The age of fit-equity: ignoring age and fitness in treatment selection for chronic lymphocytic leukemia

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In this issue of *Haematologica*, Frustaci and colleagues report on the outcomes of 271 patients with chronic lymphocytic leukemia (CLL) treated with venetoclax + obinutuzumab (VenObi) during the first year of availability of this therapy in Italy.[1] In this real-world report, the authors document the feasibility of delivering VenObi in routine clinical practice and highlight some non-traditional factors that may be appropriate to consider when selecting this or other first-line therapy for CLL. They noted that most patients completed the first two cycles of therapy, including the obinutuzumab loading doses and the venetoclax ramp-up (the 'debulking phase'), and that treatment discontinuation for toxicity was infrequent at only 11%. Despite assessing fitness by several different scores, unfit patients did not have more treatment modifications or discontinuations than fit patients. Instead, the authors' noted an impact of 'caregiver need' and prolonged steroid pre-treatment as variables associated with discontinuation for toxicity.

Hematologists and oncologists are recognized for their pursuit of 'evidence-based medicine' with treatment recommendations typically strongly based on well-performed randomized phase III clinical trials. Such trials have been performed with VenObi in CLL in two frontline clinical trials.[2,3] This requirement is important to ensure that the most effective and safe therapies are recommended for our patients. However, most clinical trials have strict inclusion/exclusion criteria and this can lead to patient selection that is not always representative of "normal" patients with the disease of interest. This problem of clinical trial generalizabilty and the desire to ensure more representative and inclusive approaches to clinical trial enrollment is now well recognized.[4]

Historically, CLL clinical trials were particularly noted to include patient populations that were not representative. CLL is a disease of older people and, as such, the majority of patients who require therapy for CLL have comorbidities with or without organ compromise that may influence their ability to tolerate traditional chemo-immunotherapies and that previously rendered them ineligible for many clinical trials. This was best exemplified by the German CLL Study Group (GCLLSG) CLL8 clinical trial that was widely hailed as transformative in the treatment of CLL by being the first study to demonstrate an overall survival advantage in previously untreated CLL patients when rituximab was added to fludarabine and cyclophosphamide (FCR).[5] The CLL8 study should have rendered FCR the standard of care for CLL but this was not possible because it was far too intensive for the "average" CLL patient. While the median age at diagnosis for CLL is 72 years, the median age in the CLL8 study was 61 years such that only a minority of CLL patients were eligible for treatment with FCR.

The GCLLSG and others quickly recognized that the best therapy was not yet clearly defined for most CLL patients and this began an era of CLL clinical trials targeted at a population of patients with advanced age and/or comorbidities. Simultaneously, trials were performed with FCR as the comparator to improve upon therapeutic options in young/fit CLL patients. Thus, over time, we have come to a situation in CLL whereby clinical trials are dichotomized to those targeting young and/or fit patients or patients who are old and/or have comorbidities. Treatment guidelines also reflect the same decision-making based on age/fitness.[6,7] However, the move from traditional chemo-immunotherapy to targeted small molecules in CLL has led us to question the need to dichotomize our treatment approach between young/fit and old/unfit. Has "old" become the new "young" and "unfit" become the new "fit" in treatment selection in CLL?

Frustaci and colleagues confirm that despite using a variety of comorbidity indices, the presence/absence or extent of comorbidities did not influence their patients' ability to be treated with VenObi. While there was some impact of age on global feasibility, the rates of treatment discontinuation for toxicity were not impacted by any validated fitness score. Their series of patients had equal representation of fit and unfit subjects as per the GCLLSG definitions.

The authors highlight some novel 'factors' to consider in treatment selection specific to VenObi, including caregiver support and prolonged steroid use. The Italian practice of providing extended administration of corticosteroids to CLL patients prior to obinutuzumab to reduce rates of severe infusion-related reactions proved to be without benefit and demonstrated some harm. While infusion-related reactions can be unpleasant for patients and nursing staff, these appear to be best managed by very slow first infusions and education/preparedness for patients and staff.[8] The value of caregiver support for this therapy is reflective of the burden of visits required for the VenObi regimen and may not apply to other therapeutic choices. It highlights the importance of a more individualized approach to treatment decision-making, which now supersedes previous measures of fitness.

Frustaci and colleagues' report of their large series of patients summarizes early access experience with VenObi suggesting that we can expect the same or better results as physicians grow more experienced with this treatment and its toxicities. Health services could learn from this study and work to provide better support for patients who lack good caregiver support. In many countries with large geographic area, the distance from home to an infusion center and/or absence of a caregiver can lead to significant health inequity and efforts should be made to reduce these barriers and ensure that rural patients can access the same effective therapies as those living near urban centers. These same principles can be applied across other hematologic malignancies and are also relevant to novel therapies, such as bispecific antibodies and chimeric antigen receptor T-cell therapy.[9]

This study of early experience with VenObi in Italy should be seen as an encouragement for the feasibility of this regimen given the reported very high rates of treatment completion and particularly high rates of completing the "debulking" portion of the therapy.

Now is the time to remove age and fitness discrimination for CLL patients!

Disclosures

CO has received honoraria for advisory board participation and/or consulting from AbbVie, Astrazeneca, BeOne, Janssen, Lilly, Merck and Roche.

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