

Introduction to a series of reviews on chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia seen by hematologists, and its incidence increases significantly with age. The course of CLL typically allows practitioners to establish long-term relationships with patients but requires them to actively manage a wide range of internal medicine problems related to chronic immune deficiency, infections, autoimmune complications, and prevention of secondary cancers through appropriate screening. In addition, elderly patients often have other comorbidities and age-related symptoms such as fatigue that require hematologists to exclude CLL as the cause through active workup. Change in the diagnosis, staging, and treatment management of CLL for many decades was quite slow, enabling physicians to rely on past knowledge and not be left behind on relevant findings related to the biology and care of these patients. Fortunately for CLL patients, this is no longer the case, as a robust field of new discoveries in genomics, classification, risk stratification, and application of current and new therapies has rapidly transformed this disease into one for which therapy changes more quickly than even the “disease-specific experts” can keep up with. This is best exemplified by the large number of genes now shown to be commonly mutated in CLL, as identified in the review by Guièze and Wu, for which functions in the pathophysiology and progression of this disease are not fully understood. Additionally, an entirely new entity, monoclonal B-cell lymphocytosis, has emerged, which is akin to the precursor to multiple myeloma’s monoclonal gammopathy of uncertain significance, with defined complications and risk of CLL progression. Finally, 2014 was a year of therapeutic revolution in CLL, for which four new medications were fully approved for marketing in the United States: ofatumumab, obinutuzumab, idelalisib, and ibrutinib. For other countries, these are all now either approved or in the process of completing regulatory review. The positive impact of adding anti-CD20 antibody treatment to more aggressive chemotherapy such as fludarabine and cyclophosphamide is well known to many. However, obinutuzumab extended this same survival benefit when combined with chlorambucil in less fit, older patients who represent the majority of individuals treated with this disease. Of even more impact to CLL was the full approval of the first kinase-directed therapies (ie, ibrutinib and idelalisib), which have the potential, together with other therapeutics currently under clinical development, to revolutionize the entire therapeutic approach to CLL. Unlike many therapies previously used in CLL, agents such as ibrutinib have, to date, produced a very modest frequency of classical resistance, as reviewed herein. Furthermore, remissions in previously untreated, symptomatic CLL patients treated with ibrutinib appear to be quite durable, with some similarity to the progression-free and overall survival curves observed with early evaluation of imatinib for chronic myeloid leukemia. Finally, CLL cellular therapy also took a big step forward with the successful application of chimeric antigen

receptor T-cell therapy. The successful attainment of undetectable disease in a subset of patients with CLL undergoing this treatment was overshadowed only by the more dramatic effect in relapsed pediatric acute lymphoblastic leukemia, where the initial research focus of this exciting treatment has been directed.

In recognition of the rapid changes that have occurred in the management of CLL, the editorial team at *Blood* commissioned reviews from select leaders in the field who pioneered each area of transformative change. If it is not yet clear to the reader that the past several years has been a time to pay close attention to continuing medical education in CLL, we hope that this editorial will provide the impetus to read and enjoy this series of reviews.

Five concise reviews related to different areas of CLL are provided in this issue, including:

- Romain Guièze and Catherine J. Wu, “Genomic and epigenomic heterogeneity in chronic lymphocytic leukemia”
- Paolo Strati and Tait D. Shanafelt, “Monoclonal B-cell lymphocytosis and early-stage chronic lymphocytic leukemia: diagnosis, natural history, and risk stratification”
- Nitin Jain and Susan O’Brien, “Initial treatment of CLL: integrating biology and functional status”
- Jennifer A. Woyach and Amy J. Johnson, “Targeted therapies in CLL: mechanisms of resistance and strategies for management”
- Anthony Mato and David L. Porter, “A drive through cellular therapy for CLL in 2015: allogeneic cell transplantation and CARs”

Given the progress in each of these areas over the past year, we have strived to assure rapid turnaround of the articles from submission to publication in an effort to minimize any outdated material. The field of CLL in these review areas is truly moving quickly, so the reader should not allow this issue to collect dust on the shelf or journal pile before reading. CLL is undergoing an exciting transition from what was for many a fatal disease to one that can be controlled for extended periods of time with an armamentarium of relatively well-tolerated therapies that to date exhibit very modest long-term risks. For the less common younger CLL patients who have decades of life ahead of them, chemoimmunotherapy, long-term single-agent targeted therapy, combinations of targeted therapies, or targeted agents with cellular therapy will all be investigated and compared in ongoing or future trials. Also, the field now is moving toward the active application of new knowledge regarding disease heterogeneity to personalized medicine approaches for CLL patients. This review series will further enable practitioners to integrate these changes into their management approach of CLL for the betterment of patients under their care.

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