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Acta
Haematologica

Acta Haematol , DOI: 10.1159/000533349

Received: July 12, 2023

Accepted: July 28, 2023

Published online: August 7, 2023

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ISSN: 0001-5792 (Print), eISSN: 1421-9662 (Online)

https://www.karger.com/AHA

Acta Haematologica

Editorial

Consensus statements highlight the need of harmonizing CLL management worldwide.

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Short Title: Consensus Statements in CLL

Running title: Consensus statements in CLL

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Number of Figures: 1

Word count: 1302

Keywords: CLL, prognostication, treatment, guidelines, consensus statements.

In addition to the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines that are reference standards for the treatment of chronic lymphocytic leukemia (CLL) in Europe and the US, several consensus statements, formulated by independent, multidisciplinary panels of specialists, have been developed to provide region-specific guidance for the management of CLL.

In this issue of Acta Haematologica, Alshemmari et al. [1] present a series of CLL consensus statements designed to provide CLL-treating hematologists in the Gulf Region with an evidence-based tool for the management of CLL. The statements encompass several CLL-related topics, including diagnosis, risk assessment, treatment decisions, therapy sequence, disease complications, and the management of CLL during the COVID-19 pandemic. Overall, the consensus statements are not intended to replace published guidelines, but rather to provide a diagnostic and treatment algorithm that may support clinicians treating CLL in the Gulf region where access to and affordability of innovative targeted drugs for CLL therapy are now comparable to those in the rest of the world.

From a methodologic standpoint, a three-step modified Delphi consensus methodology has been adopted which has been utilised and validated in numerous studies in a variety of disease states. However, despite the rigorous methodology used, some statements deserve additional comments.

The authors report an 87% level of agreement supporting the role of the CLL international prognostic index (CLL-IPI) for CLL prognostication. The CLL-IPI, which combines five parameters (age, clinical stage, TP53 status [normal vs. del(17p) and/or TP53 mutation], IGHV mutational status, and serum β2-microglobulin) to predict clinical outcome in CLL patients was established and validated in the era of chemoimmunotherapy (CIT). However, the predictive utility of CLL-IPI is irrelevant in the context of targeted therapies. The continuous individualized risk index (CIRI) which combines the CLL-IPI and assessment of minimal residual disease (MRD) more accurately describes the dynamic changes that characterize the course of CLL. This dynamic risk model seems to be superior to the use of CLL-IPI alone in the prediction of CLL outcomes. Finally, in the current revolutionized therapeutic scenario of CLL, we expect that novel prognostic models might encompass specific mechanisms of CLL progression with the ability to predict the risk of Richter transformation, one of the most severe complications associated with CLL [2].

The assessment of patient fitness is an evolving area in the transition from CIT to targeted therapy. The Cumulative Illness Rating Scale (CIRS) score developed in the CIT therapy era has shown reliability when applied to assess fitness in patients treated with targeted agents. Recently, the CLL Comorbidity Index (CLL-CI), a less time-consuming method for assessing the burden of comorbidities identified by applying a machine learning algorithm, effectively stratifies CLL patients into three groups with different event-free survival (EFS) rates. Of note, the CLL-CI has been validated in a large population-based cohort comprising 4975 CLL patients and may be a candidate for substituting the CIRS in assessing comorbidities in CLL patients to be treated with targeted agents.

The consensus statements from the Gulf Region provide recommendations for evidence-based individual therapeutic options. However, these recommendations should be regarded as provisional because some options are not fully supported by results from comparative, randomized phase III studies. This is the case of the initial choice of continuous Bruton kinase inhibitors (BTKis) versus fixed-duration (FD) venetoclax-obinutuzumab (VO) therapy, which appear to have comparable efficacy, at least in patients with genetic standard risk. The decision in relation to the administration of continuous versus FD therapy should take into account factors such as comorbidities (especially cardiac and renal diseases), molecular and cytogenetic status, potential adherence to therapy, the logistics of the therapeutic intervention, and, above all, patient preference [3] (Figure 1). The ongoing CLL17 study directly compares continuous ibrutinib and FD VO or venetoclax-ibrutinib in treatment-naïve CLL patients (NCT04608318) and will hopefully inform future practice in this area.

The combination of BTKi with an anti-CD20 monoclonal antibody has been debated in CLL. Whilst the addition of rituximab to ibrutinib did not lead to an improvement in progression-free survival (PFS) in

two randomized trials (the Alliance and MDACC trials), obinutuzumab combined with acalabrutinib, improved 5-year PFS by 12% in the ELEVATE-TN study [4].

These differences in the outcome may be due to the greater cell killing and improved antibody-dependent cellular cytotoxicity (ADCC) of obinotuzumab compared to ibrutinib. Furthermore, the higher inhibition of IL-2-inducible T cell kinase (ITK) in T cells, which impairs antibody-dependent cellular cytotoxicity (ADCC), observed with ibrutinib but not with acalabrutinib, may account for the improved clinical activity of the acalabrutinib-obinutuzumab combination in comparison to acalabrutinib as a single agent [4]. Alshemmari et al. [1] consistently highlight the association of acalabrutinib and obinutuzumab amongst the preferred upfront treatment options. In contrast, a single agent BTKi continues to be the gold standard of treatment for relapsed/refractory (R/R) CLL as the combination of a BTKi with an anti-CD20 monoclonal antibody is not supported by phase III clinical trial data in the context of R/R disease [5].

The Food and Drug Administration (FDA) and European Medicines Agency (EMA) recently approved the use of ibrutinib in an all-oral, FD combination with venetoclax (I+V) for previously untreated CLL patients. These approvals are based upon the pivotal phase III GLOW study, which demonstrated superior PFS in elderly/unfit patients treated with I+V when compared with the CIT regimen chlorambucil-obinutuzumab (Clb+O) as well as the FD cohort of the phase II CAPTIVATE study which included CLL patients younger than 70 years with high-risk features [4]. The I+V combination is not included in the therapeutic algorithm proposed by Alshemmari et al. [1]. However, we expect the Gulf Central Committee for Drug Registration (GCC-DR) to authorize such a FD combination for treatment-naïve CLL patients. This indicates that the CLL Consensus Statements from the Gulf Region should be updated early.

Historically, allogeneic hematopoietic cell transplantation (allo-HCT) can induce long-term disease control in CLL and overcome the poor prognostic impact of del(17p). Despite the efficacy of allo-HCT in high-risk disease, the number of CLL transplants has dramatically decreased over the past decade due to the introduction of novel agents. Another reason for the decline of allo-HCT use is that the traditional definition of high-risk disease mainly based on the presence of TP53 aberrations has lost some relevance in the era of targeted agents. For these reasons, the role of allo-HCT is well-defined only in the context of Richter transformation (RT) [4-5].

With the increased use of targeted agents in CLL, an emerging area of unmet need is the management of those patients who have failed both a covalent BTKi and a venetoclax-based regimen (double-refractory). Of note, double refractory CLL patients and especially those who are penta-refractory (previous covalent BTKi, chemotherapy, CD20 antibody, BCL2i, and PI3Ki) have no accepted standard-of-care therapy available. Since available information indicates that pirtobrutinib, a non-covalent BTKi, is an effective option for double-refractory patients, an FDA and EMA accelerated approval of pirtobrutinib is expected in CLL [5].

In conclusion, while praising the efforts of Alshemmari et al. [1] to provide high-quality guidance for the management of CLL patients in the Gulf area, we underscore the need for a regular update of these consensus statements. Furthermore, new evidence is continuously emerging in relation to the role of endpoints beyond the traditional survival outcomes such as PFS, overall survival (OS) and time to next treatment (TTNT). As elderly patients with CLL typically experience an impairment of quality of life (QoL), particularly in the presence of comorbidities, both guidelines and consensus statements should reserve room for assessing QoL endpoints, possibly using patient-reported outcomes (PROs). Given the increasing population of frail elderly and multimorbid individuals with concurrent CLL, an emphasis on decision-making in this population in future guidance would be a welcome addition for practitioners.

Conflict of Interest Statement

SM received honoraria from Janssen, Abbvie, and AstraZeneca. MR and DA declares no competing financial interests.

Funding Sources

The authors did not receive support from any organization for the submitted work. No funding was received to assist with the preparation of this manuscript.

Author Contributions

Contribution: S.M., M.R. and D.A. wrote the manuscript. All authors reviewed and approved the manuscript.

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Figure Legends

Decision-making factors for chronic lymphocytic leukemia (CLL) upfront therapy