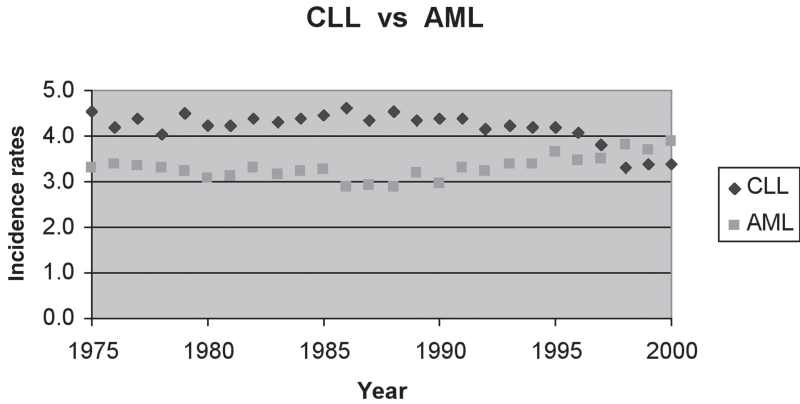

PREFACE

Chronic lymphocytic leukemia (CLL) is usually described as the most common leukemia in the United States, Canada, and Western Europe, whereas it is rare in Japan (1) and infrequent in other Asian societies (2). In the United States, CLL remained the most common leukemia between 1973 and 1991 with a mean age- and population-adjusted incidence of 4.4/100,000, whereas it was 3.2/100,000 for acute myelocytic leukemia (AML), the second most frequent leukemia during that time. However, the incidence of CLL began declining in the mid-1990s as AML's rose, resulting in reversed positions after 1997, with rates of 3.4 for CLL and 3.9 for AML in 2000, the last year of available Surveillance, Epidemiology, and End Results (SEER) data (3) (Fig. 1). Likewise, according to American Cancer Society projections for the 2000–2002 period, CLL accounted for 22.7–26.3% of all leukemias in the United States, whereas AML represented 31.5–34.4% (4), and in 2003 approximately 7300 new cases of CLL and 10,500 new cases of AML are expected in the United States (5). On the other hand, these data probably underestimate the true incidence and prevalence of CLL (6). Indeed, the ease of suspecting the disease based on blood lymphocytosis revealed by ubiquitous CBCs, coupled with the highly specific and sensitive diagnostic power of immunophenotyping, makes a cytologic diagnosis of CLL possible in many asymptomatic individuals with emerging clones that are likely to remain indolent and untreated for many years (7). This, and the fact that many of these individuals are likely to die of unrelated deaths, suggest that their leukemia might be considered incidental by their physicians and not be reported to tumor registries nor listed in death certificates.

Yet, whether it is the most common or the second most common leukemia in the Western world, it is noteworthy that CLL attracts a disproportionate amount of interest in the scientific community despite accounting for less than 1% of all new cancers and all cancer deaths in the United States in any given year (3,5), after a frequently benign course compatible with a multiyear survival (Table 1). This interest is illustrated by a recent Medline survey that yielded 4002 articles on CLL in the last 10 years (January 1993 through December 2002), compared



Age- and population-adjusted incidence rates for CLL and AML between 1975 and 2000.
(Data from ref. 3, SEER Cancer Statistics Review, 1975–2000)

Table 1
CLL vs Lung Cancer in the US: Incidence, Mortality, and Survival Rates (3,4,6)

	CLL	Lung Cancer
New cases (2003 estimates)	7300	171,900
New cases as percentage of total cancers (2003)	0.55	12.9
Age-adjusted incidence rate (1999)	3	68
Mortality (total deaths in 1999)	4300	152,480
Mortality as percentage of total cancer deaths (1999)	0.79	28.2
Age-adjusted mortality rate (1995–1999)	1.6	58
Percentage of patients surviving 5 years (1992–1998)	73	15

to 38,222 on lung cancer, the most lethal cancer accounting for 12.9% of all cancer deaths expected in the United States in 2003 (5), after a relentless progression and an average survival that barely exceeds 6 months (8). Several factors render CLL an interesting subject for study by scientists and clinical researchers. They include marked progress in understanding the molecular biology of normal and neoplastic lymphocytes and recent advances in molecular genetic techniques culminating in microarray technology. The former, facilitated by highly sophisticated and versatile flow cytometry instruments, powerful analytical software (9), and a rapidly evolving hybridoma technology with its myriad of monoclonal antibodies targeted to lymphoid antigens, enable the discriminant analysis of complex and heterogeneous cellular components within tissues and fluids, their differentiation, activation, and proliferative potential. The latter enables the study of thousands of genes, their expression and interactions, simultaneously (10). These tools together with the ease of procuring blood and bone marrow samples repeatedly with little discomfort or risk to patients, whose prolonged survival enables long-term follow-up studies, are largely responsible for the fascination of CLL. This fascination at the molecular level extends to human trials. Indeed, as of December, 2002, there were 69 ongoing National Cancer Institute (NCI)-sponsored clinical trials on CLL and 185 on lung cancer (11), a ratio of 1:2.7 despite the relative age-adjusted incidence and death ratios in the 1995–1999 period of 1:23 and 1:36, respectively (Table 1). Not surprisingly, the pharmaceutical industry has also participated in and financially benefited from these heightened bench and clinical research activities, launching new agents with activity in CLL, such as Fludarabine®, Rituxan®, and Campath®.

Because the aim of medical research is to generate the scientific database as a foundation for ultimately improving health care, a pertinent and timely question is whether this extraordinary focus on CLL has improved patient outcomes and where it is leading. Thus, the purpose of *Chronic Lymphocytic Leukemia: Molecular Genetics, Biology, Diagnosis, and Management*, is to review recent advances in molecular genetics and biology of CLL, to assess the impact on the diagnosis and management of this disease, and to suggest future directions. To do so, a panel of senior experts was assembled from the United States and Europe, and each was assigned the task of updating the status of his or her area of expertise in a comprehensive yet concise chapter. This effort yielded 23 chapters, carefully prepared by 43 scientists and clinical researchers from 24 medical centers or research institutions. Chapters were organized into five sectional themes beginning with Dr. Marti's enlightening historical perspective that sets the stage for sequentially reviewing recent progress in the molecular genetics and biology of CLL and the extent to which these

advances are being translated into the clinical setting, and ending with overviews of inherited predisposition to CLL and of the special features of juvenile CLL.

As superbly summarized in the reviews on molecular biology and genetics of CLL and their clinical correlates presented in *Chronic Lymphocytic Leukemia: Molecular Genetics, Biology, Diagnosis, and Management*, we can conclude the following. CLL appears to derive from CD5-positive naïve B-lymphocytes that accumulate unchecked by the normal processes of apoptotic cell death. Though probably a single disease, the mutational status of the IgV_H gene identifies two different disease subsets with markedly different outcomes, as described in Dr. Hamblin's chapter on the subject: patients with unmutated IgV_H genes have a more aggressive, infiltrative, and progressive disease with an unstable genome, and hence a poorer prognosis. Determining IgV_H status might also prove helpful for the assessment of inherited predisposition, as described by Dr. Houlston and colleagues. Although no cytogenetic abnormalities are specific for CLL, standard metaphase karyotyping techniques used in the clinical setting uncover single or complex clonal abnormalities in approximately 50% of patients. Survival is best in patients with normal karyotypes and decreases as clonal abnormalities develop and become more complex, as described by Dr. Julliusson. However, newer and more sensitive techniques, notably fluorescence *in situ* hybridization (FISH) (12) and comparative genomic hybridization (CGH) (13) suitable for analyzing cells in interphase, have increased the yield to 80% of prognostically stratifiable abnormalities, as described by Dr. Stilgenbauer and colleagues. Ideally, a better delineation of genetic abnormalities underlying CLL should enhance our ability to assess an individual patient and make a prognosis, an elusive task not achievable by current prognostic indicators, as described by Drs. Monserrat and Rai and their teams. However, in CLL no gene has been identified underlying the development or course of the disease, and clonal cytogenetic abnormalities and other potential clinical and biologic risk factors that reflect ongoing progressive disease have no clear independent prognostic value. Delineation of quantitative and functional immune defects associated with CLL, both at the cellular and the humoral levels, has a profound impact on our understanding the pathogenesis of CLL and on deciding the management of several of its complications, as described by Drs. Hamblin, Kay, and Bodey and their colleagues. Finally, monoclonal antibodies used to detect cell surface antigen expression and DNA content have propelled flow cytometry to the forefront of clinical tools available to confirm a clinical diagnosis of CLL, to differentiate CLL from other lympho-proliferative disorders with similar clinical and cytologic profiles but different treatment and outcomes, and to assess proliferative potential, as described by Drs. Braylan and Orfao and their teams. Therapeutic exploitation of antigenic expression on CLL cells is already underway, as demonstrated by the commercial launching of two therapeutic monoclonal antibodies specific against CD20 and CD52 with demonstrable anti-CLL activity, singly or in combination with cytotoxic agents, or as carriers of radionuclide payloads, as described by Dr. Byrd and colleagues. Thus, as described by Dr. O'Brien and her team, our therapeutic choices range from cytotoxic drugs, to purine analogues, to monoclonal antibodies, and combinations thereof. To this list Drs. Michallet, Wilson, Kipps, Frankel, and their teams add the experimental approaches of bone marrow transplantation, complementary agents, and gene and immunotoxin therapies, respectively.

Facing these multiple treatment choices, how is a physician to proceed? The answer to this question is complex and must take into account a variety of disease characteristics and patient variables, and whether the treatment is within or outside a clinical trial, as forcefully articulated by Dr. Dighiero and others (14,15). Chlorambucil, one of several mustard derivatives developed after World War II, was the first drug with proven efficacy in the management of CLL (16),

as discussed in Dr. Marti's chapter. Over the ensuing 36 years, chlorambucil and other alkylators were used alone in a variety of doses and schedules or in combination with other cytotoxic agents until fludarabine monophosphate (Fludara®) was introduced in 1991. Since then, newer agents with activity in CLL include humanized monoclonal antibodies Rituxan® and Campath®, introduced in 2001 and 2002, respectively. As was the case for chlorambucil, Fludara, Rituxan, and Campath have been or are being studied in combination with cytotoxic drugs with varying success and toxicity, as reviewed by Drs. O'Brien and Byrd and colleagues. Thus, after four decades of clinical trials the following broad conclusions can be drawn for the benefit of clinicians facing the questions of how to treat CLL in the community setting: chlorambucil and Fludara are the most active agents for CLL inducing some degree of response in most patients. The former is an oral, better tolerated, less toxic drug that is less costly and requires fewer office visits than fludarabine and other drug options. More importantly, long-term randomized trials and meta-analysis of multiple individual trials have demonstrated that although fludarabine induces faster and more complete tumor responses, and more prolonged disease-free survival than chlorambucil and other treatment options, these improved tumor responses are not translated into prolonged overall survival, in spite of greater toxicity (17,18). Thus, advocating Fludara as the drug of choice for the majority of patients with CLL (19) appears based not on past experience but on expectations that, in the future, increased complete remission rates might eventually translate into prolonged overall survival.

Another vexing problem in CLL management is who and when to treat. Indeed, although there is general agreement about early treatment of most patients who present with advanced stages (Rai high-risk or Binet C), symptoms, or with bulky disease, 40–70% of patients do not exhibit these poor prognostic indicators when first diagnosed (7). In these circumstances the goal becomes watchful observation of patients with indolent disease and the treatment of those who exhibit indications of disease progression. Attempts to predict potentially progressive disease via surrogate biological and laboratory risk factors have been hindered by technical constraints (impractical, complex, or nonstandardized), and by the fact that they derive from the analysis of patient subsets homogeneous regarding a particular indicator, but heterogeneous with respect to disease progression or lack thereof, resulting in different outcomes that cannot be predicted on an individual basis.

Hence, in circumstances in which treatment indications are equivocal, several additional considerations should be included in the treatment decision-making process. First, a distinction should be made between the clinical research approach and patient care in the community setting. Indeed, though the goal of the former is the development of better treatments, the purpose of the latter is to provide palliation, particularly symptom relief. This dichotomy of approaches is justified by the repeated observation that tumor responses in CLL, including complete remissions, are not followed by increased overall survival. Under these circumstances, risking early or late complications, inflicting additional suffering, or incurring additional costs in the pursuit of complete remissions appears unjustified outside of clinical trials, in keeping with the concept of proportionality, which emphasizes beneficence (in this case palliation rather than tumor responses), with minimal maleficence (20). Thus, except for those presenting with advanced stage, symptoms, bulky disease, or with unfavorable chromosomal abnormalities or an unmutated IgV_H clone, previously untreated patients can benefit from an open-ended period of observation until clear indications of disease progression develop. Given the cited advantages of chlorambucil over alternatives, it should be viewed as the drug of choice initially, particularly because palliation can be achieved repeatedly via intermittent courses, monthly or every fortnight. Patients refractory to chlorambucil usually

respond to Fludara, at least once. Further treatment of patients who have relapsed after chlorambucil and Fludara or are refractory to both drugs—an infrequent occurrence often related to an incorrect diagnosis—should be undertaken based on the particular circumstances of the case rather than as a matter of course, and be focused on palliation. In each case and at each step, the potential benefits and side effects of the treatment contemplated and possible alternatives should be fully disclosed to patients so that their expectations are guided by the potential and limitations of present day therapy.

In conclusion, although considerable progress has been made in molecular biology and genetic research, treatment outcomes are unsatisfactory, survival prolongation has not been achieved, and the cure of CLL remains an elusive and distant goal. We must also acknowledge that the cell-kill approach that has driven drug development and patient management for decades (21) is unlikely to achieve that goal and alternatives designed to reverse or control the molecular aberrations underlying the development and progression of the malignant clone should be explored. The first successful example of this approach is Gleevec®, a drug that blocks production of the chimeric protein encoded in the *bcr/abl* fusion gene responsible for chronic myeloid leukemia, and thus the proliferative advantage of leukemic cells, without inducing cell death. The race to uncover genetic abnormalities underlying other cancers is already underway, but none has been identified in CLL, and many challenges and difficulties lie in the path, for we stand at the threshold of understanding the cancer genetics that will drive cancer pharmacogenomics of the future. In the meantime, a judicious utilization of current therapies will ensure palliation for the 97% of patients who are treated outside clinical trials. Patients desirous to explore experimental treatment options should be encouraged to do so within the framework of a clinical trial.

It is our hope that *Chronic Lymphocytic Leukemia: Molecular Genetics, Biology, Diagnosis, and Management* will inform and guide clinicians and clinical researchers, but also inspire and encourage a rising generation of scientists to focus their attention on molecular and genetic defects responsible for the development, progression, and complications of CLL as a foundation for the therapies of the postgenomic era.

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