Chronic lymphocytic leukemia: “The times they are a-changin”

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In the last few years, the therapy of chronic lymphocytic leukemia (CLL) underwent a major transformation. Although in upfront chemoimmunotherapy remains a well-established approach in both young and elderly CLL patients, the availability of several novel targeted therapies is now changing the paradigm of treatment [1]. Among small-kinase inhibitor (KI) molecules, the most studied are the US FDA and EMA approved ibrutinib and idelalisib. The BCL-2 inhibitor, venetoclax, received FDA approval in April 2016 for patients who have 17p deletion previously treated with at least one prior therapy. Nowadays, a major challenge in CLL is how best to integrate targeted therapies into treatment programs since some practical questions, such as the optimal duration of therapy, the agent sequencing and the assessment of responses, are still unanswered. The largest multicenter analysis of CLL patients treated with these novel agents in the real life concluded that ibrutinib appears to be superior to idelalisib as first choice KI. In the setting of toxicity, alternating a KI with another one is a reasonable choice; in contrast, a change to venetoclax is mandatory when patients progress under the KI therapy. Therefore, in patients with relapsed-refractory CLL after ibrutinib, idelalisib or both, venetoclax monotherapy is associated with a high overall response rate and durable treatment response. In addition, minimal residual disease negativity was seen with some frequency in patients who received therapy with venetoclax [1]. Overall, these data provide guidance for sequencing of novel agents and support the need for trials directly comparing novel agents and sequencing strategies in CLL to achieve value-based therapies.

An attractive option in the treatment of CLL is that of combining small-KI molecules with chemoimmunotherapy under the assumption that the improvement in the quality of responses, and possibly the achievement of minimal residual disease negativity may translate into a longer duration of remission. Two randomized studies have combined ibrutinib or idelalisib, respectively, with bendamustine and rituximab (BR) [2,3]. In the Helios, double-blind, placebo-controlled, Phase III trial, patients with relapsed or refractory CLL were randomly assigned (1:1) to receive BR with either ibrutinib (420 mg daily orally) or placebo until disease progression or unacceptable toxicity. The independent review committee assessed progression-free survival at 18 months was 79% (95% CI: 73–83) in the ibrutinib group and 24% (95% CI: 18–31) in the placebo group (HR: 0.203; 95% CI: 0.150–0.276; $p < 0.0001$). In a similar designed study, idelalisib in combination with BR improved progression-free survival compared with BR alone in patients with relapsed or refractory CLL (i.e., median progression-free survival 20.8 vs 11.1 months). However, authors suggest that careful attention needs to be paid to the management of serious adverse events and infections associated with the association of BR plus idelalisib during treatment selection. In our opinion, results of these trials are not likely to immediately change the standard of care in CLL; however, they raise relevant questions concerning the optimal strategy for incorporating KIs in the treatment of patients with CLL. A relevant issue is whether a combination of chemoimmunotherapy plus KI, by improving the deep of response, would allow patients to discontinue KI. The KI discontinuation in responding patients has not yet been verified and the issue is of great interest to limit toxicity as well as cost.

Another challenge is also the application of the principles of chemotherapy to the combination of different targeted agents with nonoverlapping toxicities. ABT-199, a small molecule inhibitor of BCL2, might be rationally combined with ibrutinib in this setting. Early experiences with this combination show promising efficacy in patients with relapsed/refractory mantle cell lymphoma [4]. Combinations using immunomodulatory agents also have strong rationale given their role in the regulation of T-cell function [5]. Results of a dose-finding Phase I study, which combines ibrutinib and lenalidomide, has been reported in CLL (ClinicalTrials.gov Identifier: NCT01886859) [5]. Finally, drugs that interfere with inhibitory signaling axes between CLL cells and T cells at the PD-1:PDL-1 ‘immune-checkpoint’ have potential importance in CLL. However, PD-1 blockade in CLL patients with relapsed/refractory disease, including seven with Richter transformation, translate into a low rate of overall response (i.e., about 25%) although a patient with Richter achieved a complete remission and two achieved a partial remission. Ongoing trials are now exploring the efficacy of checkpoint inhibitors in association with idelalisib or ibrutinib in CLL or other low-grade B-cell malignancies [6].

Another novel promising targeted treatment modality is represented by autologous T cells engineered to express a chimeric antigen receptor against cancer-specific markers (CAR T cells) [7]. However, CAR T-cell therapy should be considered as an investigation, limited to patients with aggressive relapsed, refractory disease.

In conclusion, the concept of “*The times they are a-changin*,” the famous Bob Dylan’s song, really applies to the remarkable changes in the landscape of CLL therapy we are now living. The times are indeed changing in CLL with a plethora of newly approved agents, although there are many unanswered mechanistic questions that are being researched actively. However, the advent of targeted therapy in CLL requires the urgent introduction of revised clinical guidelines based not only on results of clinical trials but also including data from clinical practice and the assessment of drug-related toxicity according patients’ reported outcomes [8,9]. This is especially true for the increasing number of CLL patients diagnosed in the community who are generally elderly (i.e., >70 years) and whose burden of comorbidities is high.

Of note, with the increasing use of innovative therapies a relevant issue is the long-term pharmacoeconomic implications of their utilization. Agents such as ibrutinib, idelalisib and venetoclax are profound treatment advances; however, cost considerations may undermine the potential promise of these agents by limiting access and reducing adherence. More sustainable pricing strategies for targeted therapies are needed to avoid financial toxicity to patients [10].

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