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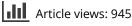
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# Telomere analysis to predict chronic lymphocytic leukemia outcome: a STELA test to change clinical practice?

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Defining the prognosis of individual chronic lymphocytic leukemia patients remains a significant clinical challenge. Consequently, there is a need to identify tests that can provide reliable personalized risk assessments. Here we discuss the problems associated with the currently used prognostic markers and emphasize the potential for using high-resolution telomere length analysis (STELA) for the accurate prediction of clinical outcome. Given the development of targeted, less toxic therapeutics in chronic lymphocytic leukemia, it is crucial to accurately identify those patients who might benefit from early treatment and equally those who may not require treatment at all. In this context, there is also a clear need for dependable predictive markers of response to drugs so that optimal treatment decisions can be made for individual patients.

A diagnosis of chronic lymphocytic leukemia (CLL) is often perceived as a 'sword of Damocles' by patients and their families. Although the diagnosis is definitive, clinicians often implement a 'watch and wait' strategy, and the projected outcome for an individual patient in this situation is anything but certain. Against this backdrop, there is a clear need to accurately identify patients with a good or poor outlook as close to diagnosis as possible, thereby providing important information to patients, their clinicians and funding agencies. Consequently, there has been a concerted search for markers that can provide this improved prognostic resolution. So much so that there is now a bewildering array of potential markers ranging from clinical parameters such as disease stage, patient age and performance status to genetic and molecular markers such as immunoglobulin gene mutational status, cytogenetics, CD38 expression and ZAP70 expression to name but a few.

The truth is that although these markers can inform what happens to cohorts of given subsets of patients, none can reliably define the prognosis for individual patients. In every case, the Kaplan-Meier curves depicting the good prognostic subsets show erosion implying that patients in the favorable groups still die from their disease. Conversely, even patients in the worst cytogenetic risk group, those with 17p deletions, do not uniformly progress and succumb to their disease. So what is to be done? Well, one approach has been to develop complex algorithms that combine these clinical and molecular markers in the hope that the multiplicity of the testing will provide improved clarity [1-3]. In the most recent incarnation of this tactic, Pflug et al. [4] were able to divide CLL patients into four prognostic groups, with the minority poor prognostic group (4%) having a 5-year survival of 18.7%. Clearly, this approach provides high discriminatory power that can be more reliably applied at the individual patient level at least for the 'low-risk' and 'very high-risk' subsets. However, the majority of the patients (69%) occupied the other two categories raising the question of the usefulness of this prognostic scoring system for the majority of individuals. Furthermore, this weighted

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algorithm is based on the combination of five separate genetic/ molecular analyses together with the performance status, age and sex of the patient. This makes the prognostic assessment expensive to perform and unwieldy to use.

Recently, we presented data on a promising alternative prognostic strategy based on single telomere length analysis (STELA) [5]. Telomeres are structures that cap the ends of chromosomes and play a critical role in maintaining genomic integrity. Telomere length is a key determinant of telomere function, with short telomeres being subjected to aberrant DNA repair activity that leads to telomere fusion and largescale genomic rearrangements. STELA is a high-resolution approach to determine telomere length and is capable of detecting telomeres within the length ranges at which fusion can occur. Using STELA, we have previously shown a link between short telomeres, telomere fusion and genomic instability in CLL [6]. In our most recent manuscript, we defined the telomere length threshold at which the chromosome end-capping function is lost resulting in telomere fusion events and genomic instability. Importantly, from a prognostic marker perspective, we showed that a subset of early-stage patients exhibited extensive telomere erosion and fusion, indicating that telomere shortening and dysfunction can precede clinical progression. Furthermore, and somewhat more unexpectedly, we also have data that show that the telomere length profiles of individual patients can remain remarkably stable throughout the course of their disease (unpublished observations). This implies that the telomere length profiles observed in individual CLL patients are fixed at an early point in the pathological process, making it ideal as a prognostic marker. To reinforce this point, in both our discovery and validation cohorts, STELA was able to define two distinct prognostic subsets of patients: the long telomere subset had a 10-year survival greater than 90% whereas the short telomere subset had a 10-year survival of just 13%. These figures compare favorably with the data reported by Pflug et al. [4] and point to a powerful, single platform, prognostic marker for CLL patients. With this in mind, we have recently developed a high-throughput version of the STELA assay that facilitates the rapid and reliable analysis of large numbers of CLL patient samples. The importance to patients of reliable prognostic information cannot be overstated. Shanafelt et al. [7] reported that even patients with early-stage CLL not requiring treatment are constantly worried about their disease. A patient being told that he/she has a >90% chance of being alive at 10 years if the telomeres are long has the potential to bring enormous emotional benefits to patients.

The biological and clinical landscape of CLL is changing rapidly. Less than a decade ago, there were few therapeutic options available to patients who required treatment and single-agent chemotherapy was the mainstay. The introduction of combination chemoimmunotherapy provided the first evidence that treatment could alter the natural pathology of the disease [8], but this combination of drugs is not suitable for large numbers of patients. However, the advent of new, highly active, small-molecule inhibitors with very modest side-effect profiles has presented the possibility that all CLL patients can be potentially treated, even the elderly less fit individuals [9,10]. Inevitably, these new agents come at a high price, and so the key question is who would benefit most from these drugs and would maximal benefit be seen in the frontline setting? Although the current prognostic markers provide useful information about the likelihood of disease progression and who will require treatment in cohorts, there is now an urgent need for predictive markers of response to treatment so that informed treatment decisions can be made. For instance, we know that patients who relapse quickly on the 'gold standard' combination of fludarabine, cyclophosphamide and rituximab have a poor clinical outlook. Can we prospectively identify these patients, and might they be better served by alternative treatment with small-molecule inhibitors without the need for prior exposure to genotoxic agents? This would potentially produce optimal responses in the frontline setting and remove the associated risks of developing treatment-related secondary malignancies. Conversely, we know that some patients achieve very durable responses with conventional treatment approaches. So it would seem that not everyone needs a small-molecule inhibitor to have a prolonged life. So the question is, can we reliably predict responses to therapy so that personalized treatment approaches can be employed? Although we have yet to publish our findings, we have evidence that STELA can predict response to chemotherapy-based regimens. Given that short telomeres are associated with increased genomic instability, it seems likely that the addition of a further genotoxic insult in the form of chemotherapy is detrimental in these patients. It is therefore possible that STELA could be a useful tool in aiding treatment decisions for individual patients by identifying those patients with an inherent predisposition to clonal evolution. This may result in the selection of the optimal frontline therapy for individuals and the development of more selective clinical trial recruitment criteria, which might be particularly useful in treatment-naïve patient populations. In conclusion, there has never been a more pressing need for accurate prognostic and predictive markers in CLL; it would seem that STELA has the potential to fit the bill on both counts.

#### Financial & competing interests disclosure

C Pepper, D Baird and C Fegan are co-authors of a patent describing the use of telomere dysfunction as a prognostic tool. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

Telomere analysis to predict CLL outcome Editorial

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