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Are we ready to use precision medicine in chronic myeloid leukemia practice?

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Over the last two decades, the introduction of tyrosine kinase inhibitors (TKI) and advances in *BCR-ABL1* monitoring using quantitative polymerase chain reaction (qPCR) have significantly improved treatment outcomes in chronic myeloid leukemia (CML) patients.[1] Not only the introduction of TKI increased the life expectancy of CML patients (98% of age-matched healthy control), but also the incorporation of *BCR-ABL1* monitoring using qPCR significantly improved outcomes of CML patients by identifying those cases developing TKI failure and progressing to the advanced phase.[2,3] However, it is still challenging to predict patients at high risk for TKI failure at initial diagnosis of CML before commencing TKI therapy. Thus, major challenges still remain, including lack of accurate risk stratification at initial diagnosis.

The current algorithm for CML management is mainly based on monitoring *BCR-ABL1* using qPCR.[3] Despite its good performance, there are still remaining issues some of which include: i) how to select upfront TKI drug in a newly diagnosed CML patient (imatinib *vs.* newer generation TKI); ii) how to switch TKI therapy in a patient who developed TKI resistance, but without *ABL1* kinase domain mutations; and iii) how to predict which patients are at high risk of progression to blastic crisis. Thus, there is an urgent demand for novel biomarkers in managing CML beyond monitoring *BCR-ABL1* fusion transcripts. Given this, how can we go forward from here?

Let us look back at routine CML practice 20 years ago when TKI therapy and qPCR-based *BCR-ABL1* monitoring were not available.[4] When a patient was newly diagnosed with chronic phase CML, the first step would be the identification of an HLA-matched donor for allogeneic hematopoietic cell transplantation (HCT) and co-ordination of allogeneic HCT within two years from initial diagnosis before the patient progressed to advanced phase. If an appropriate donor was not available, interferon therapy was a treatment of choice. Disease monitoring was mainly based on the metaphase cytogenetic test for which bone marrow aspiration should be performed every 6 months to assess cytogenetic response. Let us compare it with current CML practice, which has changed significantly over the last two decades. First, we no longer initiate a search for an HLA-matched donor search until TKI failure or intolerance to more than two TKI is suspected.[3] Bone marrow examination does not need to be repeated as frequent as *BCR-ABL1* qPCR on peripheral blood which is the mainstay of disease monitoring. So, what will happen in the future? CML practice will evolve and will be transformed again from the current routine practice. However, what we do not know yet is how this will be achieved and what changes will be applied.

Precision medicine is becoming the mainstream of future medicine. It has been implemented in the clinical practice in acute myeloid leukemia (AML),[5] and myeloproliferative

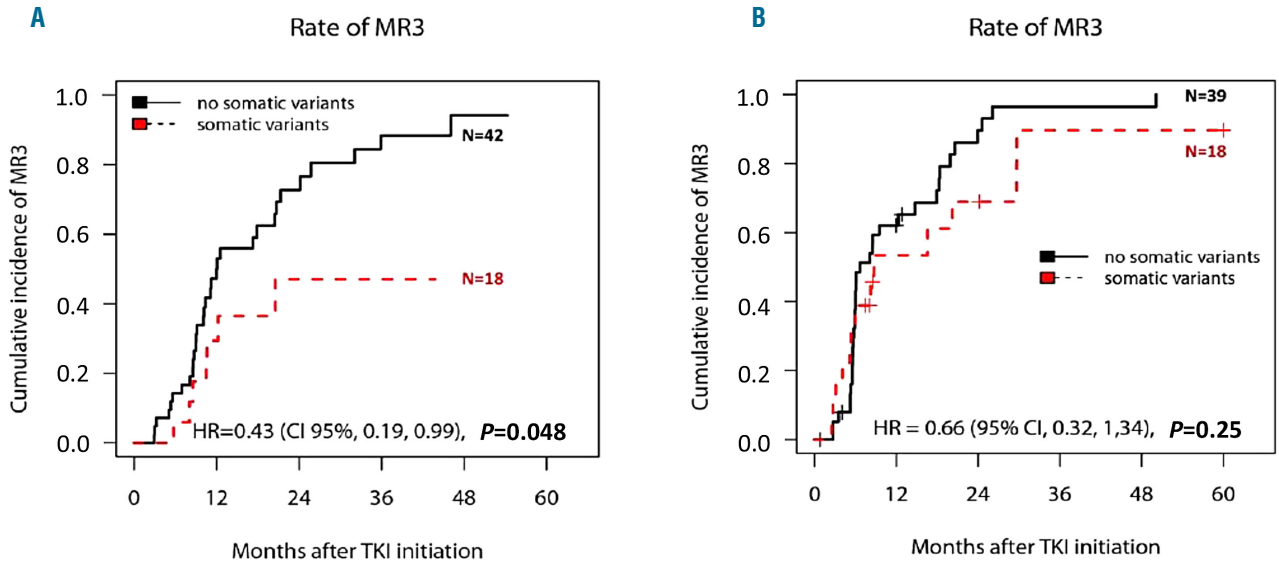

Figure 1. The use of 2nd-generation tyrosine kinase inhibitors (2G-TKI) can overcome the adverse effect of somatic mutation in epigenetic modifier genes in chronic myeloid leukemia (CML) patients. Incidence of achievement of major molecular response (MR3) following imatinib therapy (A) or 2G-TKI (B) according to the presence of somatic mutation in epigenetic modifier gene in newly diagnosed chronic phase CML patients. N: number; HR: hazard ratio; CI: confidence interval.

neoplasms (MPN).[6] For example, mutation profiles are used for the initial risk assessment of AML such as inclusion of several high-risk markers such as mutations in *TP53*, *RUNX1*, and *ASXL1* and high allelic ratio of *FLT3-ITD* in the revised European LeukemiaNet risk stratification system.[7] The decision for further consolidation therapy between allogeneic HCT *versus* conventional consolidation therapy can be made based on the ELN risk stratification system.[7] In addition, there is growing evidence to suggest that NGS-based measurable residual disease status could predict long-term outcomes in AML patients after induction chemotherapy[8] or after allogeneic HCT.[9] Accordingly, a next-generation sequencing (NGS)-based genomic test is being incorporated into clinical practice in a diverse subtype of hematologic malignancies. So, what about in CML?

A series of previous studies have reported consistent findings on the genomics in CML;[10–13] 1) somatic mutations, particularly those in epigenetic modification pathway, are recurrently identified in CML patients with a prevalence of approximately 30-40%; 2) increasing frequency of the mutation was associated with TKI resistance and progression to advanced disease in comparison to optimal response to TKI therapy or chronic phase (CP) disease; 3) somatic mutation in epigenetic modification pathway has adverse prognostic implication. The *ASXL1* mutation is most commonly detected mutation in CP-CML patients with a prevalence of 9.7%, while it was detected with a higher frequency of 15.1% in advanced phase CML patients.[13] *RUNX1* mutations and *IKZF1* exon deletions were strongly associated with disease progression, given that it was more frequently detected in advanced phases.[13] With respect to adverse prognostic implications of mutation in epigenetic modification pathway, Kim *et al.* reported that patients carrying gene mutation in the epigenetic modification pathway showed inferior complete cytogenetic response at 12 months (53% *vs.* 79%; *P*=0.02), major molecular response at two years (35% *vs.* 62%; *P*=0.04), and MR4.5 at three years (26% *vs.* 47%; *P*=0.03).[10] Although successful replication to confirm those findings is required with well-curated clinical outcome data, and inclusion of larger cohorts, the study of Nteliopoulos *et al.*[14] presented in this issue of the Journal has validated the adverse prognostic impact of somatic mutation in the epigenetic modification pathway in the patients treated with imatinib. What is interesting in this study is that an adverse prognosis from a somatic mutation in the epigenetic modification pathway can be abrogated by the use of 2nd generation TKI, which is very intriguing.

Nteliopoulos *et al.*[14] have profiled genetic variants in epigenetic modifiers, including 71 candidate genes for predicting response to TKI therapy and progression to advanced disease. Out of 124 patients (including 62 patients treated with imatinib and 62 patients with 2nd generation TKI), they reported that 30% of patients carry somatic variants in at least one of *ASXL1*, *IKZF1*, *DNMT3A*, *CREBBP*, which is consistent with results from the previous studies. Non-responders have higher frequencies of somatic variants in those genes as compared to responders. When treatment outcomes were analyzed according to the TKI subtype and the presence of a mutation in epigenetic modifier gene, molecular response (MR3) in those with the mutation was significantly inferior to those without mutation when treated with imatinib (*P*=0.048) (Figure 1). On the other hand, the similar prognostic effect of a mutation in the epigenetic modifiers was not observed in patients treated with 2nd generation TKI (*P*=0.25) (Figure 1). Not only for MR3, but also analyses on other clinical end points showed that an adverse prognostic effect from mutations in epigenetic modifier genes are significantly reduced by the use of 2nd generation TKI. The next step is validation and confirma-

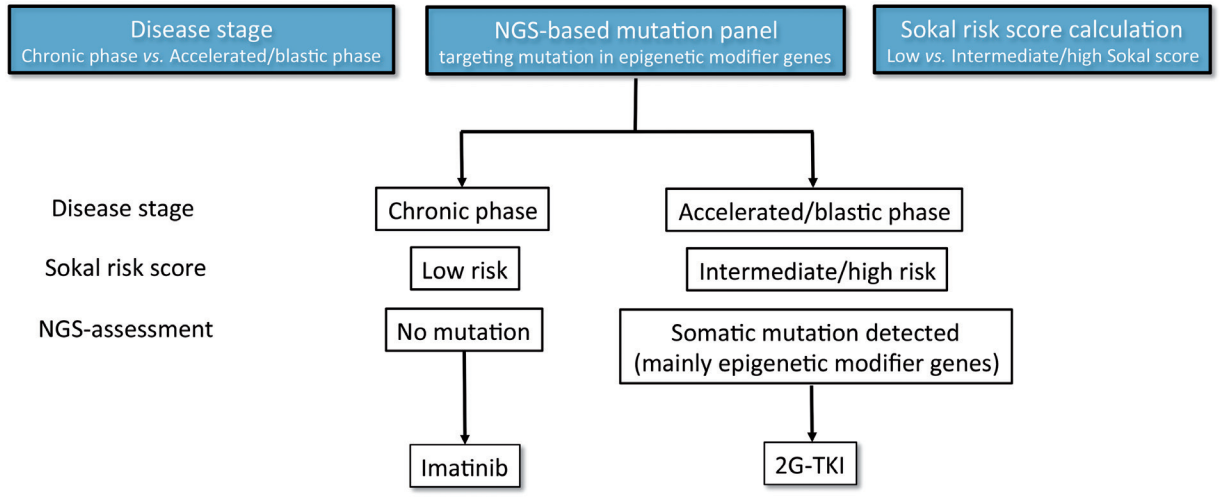

Figure 2. Treatment algorithm of chronic myeloid leukemia (CML) patients in future medicine incorporating next-generation sequencing (NGS)-based risk assessment and up-front tyrosine kinase inhibitor (TKI) drug selection.

tion of the finding before appropriate recommendations can be made, with the inclusion of NGS screening at initial diagnosis of CML.[13] Moreover, clinical risk scores at diagnosis may inform the selection of patients for NGS-based screening. Figure 2 shows an example of future therapies incorporating NGS-based testing at diagnosis in CML management. Once the diagnosis of CML is made, the next step for risk assessment will include NGS-based risk assessment in addition to clinical disease staging (chronic phase *vs.* accelerated phase *vs.* blastic phase) or Sokal risk score calculation. In the case of advanced disease phase, intermediate to high Sokal risk score or those with a somatic mutation in epigenetic modifiers pathway such as *ASXL1*, *DMNT3A*, *TET2* will be strong candidates for upfront therapy using the 2nd generation TKI.

In the context of somatic mutation profile in CML, some questions remain: 1) what is the role of age-related clonal hematopoiesis in the development of cardiovascular toxicity following TKI therapy; 2) what is the role of somatic mutations in TKI switch for TKI resistant cases without carrying *ABL1* kinase domain mutation; 3) what is the clinical relevance of somatic mutations with respect to treatment-free remission? Future studies are warranted to answer these questions so that somatic mutation profiles can be incorporated into future CML practice not only for upfront TKI drug selection but also during follow up with TKI therapy.

There is a limitation in the study by Nteliopoulos *et al.*[14] the study cohort did not consist of a consecutive set of patients. Thus, further study is strongly warranted to reach a clearer conclusion with a larger prospectively collected cohort. Upon successful validation of these data, this approach using NGS-based precision medicine will eventually be incorporated into a clinical algorithm of CML management such as future ELN recommendations. Precision medicine will soon be part of our practice even in CML.

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