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Prognosis in chronic lymphocytic leukemia: let's have a look!

Chronic lymphocytic leukemia (CLL) has a variable clinical course. The clinical staging systems independently developed by Rai *et al.*[1] and Binet *et al*.[2] are very useful for assessing prognosis in patients with CLL. In addition to clinical stages, parameters with proven independent prognostic value are the number of lymphocytes in peripheral blood, the degree of bone marrow infiltration, the proportion of atypical lymphoid cells in peripheral blood, and the lymphocyte doubling time.[3] Moreover, other variables have recently been shown to have prognostic value in CLL. These include serum markers (e.g., lactate dehydrogenase, thymidine-kinase, β_2-microglobulin, and sCD23), CD38 expression on neoplastic lymphocytes, cytogenetic abnormalities, and the mutational status of IgV_H genes.[3-5] Whether classical prognostic factors should be replaced by the newer and more biologically meaningful parameters is a matter of debate and investigation. This is particularly important since, as treatments become more effective, prognostic factors may change.

In this regard, the paper by Mauro *et al.* published in this issue[6] fails to demonstrate a clear-cut correlation between lymphocyte morphology *at the time of disease progression* and the outcome of the disease in 69 patients treated with fludarabine and prednisone. As in other studies, atypical morphology was associated with advanced disease and atypical immunophenotype. In the univariate analysis atypical morphology correlated with a shorter survival, but this effect was not corroborated in the multivariate analysis. The only variables showing independent prognostic value for response duration were the duration of the disease before therapy, bone marrow histology, and the degree of the response. Why this is so is unclear. Although one might wonder what the results would have been in a larger series and with a longer follow-up, two explanations appropriately discussed by the authors should be taken into account. First, it is likely that classic prognostic factors do not necessarily apply to patients receiving newer and more effective treatments. Second, the fact that lymphocyte morphology is only a reflection of genetic alterations such as trisomy 12, del(6q), del(17p) or unmutated IgV genes, variables not analyzed in the present report, should be considered.

The time to have another look at prognostic factors in CLL has certainly come.[7] To determine the most important variables, prospective studies are required. Besides classical parameters, relevant variables to be included in such studies are serum markers (e.g., β_2 microglobulin, thymidine-kinase, and sCD23), CD38 expression on the neoplastic B-lymphocytes, cytogenetics, and the IgV mutational status, which at present remains a rather cumbersome analysis. Meanwhile clinical staging systems should continue to be the backbone for prognostic assessment in CLL. At the same time, hematologists should not forget a gesture which comes so naturally to their discipline, that is, to have a look at peripheral blood films, not only to diagnose what disease their patients have, but also to monitor the disease, its pace and evolution.

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Acute myeloid leukemia: something more than a simple molecular defect

Remarkable advances have been made in the past decade in our understanding of the molecular genetic basis of acute myeloid leukemias (AML). Many of our insights have been gained through the cloning and characterization of chromosomal translocation breakpoints, which have identified genes that are causally implicated in disease pathogenesis targeting the transcriptional apparatus in hematopoietic cells either directly or indirectly.[1] There is convincing evidence that gene rearrangements in AML involving transcription factors such as CBF, RARα, the ETS family and the HOX family are necessary for the onset of the disease,[2] but there is also equally compelling evidence that these events are not sufficient to cause a full leukemic phenotype, as evidenced in part by the long latencies required for disease development in the murine models of the disease.[3] These data support the hypothesis that multiple genetic abnormalities rather than a unique molecular defect are necessary for the phenotype of AML. An emerging paradigm is the co-operation between transcription factor fusions and other molecular events such as mutations in the FLT3 and c-kit receptor tyrosine kinases,[4] ras and NF-1 mutations,[5] aberrant activation of the Jak/Stat pathway,[6] epigenetic changes in the promoter regions of tumor suppressor genes[7] and dysregulation of the cytokine network genes in the pathogenesis of AML.[8] In such a model, additional abnormalities confer proliferation and/or anti-apoptotic activity to the hematopoietic cells, while the transcription factor fusion impairs normal differentiation pathways.

This issue of the Haematologica contains two interesting pieces of this still unsolved puzzle. First, Larramendy *et al.*[9] using cDNA microarray analysis show that several genes which are known to be involved in chromosomal translocations and fusions (i.e., FGFRI, MYC, NPM1 and DEC) were differentially expressed in AML. As none of these translocations was observed in their cases, the finding suggests that these genes are also activated by mechanism other than translocations. Second, Bruserud *et al.*[10] in a large series of consecutive AML patients demonstrated that leptin, a regulator of fat metabolism and angiogenesis, enhances spontaneous proliferation and constitutive cytokine release by native AML blasts.

Although the findings reported here may be the result of targeting the same signal transduction and transcriptional pathways by groups of genetically heterogeneous AMLs, the papers also extend our view of the AML as a collaboration between several oncogenic proteins. Many oncoproteins confer a proliferative and/or survival advantage, whereas other proteins impair hematopoietic differentiation. The two together cause the AML phenotype of enhanced proliferation and survival with impaired differentiation.

Much effort must be made to understand the wealth and complexity of these molecular genetic data. We need to identify the downstream effectors that are activated by mutations in leukemia. We need to know more about the genetics of deletions associated with AML, the role of transcriptional silencing induced by promoter hypermethylation, and the role of cytokine disturbances and angiogenesis in AML in order to answer two definitive questions: how does one identify therapeutic strategies that might be effective for a majority of leukemias when there are more than a hundred known molecular alterations and, how do we rationally approach targeted therapy for hematologic malignancies that are the consequence of more than one genetic event – is targeting one mutation adequate?[11]

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