HOW I TREAT: PROGNOSTICATION IN CHRONIC LYMPHOCYTIC LEUKAEMIA: A GAZE INTO THE FUTURE

Dr Tycho Baumann, Dr Julio Delgado, Prof Emili Montserrat

Department of Hematology, Institute of Hematology and Oncology, Hospital Clínic, University of Barcelona, Barcelona, Spain

Chronic lymphocytic leukaemia (CLL) is due to the relentless accumulation of monoclonal B lymphocytes with a distinct immunophenotype (i.e. surface membrane immunoglobulin [weak], CD5+, CD19+, CD23+) in bone marrow (BM), peripheral blood, and lymphoid tissues. CLL is a frequent disease with an incidence of around 5 per 100,000 in Western countries. The median age of patients at diagnosis is approximately 70 years, and the incidence of the disease dramatically increases with age, reaching >20 per 100,000 in individuals older than 70 years.

The median survival of patients with CLL has improved over the last few decades but there is not yet a curative therapy for this disorder. While the overall median survival of patients with CLL is now about 10 years, the individual prognosis ranges from a few months to a normal lifespan. Therefore, prognostication is an essential component in the management of patients with CLL.

Although somewhat overlapping, it is useful to distinguish prognostic factors (parameters that predict the likelihood of disease progression and hence the need for therapy) from predictive factors (markers that inform about the probability of response to a given therapy). For the sake of clarity, it is better to cluster these two groups of parameters under the name of outcome predictors, rather than prognostic factors (Figure 1). In this context, it is important to underscore that the correlation of a parameter with an outcome does not qualify it as a prognostic factor unless a number of criteria (e.g. harmonisation/standardisation, reproducibility, independent prognostic value, and superiority over other parameters that predict the same outcome) are fulfilled.

In CLL, prognostic factors at diagnosis foretell the clinical behaviour of the disease, particularly the likelihood of disease progression, and also provide a raw estimate of the life expectancy. They are useful to inform the patient and to advise the frequency and characteristics of the follow-up, and whether it is preferable that the patient can be controlled in a general setting or in a specialised CLL centre. Although developed 40 years ago, clinical staging systems independently devised by Rai and Binet continue to be employed. Clinical staging systems are based on the concept that CLL cells first accumulate in blood, subsequently in lymph nodes and spleen, and eventually in BM, leading to its functional failure. Patients with early, low-risk disease have a median survival of >15 years, while those with advanced, high-risk disease have a median life expectancy of <3–4 years. Importantly, assigning a clinical stage to a given patient only requires a physical examination and a complete blood cell count; such simplicity is a great advantage as it permits the use of clinical stages in any setting.

Although useful, clinical stages have some limitations. Firstly, in Western countries, approximately 80% of patients are presently diagnosed in asymptomatic, early-stage routine blood analysis, and this blurs the usefulness of clinical stages as a whole. Secondly, clinical stages do not identify patients whose disease will progress as compared to those in whom the disease will remain stable. Thirdly, patients are classified as in an advanced stage based on the presence of anaemia or thrombocytopaenia, regardless of their origin. However, patients with advanced disease because of immune cytopaenia have a better outcome than those with cytopaenia due to a heavy infiltration of the BM by lymphocytes. Fourthly, clinical stages do not predict response to treatment. Finally, current therapies are overcoming the poor prognostic significance of clinical stages. As an example, the prognosis of patients with advanced or high-risk disease is getting closer to the prognosis of patients with intermediate-risk disease thanks to more effective therapies.

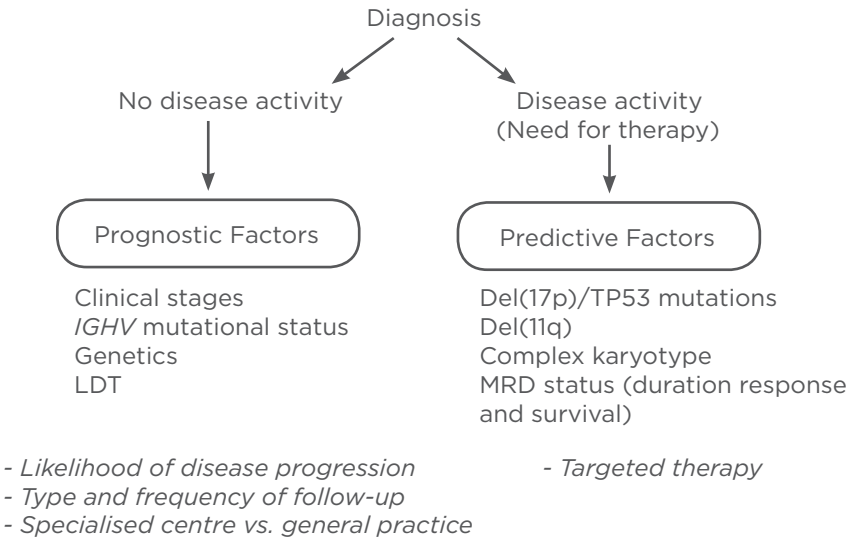

Figure 1: CLL: From prognostic factors to predictive factors.
CLL: chronic lymphocytic leukaemia; LDT: lymphocyte doubling time; MRD: minimal residual disease; vs.: versus.

There are a number of parameters that add prognostic power to clinical stages, including *IGHV* mutational status, ZAP70, and CD38 expression, genetic lesions, lymphocyte doubling time, and serum beta-2 microglobulin level. Among them, *IGHV* gene mutational status is the most important prognostic factor. In landmark studies conducted at the end of the last century it was demonstrated that in CLL the *IGHV* gene can either be mutated (50-70% of cases) or unmutated (30-50% of cases), and that *IGHV* mutational status correlates with biological and clinical features. Thus, while patients with mutated *IGHV* usually have indolent disease not needing therapy and good prognosis, those with unmutated *IGHV* tend to have a rapidly progressive disease, require early intervention, respond poorly to therapy, and have short survival. Notably, many adverse prognostic features, such as advanced clinical stage, del(11q), del(17p), *TP53, NOTCH1,* and *SF3B1* mutations predominate in unmutated cases, whereas the opposite is true for patients with mutated *IGHV. IGHV* mutational status is thus not only the backbone for two different forms of CLL but also a central feature around which revolve many other prognostic factors.

As for the future, clinical stages should continue to be used since they give valuable information about the tumour burden and allow the comparison of series of patients seen over decades. However, clinical stages should be complemented by biomarkers, particularly *IGHV* mutational status. Other valuable prognostic parameters are genetic lesions; del(13q) as sole abnormality identifies patients with an excellent prognosis, whereas del(11q), del(17p)/*TP53* mutations, or complex karyotype (≥2 lesions) are associated with poor outcome, mainly because patients harbouring these lesions respond poorly to therapy.

As in many other tumours, CLL prognostication is rapidly shifting from prognostic to predictive factors. Response to therapy and degree of response are the most important predictors of life expectancy in cancer patients. CLL is not an exception to that rule. Although it could be argued that new treatments such as BCR inhibitors (ibrutinib), the PI3K inhibitor IPI-145 (duvelisib), or the BCL2 antagonist ABT-199 that result in long-term survival with no need of complete response may eventually challenge the 'response-survival' paradigm, a longer follow-up of clinical trials investigating these agents is necessary to draw firm conclusions.

Unfortunately, the number of response predictors in CLL is limited. The presence of del(11q) is associated with poor response to fludarabine alone and demands the use of chemoimmunotherapy as treatment. More importantly, del(17p)/*TP53* mutations convey resistance to fludarabine-based treatment, including chemoimmunotherapy, and a very short survival (median <2 years). Patients with the latter lesions should be treated with new agents, active across all genetic subgroups

or, in selected cases, allogeneic stem cell transplantation. There is also some notion that patients with *NOTCH1* mutations might gain no benefit from anti-CD20 monoclonal antibodies (rituximab, ofatumumab).

Now, next generation sequencing platforms are making it possible to investigate the correlation of genetic lesions, even at subclonal level, with clinical outcomes. There is evidence, for instance, that subclonal *TP53* mutations detected at diagnosis result in refractoriness to chemoimmunotherapy (as in clonal mutations) and short survival. In contrast, the same does not seem to be true for *NOTCH1, SF3B1,* and *BIRC3* mutations.

Importantly, outcome predictors can change as a result of better therapies. In line with this, there is not a unique 'one size fits all' set of predictive markers; for example, response predictors to ibrutinib may differ from those of chemoimmunotherapy. On the other hand, novel agents may trigger mechanisms of resistance to therapy, as it occurs with ibrutinib and *BTK* and *PLCγ2* mutations that induce (and become markers of) treatment failure. Finally, although not yet incorporated into the routine evaluation of response to treatment, patients with undetectable minimal residual disease (MRD) after therapy have a longer progression-free and overall survival; this opens the door to MRD-guided clinical trials and management.

In summary, profound changes in our understanding of CLL are taking place, including the way prognosis is assessed. A number of biomarkers are being incorporated to already existing outcome predictors. Nevertheless, applying all available and claimed 'new' prognostic factors to every single patient with CLL would be not only unrealistic but also more confusing than informative. Therefore, only robust predictors identified with strict methodology and considered more informative than other markers for the same event should be taken into consideration. Building up prognostic models for CLL is on the agenda of many groups of investigators, the important challenge being to construct reproducible, reliable, and easy-to-apply tools.

FURTHER READING

1. Montserrat E. Prognostic factors in chronic lymphocytic leukemia: a conceptual approach. Int J Hematol Oncol. 2014;3(2):145-52.
2. Stilgenbauer S et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. Blood. 2014;123(21):3247-54.
3. Sargent DJ et al. Clinical trial designs for predictive marker validation in cancer treatment trials. J Clin Oncol. 2005;23(9):2020-7.
4. Sutton LA, Rosenquist R. Deciphering the molecular landscape in chronic lymphocytic leukemia: time frame of disease evolution. Haematologica. 2015;100(1):7-16.