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Genetic lesions in chronic lymphocytic leukemia: what's ready for prime time use?

Carol Moreno and Emili Montserrat

Carol Moreno and Emili Montserrat, Institute of Hematology and Oncology, Department of Hematology, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, University of Barcelona, Spain.

E-mail: emontse@clinic.ub.es. *doi:10.3324/haematol.2009.016873*

Chronic lymphocytic leukemia (CLL) is a frequent CD5$^+$ B-cell neoplasia that involves peripheral blood, bone marrow, lymph nodes and other lymphoid tissues. The median age of patients at diagnosis of CLL is around 70 years old and the prognosis is extremely variable. In spite of some advances in its therapy, CLL continues to be incurable. Due to this fact, and to the prognostic heterogeneity of the disease, individual, risk-adapted therapies are needed.

A number of clinical parameters identified in the 1980s and 1990s, particularly clinical stages, enable a prediction of the clinical outcome of patients with CLL. These parameters do not, however, indicate which patients will have rapidly evolving disease and which will have stable

disease. More importantly, these parameters are a mere reflection of the biology of the disease.

Two papers published in this issue of the journal add to our understanding of genetic lesions in CLL and their clinical relevance.[1,2] In the first one, Kienle *et al.* show that genetic prognostic factors cannot be replaced by expression markers, thus highlighting the need to compare potentially new prognostic parameters with well recognized and validated predictors.[1] In the second paper, Zhuang *et al.* demonstrate that CLL clones contain activated Akt, which contributes to cell survival, indicating that inhibition of Akt could be a novel target for CLL therapy.[2]

As exemplified by these two papers, unfolding the biological diversity of CLL has become one of the priorities in hematologic research. The discovery that *IGVH* genes in CLL can be either mutated or unmutated was a major advance in the understanding of CLL and its prognosis: patients with mutated *IGVH* genes (mutated CLL) have much better outcomes than those with unmutated *IGVH* genes (unmutated CLL).[3,4] The exception to this rule is those cases in which *IGVH3.21* family genes are used (around 8%) which have poor prognosis independently of *IGVH* mutational status.[5,6] Another important finding is that ZAP-70 is a powerful prognostic marker[7] that correlates, although not completely, with *IGVH* mutations, the prognostic value of these two markers being complementary.[8]

In the process of unraveling the complexity of CLL biology, genetic studies are important not only for research purposes but also in clinical practice.

From the diagnostic stand-point, genetic studies can exclude non-Hodgkin's lymphomas with leukemic expression that can be confounded with CLL such as mantle-cell lymphoma, which displays t(11;14)(q13;q32) or follicular lymphoma, which shows t(14;18)(q32;q21).[9]

Following seminal contributions by Döhner's group,[10] studies in large series of patients have consistently shown that about 80% of patients have cytogenetic abnormalities that can be detected by fluorescence *in situ* hybridization (FISH). The incidences of the most relevant genetic abnormalities range from 14% to 40% for del(13q) as an isolated abnormality, 10% to 32% for del(11q), 11% to 18% for trisomy 12, 3% to 27% for de(17p), and 2% to 9% for del(6q), depending on the stage of the disease and whether or not the disease is resistant to conventional therapy.[11, 12]

Cytogenetic abnormalities have independent prognostic value and identify subsets of patients with different clinical forms, times to progression, and survival rates. According to recent studies, three risk groups can be differentiated: (i) low-risk: patients with a normal karyotype or isolated del(13q); (ii) intermediate-risk: subjects with del(11q), trisomy 12 or del(6q); and (iii) high-risk: patients with del(17p), 14q32 translocations or a complex karyotype.

In further detail, patients with del(13q) as a single anomaly either do not require or respond well to therapy and have an excellent prognosis. Trisomy 12 is linked to both atypical morphology and immunophenotype of the leukemic cells, and del(6q) is more frequently observed in patients with an intermediate prognosis whose lymphocytes display plasmacytoid features.[11] In contrast, del (11q), which involves the *ATM* gene, is found in younger patients, frequently males, who have bulky disease. If treated only with purine analogs, the clinical outcome of patients with del(11q) is worse than that of patients with other abnormalities, with the exception of del(17p), which has the poorest prognostic significance.[12,13] However, current treatment combinations such as fludarabine plus cyclophosphamide or fludarabine, cyclophosphamide, and rituximab have significantly improved the response rate and progression-free-survival of these patients by overcoming the negative impact of del(11q).[14,15] Although infrequent, 14q32 translocations have been found in approximately 7% of patients with CLL and predict an unfavorable outcome[16,17] Clonal evolution and complex karyotype also imply an aggressive disease and poor prognosis.[18,19]

Among all genetic abnormalities, those involving 17p, reflecting lesions in the *TP53* machinery, are associated with the worst clinical prognosis. Patients with these lesions do not respond to standard fludarabine-based regimes and have rapidly evolving disease (median survival < 4 years)[12]. Although patients with these abnormalities may respond transiently to alemtuzumab (with or without corticosteroids), allogeneic stem cell transplantation should be considered when initial therapy fails. Flavopiridol and lenalidomide might also be useful in these instances.

The most common type of *TP53* alteration is the mutation of one allele accompanied by the deletion of the other. However, cases with *TP53* mutation in the absence of 17p deletions (5-20%) have a similar clinical course to those with the deletion.[20,21] It should be noted that del(17p) is more frequently observed in treated patients than in untreated ones (20%-20% *versus* 5-10%), which most likely reflects a treatment-driven clonal selection.

The above observations have a number of practical consequences (Table 1). Firstly, patients with del(11q) should not be treated with fludarabine (or other purine analogs) alone but with combinations such as fludarabine plus cyclophosphamide with or without rituximab. Secondly, patients with del(17p) should not receive fludarabine-based therapy but agents whose mechanism of action is *TP53*-independent, including allogeneic stem cell transplantation in selected candidates.

On the other hand, just as important as the achievement of complete remission is its duration. There are not may data on response duration according to genetic abnormalities, although, not surprisingly, poor-risk cytogenetics have been associated with a shorter response in recent studies.[14] Interestingly, unmutated *IGVH* genes have been found to correlate with a shorter progression-free interval.[22] It would, however, be premature, to use these, and other, biomarkers to guide therapy in CLL. Nevertheless, it is strongly recommended that these issues are investigated in clinical trials.

With regards to the significance of del(17p), the concept that this aberration invariably implies a poor prognosis is largely based on data obtained in patients included in clinical trials, requiring therapy and, therefore, with a poor prognosis. There are no large analyses of the natural history of 17p- CLL. In this light, a recent study including cases from the MD Anderson Cancer Center and the Mayo Clinic is of interest. In this study the outcome of a large series of untreated patients with 17p- CLL was investigat-

Table 1. Genetic studies of clinical relevance in the diagnosis and management of chronic lymphocytic leukemia.

	Genetic lesion	Genes involved	Clinical features
Differential diagnosis			
	t(11;14) (q13;q32)	*Cyclin D, IgH*	Mantle cell lymphoma
	t(14;18) (q32;q21)	*Bcl-2, IgH*	Follicular lymphoma
Prognosis			
	13q-isolated	miR-15a, miR-16-1	Low risk
	11q-	*ATM*	Intermediate-risk
	17p-	*TP53*	High-risk
	Mutations *TP53*	*TP53*	High-risk
	Complex karyotype	Multiple genes	Aggressive disease
	14q32 translocation	IgH+others	High-risk
	Mutated *IGHV*	*IGVH*	Low-risk
	Unmutated *IGHV*	*IGHV*	High-risk
	IGHV 3.21		High risk
Response to therapy			
	17p-	*TP53*	Resistance to fludarabine-based therapy
	11q-	*ATM*	Lower response to fludarabine
	Unmutated *IGHV*	*IGHV*	Shorter response duration

ed, showing that a substantial proportion of patients with this abnormality may have a rather indolent disease for a number of years.[23] This indicates that treatment should only be initiated in the presence of clinically aggressive disease.

Recently, a new class of small, non-coding RNA, called microRNA (miRNA), has been linked to several types of cancer. The role of miRNA as prognostic factors has already been established in CLL irrespective of the genetic alterations, with various studies showing that miRNA223 and miRNA29 correlate with progressive disease and poor prognosis.[24,25] Recently, specific miRNA signatures that discriminate del(11q), del(17p), trisomy 12, del(13q) and normal karyotype cytogenetic subgroups have also been identified.[26] Despite the unquestionable importance of these markers, they need further validation before they are used on a routine basis.

What about the future? Although FISH is considered to be the method of choice for detecting chromosomal aberrations in clinical practice, this technique is limited by the fact that it can only detect changes specific to the probes utilized and thus underestimates the extent of existing aberrations.[27] There is, therefore, a growing interest in applying other, more sensitive techniques to study genetic lesions in CLL (e.g., comparative genomic hybridization, CD40 or CpG-stimulated metaphase cytogenetics, single nucleotide polymorphism arrays, multiple ligation-dependent probe amplification). Furthermore, epigenetic lesions, previously largely ignored in CLL, are being increasingly investigated.[28]

The introduction of new technologies that allow sequencing of DNA in an extremely efficient way has paved the road to genomic expression profiling analyses that will, it is hoped, make possible further, important progress in understanding blood cancers, including CLL.[29] There are a number of large collaborative ongoing projects whose first, descriptive reports should be published shortly. The undertaking here is as challenging and controversial, but also as thrilling and worthwhile, as was the human genome project 20 years ago.[30,31]

It should be kept in mind, however, that the main goal of these studies is not to provide a "magic recipe" to predict the risk of individual patients or identify revolutionary, curative treatments, but rather the discovery of biological pathways underlying different forms of the disease. In this regard, it is also worth remembering that it has taken many years to gather enough meaningful information for cytogenetic alterations to be part of the clinical assessment of patients with CLL and that, among all the genetic markers identified, del(17p) is still the only undisputed alteration used in clinical practice.

While times have changed and advances are now quicker, there is still much work to be done before new technologies find their translation into the clinical arena. Let us, therefore, work hard and be patient.

Emili Montserrat is Professor of Medicine at the University of Barcelona, Department of Hematology, Hospital Clínic, Barcelona. He is a founding member of the International Workshop on CLL and Chairman of the European Research Initiative on CLL. His main area of interests is chronic lymphoproliferative disorders, particularly chronic lymphocytic leukemia, a field in which he and his group have made numerous contributions. Carol Moreno is a Postdoctoral Fellow at the Department of Hematology, Hospital Clínic, Barcelona. She is mainly interested in clinical and translational research in chronic lymphocytic leukemia.

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T-cell receptor gene transfer for the treatment of leukemia and other tumors

Mirjam H.M. Heemskerk

Department of Hematology, Leiden University Medical Center, Leiden, The Netherlands
E-mail: mhmheemskerk@lumc.nl. *doi:10.3324/haematol.2009.016022*

Almost two decades ago the potency of adoptive T-cell therapy was demonstrated by the success of donor lymphocyte infusions for the treatment of chronic myeloid leukemia after allogeneic stem cell transplantation. Since then several studies have demonstrated the clinical efficacy of adoptively transferred T cells for the treatment of viral infections as well as cancers. The broad application of adoptive immunotherapy using antigen-specific T cells is, however, hampered by the inability to isolate and expand large numbers of T cells with a defined