The last decade has seen major changes in the treatment of chronic lymphocytic leukemia (CLL), with randomized trials now demonstrating improved survival with the use of chemoimmunotherapy.\[1\] This has led to a paradigm shift in the treatment expectations in CLL, from palliation of symptoms to improved survival, achievement of complete remission, and eradication of minimal residual disease; complete remission and eradication of minimal residual disease are both now felt to be surrogates for prolonged progression-free and overall survival. During the same time period there have been major advances in our understanding of the basic pathophysiology of CLL; multiple prognostic factors have emerged, which have largely been explored for their importance in predicting time from diagnosis to requirement of next treatment—but which are increasingly being evaluated for their ability to predict response to therapy, or even to drive the choice of therapy.\[2\] While it would be ideal if new therapies could be designed based on the underlying pathophysiology of the disease, to date the advances in treatment and the understanding of pathophysiology have largely occurred in parallel. However, we are now entering an era in which we hope that more treatments can be developed that target the underlying molecular defects within the CLL cell.

In their article, Drs Mougalian and O'Brien review the current status of the role of assessment of adverse genetic features in the management of CLL. There are now a panoply of prognostic factors that can be assessed in CLL, and it is vital that these be assessed in clinical trials so that we can determine whether all CLL subgroups respond equivalently, and whether there is evidence that alterations in treatment are able to overcome the effects of adverse prognostic factors.\[3\] However, in routine clinical practice, it is possible to pose other questions:

- Is there any benefit in assessing prognostic factors in CLL patients at presentation?
- Which prognostic factors need to be determined at the time treatment is required?
- Do these prognostic features alter our approach to therapy?
- What is the benefit in assessing prognostic features at presentation?

There are no data to support the notion that patients with high-risk disease should be treated earlier in the course of their disease. There are a number of ongoing trials that explore the question of whether patients with high-risk disease might benefit from modern chemoimmunotherapy approaches. One such trial, the German/French CLL 7 study (EUDRACT-2005-003018-14, NCT00275054), has completed enrollment, but we have no data yet from this study. Until there are clinical trial data demonstrating an
advantage in treating high-risk patients, these patients should continue to be followed with a watch-and-wait approach.

The benefit of assessing prognostic markers at diagnosis is that it makes it possible to inform patients of their likely disease course. However, none of these markers are absolutely determinative, and it is a rare patient who has only all good or all bad prognostic factors. Thus it is possible that assessing many prognostic markers will simply create confusion. The value of testing for each marker should be discussed by the clinician and the patient, although such discussions require considerable time.

Assess prognostic markers at time of treatment?

There is increased value in assessing prognostic markers at the time treatment is required. Genetic abnormalities detected by FISH are not stable and change over time. Therefore, even if a full FISH panel was performed at the time of diagnosis, this would have to be repeated. Other factors, such as immunoglobulin mutation status, are stable, but this assay is complex and not readily available in routine laboratories. Assessment of ZAP-70 expression is fraught with the difficulties of both the relative non-reproducibility of the assay and the need to determine an appropriate cut-off that has prognostic significance. While I perform a full prognostic marker work-up, this is for academic reasons; in practice, assessment of stage, performance status, beta-2-microglobulin level, and CD38 level, along with cytogenetic analysis by FISH, may well be sufficient.[4]

Prognostic markers and choice of treatment

Here the authors make the case that identifying whether patients have del(17p) and del(11q) can have an impact on treatment. This is certainly the case. Patients whose CLL cells harbor del(17p) have a poorer response to chemoimmunotherapy. It is now the practice in Europe to offer these patients alemtuzumab-based therapy. However, as was pointed out in the article, the duration of response to alemtuzumab appears comparable but not much better than the response to fludarabine, cyclophosphamide, and rituximab (Rituxan) (FCR). These patients therefore continue to have a poor prognosis, and guidelines suggest that they be offered allogeneic stem cell transplant during their first response.[5] Patients with CLL who have del(11q) appear to derive particular benefit from FCR, and although there has not been a direct comparison of FR and FCR, a case can be made, as the authors point out, for treating patients who have del(11q) with FCR.

Taken together, the impact that the advances in our understanding of the pathophysiology of CLL has made on the management of the disease remains rather modest. The challenge going forward is to align our scientific advances with our clinical practice.

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