tailored treatment strategy harmonizing treatment efficacy and toxicity or tolerance [26]. Because of aforesaid limitations of ibrutinib therapy, a fixed duration time chemotherapy-free regimen seems to provide a reasonable approach for patients with pre-existing medical conditions. The phase 3 CLL14 trial addresses the issue investigating the efficacy of the fixed duration venetoclax–obinutuzumab combination given for 12 months compared to the previously established regimen of chlorambucil–obinutuzumab in patients with untreated CLL and coexisting conditions [12]. The 2-year PFS for the venetoclax–obinutuzumab group was significantly higher compared with the chlorambucil–obinutuzumab group: 88% compared with 64%. This benefit also included the patients with TP53 deletion/mutation in addition to patients with unmutated IgHV. Three months following treatment completion, a higher number of patients in the venetoclax–obinutuzumab group had achieved MRD negativity in peripheral blood (PB, 76% vs 35%) and in bone marrow (BM, 57% vs 17%). The median OS was not reached in either group. The differences in grade 3 or 4 neutropenia, infections, and all-cause mortality were not statistically significant between the two arms. Tumour lysis syndrome (TLS) was reported in three patients in the venetoclax–obinutuzumab group and in five patients in the chlorambucil–obinutuzumab group. The superiority in PFS benefit favouring the venetoclax–obinutuzumab group matched the acceptable toxicity profile and resulted in the approval of venetoclax–obinutuzumab in patients with untreated CLL and multiple comorbidities by the FDA in May 2019.

Although venetoclax adds an important option to frontline treatment of CLL, without studies of direct comparison between ibrutinib and venetoclax, it is difficult to establish the relative efficacy of these two agents. The German CLL group has announced the launch of the upcoming CLL17 trial investigating the efficacy and safety of single-agent ibrutinib compared with venetoclax–obinutuzumab compared with ibrutinib plus venetoclax. When results of this trial will be available, some of the ambiguities around frontline novel agents in CLL will be further deciphered, potentially translating into more positive change for patients with CLL.

MRD: a Novel Endpoint with Targeted Agents

In both treatment-naïve or R/R CLL patients, the highly selective BCL2 inhibitor venetoclax, alone or in association with an anti-CD20 monoclonal antibody, induces deep responses, including undetectable minimal residual disease (uMRD) [12, 27]. As shown in studies of CIT [1••, 28, 29], also with venetoclax uMRD translates into a longer PFS [27]. Therefore, a question is whether combination strategies, based on the association of agents which target different pathways (i.e. BCR and BCL-2), may improve the depth of response obtained with single agents. Preclinical studies have suggested synergism between ibrutinib and venetoclax [30]. These

agents have complementary activity in controlling CLL across anatomical compartments. Ibrutinib is also more active in lymph nodes, while venetoclax is more active in blood and marrow [3, 30, 31]. These observations have represented a strong rationale for testing in venetoclax-ibrutinib combinations of clinical trials.

In the CLARITY study, R/R CLL patients were treated with a combination of ibrutinib and venetoclax with primary and secondary endpoints MRD eradication after 12 and 6 months of combination therapy, respectively [32]. The overall response rate (ORR) was 89% in 53 enrolled patients, and 36% of them reached MRD negativity after 12 months of combination therapy. The same combination evaluated in 80 previously untreated high-risk and older patients with CLL led to an 88% CRs, 61% showing uMRD [33].

CAPTIVATE (PCYC-1142) is a multi-centre phase 2 study (NCT02910583) evaluating the combination of ibrutinib *plus* venetoclax in first-line treatment of CLL/SLL patients younger than 70 years [34]. Enrolled patients received single-agent ibrutinib lead-in for 3 cycles followed by ibrutinib *plus* venetoclax for 12 cycles. In total, 151/162 enrolled patients (92%) completed ibrutinib lead-in and all 12 cycles of ibrutinib *plus* venetoclax. uMRD was achieved at any time after baseline in more than 70% of patients in both PB and BM.

The triplet combination of umbralisib (a novel PI3K inhibitor) and ublituximab (U2) *plus* venetoclax demonstrated a tolerable toxicity profile in patients with R/R CLL in a phase 1–2 clinical trial producing an ORR of 90% (CR, 29%) and a 2-year PFS of 90% [35]. Undetectable MRD was achieved in PB and BM in 58% of patients.

Efforts are under way to examine the ibrutinib, venetoclax, obinutuzumab (IVO) combination triplet that is highly active R/R CLL with a high number of patients achieving uMRD, particularly given that this was in the relapsed setting [36].

The first-line triplet regimen consisting of acalabrutinib, venetoclax, and obinutuzumab (AVO) induced uMRD in the BM after only 8 monthly cycles of therapy in 48% of patients with CLL, which improved to 75.0% after cycle 16 [37]. The safety profile of AVO was favourable. Notably, the rate of infusion-related reactions was markedly lower with AVO when compared with historical data for obinutuzumab alone or with chemotherapy. In addition, pretreatment with acalabrutinib and obinutuzumab reduced the risk of TLS at the time of venetoclax administration.

Two phase 3 studies are evaluating a time-limited combination including ibrutinib, venetoclax, and obinutuzumab (IVO) with the current standard of indefinite ibrutinib (*plus* obinutuzumab) (Clinical-Trials.gov identifier:NCT03701282; ClinicalTrials.gov identifier: NCT03737981).

Thus, the MRD measurement might become an appropriate tool to assess efficacy and direct therapeutic decisions also in the clinical management of CLL, with a modulation of treatment on the basis of patient need. However, the predictive value of MRD status, durability of response, fixed treatment durations and, importantly, criteria for selection of patients for the optimal combinations are still unanswered questions.

Evolving Role of BTK Inhibitors in CLL

Adverse events (AEs) have led to discontinuation of ibrutinib in 9–14% of patients in clinical studies and about in 22% of patients in routine clinical practice [5••, 11••, 18–20, 21•, 38]. In this respect, it is of interest to note that with acalabrutinib, a potent, highly selective covalent BTK inhibitor, toxicities which are associated with ibrutinib were less frequently observed. Among 33 R/R CLL patients who had discontinued ibrutinib because of intolerance, no acalabrutinib dose reductions were needed, although treatment grade 3/4 AEs occurred, most commonly neutropenia (12%) and thrombocytopenia (9%) [39]. Of note, acalabrutinib, based on findings from the randomized phase 3 ELEVATE-TN [40•] and ASCEND [41•] trials, received approval from the FDA for the treatment of adult patients with CLL or SLL. These results allowed acalabrutinib approval for both indications (i.e. treatment naïve and R/R CLL patients) in November 2019 by FDA [42].

Of note, ELEVATE-TN study examined chlorambucil/obinutuzumab versus acalabrutinib alone versus acalabrutinib *plus* obinutuzumab [39]. Acalabrutinib alone and acalabrutinib/obinutuzumab had significantly improved PFS along with a 2-year PFS rate of about 90%.

In the acalabrutinib monotherapy arm ($n = 179$), the most common AEs of any grade (30%) included headache (36.9%) and diarrhoea (34.6%). These results are encouraging for a patient population that is known to face multiple comorbidities and where tolerability is a critical factor in their treatment. There appears also to be a beneficial trend with the addition of obinutuzumab to acalabrutinib, which demonstrates, for the first time, the potential PFS benefit of adding obinutuzumab to a BTK inhibitor in a randomized trial.

Other second-generation irreversible BTK inhibitors (i.e. zanubrutinib, tirabrutinib) are also being studied now [43, 44]. In particular, a phase 3 study comparing zanubrutinib to ibrutinib (NCT03734016) will further assess the safety and efficacy of this novel second-generation irreversible BTK inhibitor in R/R CLL. Results of the safety and efficacy for zanubrutinib in treatment-naïve patients with del(17p) CLL/SLL who are enrolled in the non-randomized arm C of the SEQUOIA (BGB-3111-304) trial have been recently presented [45]. The ORR was 92.2%. Importantly, only two patients had disease progression due to RT, and only one patient died due to grade 5 pneumonia. In this study, including one of the largest prospective cohorts of treatment-naïve patients with del(17p) CLL/SLL zanubrutinib was active and generally well tolerated.

Conclusions

Recent trials in upfront suggest that ibrutinib or an ibrutinib combination with an anti-CD20 monoclonal antibody should be considered standard of care for most patients with CLL [13••, 14, 15••, 46]. Acalabrutinib was shown as a single agent to have very impressive results, and the association with obinutuzumab seems to improve the depth of response [39]. These results suggest that acalabrutinib is the more direct competitor of ibrutinib. A number of questions remain, however, with MRD, in particular regarding criteria for selection of patients for the optimal combinations [47]. On the basis of the available evidence, it can be hypothesised that a combination of targeted agents, having uMRD as endpoint and given for limited time, could be most useful in patients with high-risk disease (e.g. pre-treated patients or patients with TP53 aberrations or complex karyotypes) in whom rapid eradication of the disease is desirable to prevent the emergence of resistant clones and to prolong, possible, survival. In contrast, a sequential continuous approach might be satisfactory for patients with low-risk disease, especially in older patients (aged > 70 years) with an acceptable burden of comorbidities.

Compliance with Ethical Standards

Conflict of Interest Valentina Gianfelici, Luciano Levato, and Stefano Molica do not declare any conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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