New patterns of genetic instability in chronic myeloid leukemia: interesting, but not ready for clinical use

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Received: April 7, 2023.
Accepted: April 13, 2023.
Early view: April 20, 2023.

https://doi.org/10.3324/haematol.2023.283059

The impact of tyrosine kinase inhibitors (TKI) on the treatment of chronic myeloid leukemia (CML) has been extraordinary, with overall survival of patients treated in chronic phase now approximating that of the normal population and the elimination of the need for allogeneic transplantation to produce functional cure. However, occasional patients do not respond adequately to standard TKI therapy. I was taught by Dr. Emil Freireich that one frequently develops new insights into the biology of diseases by studying exceptions to the "average" patient, avoiding what he termed "median disease".[1]

And indeed, there have been many attempts to identify mechanisms of TKI failure, including studies of pharmacokinetic variability, overexpression of the multidrug resistance phenotype,[2] the involvement of other signaling pathways including those associated with immune regulation,[3] the presence of RNA expression signatures more consistent with blast phase (BP),[4] amongst others. However, none have resulted in changes in the standard treatment approach.

In this issue of *Haematologica*, Shanmuganathan and colleagues,[5] expanding their earlier observations,[6] used data from the Australian TIDEL trial to explore the effects of additional genomic changes on response to TKI. The TIDEL trial used a somewhat more aggressive regimen, administering a higher (600 mg) dose of imatinib as initial therapy, with a rapid switch to nilotinib if molecular responses were not satisfactory.[7] The overall outcomes of this well-conducted and thoughtfully analyzed study were excellent, although similar to results from large randomized trials comparing imatinib with other TKI.

The authors used an RNA-based capture technique and/or whole genome or transcriptome sequencing to identify changes in addition to the expected *BCR::ABL1* in samples from newly diagnosed chronic phase patients. Cancer-associated abnormalities were found in approximately 16% of 200 patients, most commonly "AML-associated" mutations such as *ASXL1* (found in 9% of patients), *RUNX1*, *BCORL1*, *IDH2*, *DNMT3A*, and *TET2*. In addition, what was termed "Ph-associated rearrangements" were detected in 36 (18%) patients, defined by the authors as "aberrant fusions formed at the time of the Ph translocation, involving genes or sequences on the translocated chromosomes". These variants contained material from multiple chromosomes other than 9 and 22, linked to either *BCR* or *ABL1*. The *Online Supplementary Appendix* to the paper provides elegant descriptions of these findings. These two patient groups were combined and termed "additional genetic abnormalities" (AGA), with their outcomes compared to patients without these additional changes.

Overall survival was 94% at four years of follow-up, of which 6 of 11 deaths were not related to CML. Eight patients progressed to BP with no apparent association with the presence of AGA. However, after some somewhat complex statistical gymnastics, it was concluded that imatinib-treated patients with AGA had inferior failure-free survival (FFS), most commonly due to failure to reach molecular milestones, but also including accelerated phase (AP) / BP, detection of *BCR::ABL1* kinase mutations or death. A host of comparisons between those with or without AGA were made, some incorporating consideration of the EUTOS long-term survival (ELTS) risk score, all of which numerically and sometimes statistically "significantly" (if P=0.04 is considered "proof") suggested poorer outcomes in those with AGA.

The legitimacy of combining Ph-associated arrangements with other molecular rearrangements is an important issue. To use a baseball analogy, singles and home runs are both classified as 'hits', but the latter are much more impactful (and home run hitters get paid much more!). Given the paucity of information about the biology of Ph-associated rearrangements, a further rationale is needed to justify giving both equal statistical weight and analyzing them as a homogeneous group. All the Ph-associated arrangements were molecularly unique, suggesting that the specific arrangement was not the culprit, but rather that this finding could hypothetically be a marker of "genetic instability" and/or deficiencies in DNA repair. That said, it

has been known for decades that *BCR::ABL1* is permissive of the accumulation of as yet poorly characterized additional mutations contributing to disease progression.

It is also important to acknowledge that the correlation of discrete genotypes with outcome does not necessarily provide insights into mechanisms of treatment failure or generate hypotheses about how to address this therapeutically. A humbling example is the recognition, known since the early 1980s, of the favorable influence of Core Binding Factor mutations, initially identified cytogenetically by t(8;21) or inv(16), on the outcome of AML treatment with chemotherapy. Despite the explosion of technology and increased dissection of the biology of AML in the last 40 years or more, the mechanism(s) by which these mutations seem to confer sensitivity to cytotoxic chemotherapy are still not known. Furthermore, there is little understanding of the mechanisms by which additional Ph chromosomes, isochromosome 17 and other aneuploid karyotypes contribute to the block in differentiation leading to blast crisis. The multiple non-discrete "partners" described within the Ph-associated rearrangements would make it even less likely to be able to identify specific pathways to study and target in the future.

Mutated *ASXL1* was the most common cancer-associated finding, and while FFS was somewhat lower in *ASXL1*-mutated patients (P=0.045), only one of these 18 evolved to blast crisis and in this patient the *ASXL1* had not been present at the time of deterioration, raising questions as to its relationship to disease progression.

These results, and similar observations in an additional small series of CML patients,[8] raise the question of whether all newly diagnosed patients be screened molecularly for changes other than *BCR::ABL1*. Certainly, the technology used to detect the Ph-associated arrangements is quite complex, not standardized and, as mentioned, they are not clearly associated by themselves with outcome. It is, however, now routine to search for molecular changes in patients with AML, particularly those with normal karyotypes. Nonetheless, there is no evidence that these additional changes alone are prognostic or contribute to CML progression, and *ASXL1*, known to be a poor prognostic finding in AML, is not "targetable". Hence, more information is needed before such additional molecular screening should be done routinely at diagnosis.

Lastly, there is the question of whether initial treatment with second generation TKI might be more successful in patients with AGA. Randomized trials have not shown a survival advantage using second generation TKI compared to 400 mg of imatinib, although many clinicians opt for the more potent TKI in patients with other poor-risk features. This is a clinically relevant question, and it should be possible to reanalyze material stored from the completed randomized trials rather than waiting the many years that it would take to evaluate this prospectively.

In summary, this interesting paper raises more questions than it answers. We still have a poor understanding of how "genetic instability" results in progression and treatment resistance in CML and other cancers. Although a relatively uncommon problem overall in CML, patients in less economically developed countries more often present with more advanced disease, and further studies building on these observations could be important to develop hypothesis-driven new treatment approaches for such individuals.

Disclosures

No conflicts of interest to disclose.

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