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Chronic lymphocytic leukemia: recent progress and current challenges

Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia, and since the last issue of *Seminars in Oncology* devoted to CLL in 2006, the landscape of this disease has changed dramatically (Fig. 1). In the past 5–10 years striking progress has been made both in understanding the biology of this disease and advancing of its therapy. The basis of much of this progress has been a better understanding of the molecular underpinnings of the disease as well as that of B-cell malignancies in general. Additionally, the science of drug development relative to small molecules, peptide based therapies, and cellular therapies has advanced tremendously. This has changed CLL from a disease with an almost predictable poor outcome after initiation of therapy to one where deaths due to disease have decreased dramatically. For the first time, our goal is to determine which patients can be cured with chemoimmunotherapy and which should be directed toward effective but non-curative BCR signaling antagonist therapy. Other targeted therapies directed toward bcl-2, CD20, CD19, CD37, and immune checkpoints similarly offer potential for combination treatments that might be curative or induce prolonged remissions.

CLL is a heterogeneous disease, with a large proportion of initially diagnosed patients having a very indolent course and requiring no therapy, and others requiring therapy at or soon to diagnosis, experiencing many relapses, and eventually succumbing to disease. The biologic basis for this heterogeneity continues to be teased out. Classic clinical prognostic factors, such as stage and lymphocyte doubling time, have been replaced by molecular factors including immunoglobulin heavy chain variable region gene mutational status, interphase/stimulated metaphase cytogenetics, and zap-70 expression (or absence of ZAP-70 methylation). As well, prognostic scoring systems which take multiple factors into account are currently undergoing validation. Advances in sequencing of the genome as well as transcriptome have the potential to greatly advance our knowledge of the genetics of this disease, and already recurrent mutations in TP53, BIRC3, NOTCH1, and SF3B1 have proven to be important prognostic factors. Unlike many other diseases, there is no common mutation in CLL, but it is clear that increasing genomic complexity is associated with more aggressive disease and that certain driver and passenger mutations have the potential to greatly influence disease course. With continued study, next generation sequencing will likely move to the clinical realm to help physicians counsel patients on prognosis and choose therapies.

Perhaps even more important than the biological knowledge that has been gained over the past few years are the therapeutic advances that are allowing our patients to live longer than ever before. The advent of small molecule inhibitors, including inhibitors of Bruton agammaglobulinemia tyrosine kinase (BTK), phosphoinositide 3-kinase (PI3K) p110 delta, and B-cell lymphoma 2 (BCL2) has changed the paradigm of treatment of relapsed disease, from the administration of immunosuppressive chemoimmunotherapy regimens to less toxic, more convenient oral medications. There remain many open questions regarding these drugs including combination versus single agent therapy, sequence of administration, and duration of therapy, and these questions will continue to be addressed in the coming years. As well, increasing knowledge of the role of the microenvironment and immune system in CLL has led to advances in therapeutic monoclonal antibodies as well as immune modulatory therapies that are currently finding a place in the therapeutic arsenal. This is certainly an exciting time for patients with CLL as well as the physicians caring for them. There has been no time in the past 40+ years where CLL treatment approaches are changing so quickly with dramatic improvement in patient outcome.

Given the advances in biology, prognostication, and therapy, we are optimistic that outcomes for our patients will continue to improve over the next few years as the kinase inhibitors and other new therapies become more widely available. Just as the therapy of relapsed disease has changed dramatically with the US Food and Drug Administration approval of ibrutinib and idelalisib, we are preparing for the potential of a paradigm shift for treatment-naïve patients. A recently completed study of ibrutinib versus chlorambucil in elderly, untreated CLL has been reported to have a pronounced improvement in response, progression-free survival, and overall survival with the former treatment. However, chlorambucil is not viewed as a true treatment for untreated CLL so true adaption of moving ibrutinib forward as initial treatment will likely depend upon two ongoing phase III intergroup studies (NCT02048813 and NCT01886872) that are trying to answer the question of whether ibrutinib or ibrutinib combination therapy is better than standard of care than chemoimmunotherapy. We expect, and hope, that the outcomes of these studies and others will shift the paradigm of CLL treatment away from chemoimmunotherapy for the vast majority of patients, especially those who are older and those with unfavorable prognostic factors. In fact, we find it conceivable that within the next 5 years, the majority of patients could receive ibrutinib or ibrutinib plus rituximab as front-line therapy, with chemoimmunotherapy reserved for those patients who are young with mutated IGHV and favorable cytogenetics, who have the potential for very long-term remissions or even cure with upfront chemoimmunotherapy. We also expect that a paradigm shift like this will lead to a next set of studies where our next generation of prognostic markers are used to risk stratify to truly personalize therapy for our CLL patients.

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