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Editorial

Relapsed/Refractory Chronic Lymphocytic Leukemia: Chemoimmunotherapy, Treatment until Progression with Mechanism-Driven Agents or Finite-Duration Therapy?

Antonio Cuneo[1] and Robin Foà[2].

[1] Hematology, Department of Medical Sciences, University of Ferrara, Italy.
[2] Hematology, Department of Cellular Biotechnologies and Hematology, Policlinico Umberto 1, 'Sapienza' University , Rome , Italy.

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Abstract. Treatment of relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) has dramatically improved thanks to the development of mechanism-driven agents including drugs that inhibit kinases in the BCR pathway or BCL2. The treating physician has now the opportunity to decide i) which patient can be still offered chemoimmunotherapy as salvage treatment, ii) which patient at relapse is a candidate to receiving, continuous treatment with ibrutinib, idelalisib and rituximab or venetoclax and iii) which patient may benefit from a fixed-duration treatment using the BCL2 antagonist venetoclax in association with rituximab.
Ibrutinib is the most actively investigated drug in R/R CLL and data at a 7-year follow-up were reported, showing durable efficacy and favorable efficacy profile. The patients with cardiac disease, hypertension, and anticoagulant therapy are not ideal candidates for continuous therapy with this agent. Idelalisib and rituximab were tested in patients with unfavorable characteristics including cytopenias. The short follow-up and treatment-emergent adverse events limit its role to patients unlikely to get a benefit with other agents. Venetoclax and rituximab is the only effective chemo-free approach for the treatment of R/R with a fixed duration (up to 24 months) schedule capable of inducing deep responses in the majority of cases with a reassuring safety profile.
While a deep knowledge of the growing body of scientific evidence is required to inform and guide the appropriate treatment choice and management, physicians cannot disregard the growing problem of sustainability.

Keywords: Chronic lymphocytic leukemia; Finite-duration treatment; Venetoclax; Ibrutinib; Idelalisib.

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Correspondence to: Antonio Cuneo. Hematology, Department of Medical Sciences, University of Ferrara, Italy. Via Ariosto, 35 – 44121 Ferarra, Italy.Telephone Int+39 0532 236977, Fax: int+39 0532 236654. E-mail address: cut@unife.it

Introduction. Treatment of chronic lymphocytic leukemia (CLL) has dramatically improved over the years thanks to the development of effective chemoimmunotherapy (CIT) regimens[1] and of mechanism-driven agents including drugs that inhibit kinases in the BCR pathway or BCL2.[2,3] In treatment-naïve patients, the addition of anti-CD20 monoclonal antibodies to fludarabine-based combinations or to

chlorambucil has prolonged survival[4,5,6] and allowed to obtain a minimal residual disease (MRD) negative status in a proportion of cases. In the relapsed/refractory (R/R) setting, the introduction of ibrutinib, idelalisib, and venetoclax have had a major role in prolonging progression-free survival (PFS) and overall survival (OS) in patients with advanced disease and with limited therapeutic options.[7-9] It has also been documented that these novel agents produce better results when used in earlier phases of the disease,[10] though formal proof that they may prolong survival compared with CIT in the first salvage setting is still lacking.[11]

While these new agents were initially developed and received marketing approval as continuous oral treatment given until disease progression or unacceptable toxicity, the design of new trial using venetoclax with the anti-CD20 monoclonal antibody rituximab for a predefined number of cycles, led to the demonstration that a fixed-duration treatment without chemotherapy in R/R CLL may produce complete responses, with many patients becoming MRD-negative in the peripheral blood (PB) and bone marrow (BM).[12-16]

Since these findings appear to hold promise at an extended follow-up[17,18] and since the regulatory agencies granted market authorization to venetoclax and rituximab based on the 24-month schedule of the MURANO study, we are witnessing a rapid paradigm shift in the treatment of R/R CLL. Indeed, the treating physician has now the opportunity to decide i) which patient can be still offered CIT as salvage treatment, ii) which patient is a candidate to receiving continuous treatment at relapse and iii) which patient may benefit from a fixed-duration treatment.

A Role for CIT in the R/R Setting? The efficacy of new agents in the presence of *TP53* disruption mandates their use in this genetic subset of CLL.[19,20] Furthermore, the progressive lack of efficacy of CIT in patients with multiple relapses[21] and the survival advantage of new oral agents in randomized trials[22] clearly indicate that there is no longer a role for CIT in advanced phases of the disease, independent of the genetic profile. However, the trials comparing CIT with ibrutinib, idelalisib, and rituximab or venetoclax and rituximab were not designed to allow a comparison of the subset or patients receiving the study drugs as first salvage treatment. A recent matched adjusted indirect analysis of ibrutinib compared with bendamustine plus rituximab (BR) in second line showed no difference in OS in a real-world analysis.[11] Traditional prognostic markers, including disease stage and *IGHV* mutational status allowed to identify patients witnessing a shorter PFS under CIT.[23] In the GIMEMA-ERIC analysis of BR in second line, the PFS was 19 months vs 25 in stage 0-II and stage III-IV, respectively and 21 vs 32 months in patients carrying *IGHV* gene unmutated and *IGHV* gene mutated configuration, respectively. The OS with BR as first salvage was 41 months vs 75 months in Rai stage 0-II and III-IV, respectively (unpublished data). Therefore, according to these data and in line with a recent review[24] BR may still represent an option for a limited number of patients preferring second-line treatment of short-duration, provided that they show a favorable genetic profile, have a limited disease and have had a long duration of response to first-line CIT.[25]

Treatment Until Progression. With their unique mechanisms of action disrupting CLL-microenvironment interactions,[26] with consequent redistribution and death of lymphocytes,[27,28] both ibrutinib and idelalisib have been shown to induce a response in over 80% of the R/R patients. Complete responses were achieved in a minority of patients, and these drugs were administered in a continuous schedule until progression or unacceptable toxicity. Initially, venetoclax was given continuously as a single agent in clinical trials enrolling R/R patients,[9] patients with a 17p-[29] and patients relapsing after ibrutinib and/or idelalisib.[30,31] However, thanks to the ability to produce complete and deep responses, protocol-guided drug cessation was allowed in a subsequent phase Ib trial of venetoclax used in combination with rituximab.[32] The durability of responses following drug cessation in deep responders was documented.[33]

Ibrutinib is the most actively investigated drug in R/R CLL and data at a 5-year follow-up of 101 R/R patients were published[10] and recently updated with a 7-year follow-up.[18] Patients had a median age of 64 years, had a good performance status (PS) and had received a median of 4 previous therapies. In this phase 1b-2 study, ibrutinib was able to provide excellent disease control for a prolonged period in the majority of patients, with 52% of patients alive at 7 years and with 5- and 7-year PFS rates of 44% and 32%, respectively. Grade ≥3 cumulative toxicity events after a median exposure to the drug of 39 months included pneumonia in 27% of patients, hypertension in 25% and atrial fibrillation in 9%.[10] At 7 years, 55% of patients developed a serious infection and 9% a major hemorrhage.[18] However, observational studies of ibrutinib clearly showed that elderly patients with comorbidities and/or an ECOG PS >1 were more likely to discontinue treatment due to toxicity[34-38] and that atrial fibrillation occurred more frequently in elderly patients with previous arterial hypertension and pre-existing cardiologic comorbidities.[39] In the real world experience of the Swedish registry[36] an updated analysis at 30-month follow-up of 95 R/R patients (median age of 69 years, del(17p)/TP53 mutation in 63% of the patients, PS grade 2-3 in 27%) showed that 51% of patients had a grade 3-4 infection, 15% developed any grade atrial fibrillation and 20% discontinued due to adverse events. In another analysis, 116 out of 536 R/R patients (21.6%) treated in

the U.S. discontinued ibrutinib due to toxicity at a median follow-up of 17 months.[40]

Idelalisib given continuously in association with 8 doses of rituximab showed efficacy in a heavily pre-treated patient population with unfavorable baseline characteristics (median age 71 years, grade ≥3 cytopenia in 1/3 of the cases advanced stage in 2/3 of the cases, high burden of comorbidities in 85% of cases), with an estimated PFS of 66% at 12 months[41] and a discontinuation rate of 8% due to adverse events after a median time of exposure to the dug of 3.8 months.

Venetoclax, given as single-agent until progression, is the only drug of proven efficacy which has been used in phase II trials for CLL progressing after ibrutinib or idelalisib.[30,31] A response was observed in approximately 2/3 of patients, with approximately 3/4 of patients alive without progression at 12 months. The most frequent treatment-emergent adverse events were primarily hematological and included mainly neutropenia in approximately 50% of patients, with grade 3-5 infections occurring in approximately 15% of patients. Laboratory tumor lysis syndrome was recorded in 5% of patients.[29] In a real-world analysis of 141 patients treated in the U.S (median age 67 years, 17p- in 45% of patients, previous exposure to a BCR antagonist in 89%), 72.1% of patients responded, with a projected PFS and OS for the entire cohort at 12 months of 68% and 88%, respectively. Venetoclax was discontinued in 41 patients (29%) due to disease progression (53.8%, n=21), toxicity (20.5%, n=9) or other reasons (25,7%, n=10).[42]

Fixed-Duration Treatment. Growing attention is being devoted by the scientific community to fixed-duration chemo-free approaches in CLL which are able to induce complete responses. The efficacy of several studies in R/R CLL have been published or presented in an abstract form (**Table 1**).

Recently, the results of the phase-3 MURANO trial comparing venetoclax for a maximum of 24 months associated with rituximab (VR) for the first six months with the classical bendamustine and rituximab (BR) regimen given for six months in R/R CLL have been reported.

Ninety-two % of patients responded to VR, and 62% attained an undetectable MRD (uMRD) in the PB at six months, compared to 12% in the BR cohort. Sixty-four % of 130 patients who completed the two years of planned treatment with venetoclax had uMRD. Patients with uMRD or detectable MRD at low levels (10^{-2} to 10^{4} residual cells) had a longer PFS than the remaining patients.[17] At a median of 9.9 months after cessation of venetoclax only 12% of 130 patients who completed the planned treatment progressed and 90% of all patients assigned to the VR arm had not undergone a further treatment for their disease at two years.[12]

In the intention to treat analysis, the VR regimen significantly improved PFS (HR: 0.16; IC 95%: 0.12-0.23; p <0.0001) and OS (HR: 0.50; 95% CI: 0.30-0.85; p = 0.0093; OS rate at 3 years: 87.9% vs 79.5%) compared to BR, which represents one of most widely employed CIT regimen in R/R CLL. Noteworthy, though crossover to venetoclax at progression in the BR arm was not pre-planned, the majority of patients received effective salvage regimen with new drugs.[17]

These findings show for the first time that a fixed-duration treatment may achieve deep and durable response and improve survival in R/R CLL, and are likely to have a significant impact in the treatment of R/R CLL in the clinical practice as the regulatory agencies FDA and EMA granted this regimen marketing authorization.

Table 1. Efficacy of recently developed fixed-duration approaches based on novel agents for the treatment of R/R CLL.

Regimen	Phase	N. of pts with R/R CLL	Duration of the treatment (months)	Primary Endpoint	Salient results	Reference
Venetoclax and rituximab	3	194	24	PFS	MRD-negative in 62,4% of the patients PFS rate: 71,4% at 3 yrs OS rate: 87,9% at 3 yrs	12
Obinutuzumab venetoclax and ibrutinib	1b	25	14	Response rate	92% overall response rate after 8 cycles with 70% MRD-negative	13
Venetoclax and ibrutinib	2	54	12-24	MRD rate	41% MRD-negative at 12 months	16
Bendamustine* obinutuzumab and venetoclax	2	31	up to 24	Response rate	90% overall response, 83% MRD-negative (PB) at final restaging after induction (month 10)	14
Bendamustine* obinutuzumab and ibrutinib	2	31	up to 24	Response rate	100% overall response, 41,9% MRD-negative (PB) at final restaging after induction (month 10)	15

(*only 2 cycles for debulking), PB: peripheral blood: MRD-negative: $<10^{-4}$ cells.

Advantages and Disadvantages of Finite Duration vs Continuous Treatment. While the CIT approach to the treatment of R/R CLL has a marginal role in high-income countries nowadays, the development of chemo-free approaches using venetoclax and the antiCD20 monoclonal antibody rituximab poses a challenge to the treating physician who has to discuss with each patient with R/R CLL advantages and disadvantages of continuous oral treatment with new agents or fixed-duration treatment. Since FDA and EMA have approved the use in R/R CLL of ibrutinib, idelalisib with rituximab and venetoclax on a continuous schedule, or venetoclax and rituximab for a fixed duration, the following considerations might be taken into account in the decision process, in the absence of a direct comparison.

- Ibrutinib has been tested in many trials which have now reached a mature follow-up[43,10] and is the only drug with a large body of literature describing the outcome in the real world patient population.[34,36,37,40] Importantly, the excellent efficacy and safety profile was consistent throughout trials which included patients with a good PS. Notably, treatment-limiting adverse events were more frequent during the first year of follow-up; however, the incidence of newly diagnosed hypertension and atrial fibrillation appeared to be constant over a long follow-up period.[10] Outside of clinical trials, elderly patients with comorbidities showed a higher discontinuation rate compared to those on trial.[35] Patients with ECOG PS >1, patients with cardiac disease, hypertension, and on anticoagulant therapy are not ideal candidates for continuous therapy with ibrutinib.[44] Severe infections, including fungal infections[45] represent an emerging issue, even though their incidence is clearly influenced by the longtime of exposure to the drug.
- Idelalisib has been used in a phase 3 trial that mostly included patients >70 years with unfavorable characteristics, many of whom were not enrolled in phase-2 trials of ibrutinib and venetoclax. The short follow-up and treatment-emergent adverse events[41] limit its role to patients unlikely to get a benefit with ibrutinib or venetoclax. The emergence of immune-mediated side effects under treatment may be attenuated in elderly patients with multiple prior therapies.
- Venetoclax and rituximab is the only effective chemo-free approach for the treatment of R/R with a fixed duration (up to 24 months) schedule capable of inducing a response in virtually all cases, with a majority of patients attaining an uMRD in the PB and BM. A complete response was observed in a minority of patients due to a small residual size (<30 mm) adenopathies. Even though the durability of response needs to be established with a longer follow-up, preliminary data on patients attaining an uMRD are unprecedented in this setting of patients. Importantly, preliminary data on few patients indicate that responses can be observed when venetoclax is resumed at disease progression after cessation of treatment.[17,33] The safety profile at a 30-month follow-up is reassuring, and fixed-duration treatment will translate into a lower incidence of treatment-related adverse events compared to continuous treatment.

Treating physicians bear today a great responsibility in offering the best treatment option to each patient with R/R CLL. While a deep knowledge of the growing body of scientific evidence is required to inform and guide the appropriate treatment choice and management, physicians cannot disregard the growing problem of sustainability. In high-income countries, with or without a universal health system coverage, the prices of pharmaceuticals are among the major drivers of the differences in overall health care costs between countries.[46,47] The possibility of using effective regimens for a fixed-duration period may represent a unique opportunity to guarantee a lower cost of treatment and, in the absence of a documented advantage of a given treatment over another potentially equally effective and tolerable, the payer can suggest the practicing hematologist to consider the economic implication of his/her choice. Meanwhile, and most importantly, the regulatory agencies should be able to undertake some recommended actions to negotiate fair prices.[48] Moreover, the definition of validated approaches to stratify the magnitude of clinical benefit[49] along with payment-by-result strategies are urgently required to guarantee the sustainability on national health systems.

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