Precision tyrosine kinase inhibitor dosing in chronic myeloid leukemia?

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Therapy for chronic myeloid leukemia (CML) with tyrosine kinase inhibitors (TKIs) has made this a potentially curable disease.[1,2] However, many challenges remain, including: i) defining the best TKI, dose and schedule; ii) how to reduce the frequency and severity of adverse events (AEs); iii) how to increase the number of subjects who can achieve therapy-free remission (TFR), and others. In this issue of *Haematologica*, using data from the German CML-Study IV,[2] Michel *et al.*[3] tackle two of these challenges: the best TKI dose and reducing AEs. They report that subjects randomized to receive high-dose imatinib, 800 mg/day (d), achieving a stable major molecular response (MMR, 0.1% of *BCRABL1*^{IS}) can have their imatinib dose reduced to 400 mg/d without losing their response, with the additional benefits of reducing AEs and cost, and likely increasing compliance.

Several prior clinical trials tested whether high-dose imatinib, 800 mg/d, was more effective than the approved dose, 400 mg/d.[4-6] The primary end point of most of these trials was the proportion of study subjects achieving a MMR at 1 year, a landmark associated with a very low risk of leukemia progression and death from CML-related causes.[7] A secondary end point was the time to MMR achievement. The conclusion of most studies was that high-dose imatinib resulted in faster MMRs but later led to a similar proportion of MMRs after 1 or 2 years.[4-6] However, high-dose imatinib was associated with increased rates of ≥ grade 3 AEs, worse compliance, and higher costs.[4-6] Consequently, many study subjects assigned to high-dose imatinib reverted to 400 mg/d. Recently, a landmark analysis of data from the CML-Study IV reported that study subjects receiving an optimized high-dose of imatinib (median dose, 600 mg/d) achieved deeper and faster molecular responses (MMR, MR4 and MR4.5) compared with those receiving 400 mg/d, with no increase in ≥ grade-3 AEs.[8] Importantly, the conventional and optimized strategies of giving imatinib resulted in similar event-free survival (EFS), progression-free survival (PFS), and overall survival (OS).[2]

There are several caveats to accepting these conclusions including biases associated with landmark analyses and discordances between molecular responses (surrogate end points) and clinically important end points such as EFS, PFS and OS.[9,10] Such discordances are common to many, if not most, clinical trials and underscore the limitations of surrogate end points.[11] This is not surprising in chronic

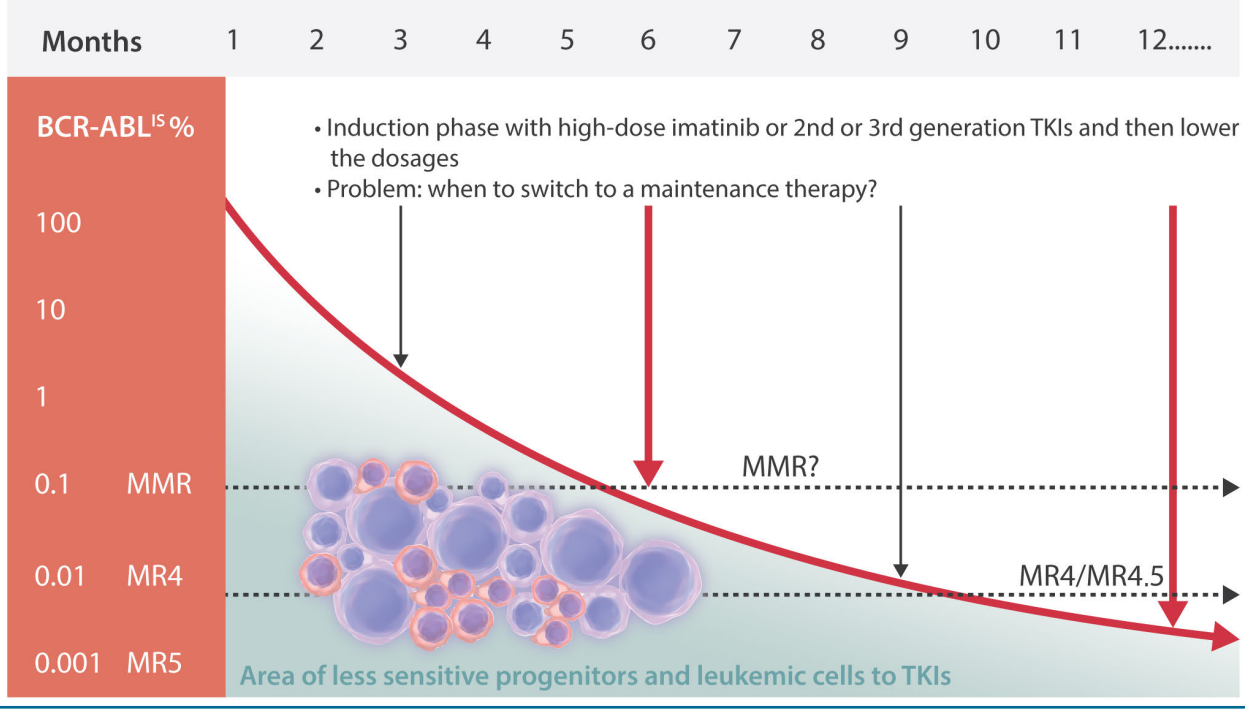

Figure 1. Possible future therapeutic strategy for CML. TKI: tyrosine kinase inhibitors; MMR: major molecular response; MR: molecular response.

phase CML where more than half of the deaths are not related to CML.[2] However, the bottom line at a time of generic imatinib is that a starting dose of 800 or 600 mg/d reduced to 400 mg/d in subjects achieving a stable MMR is probably a safe and effective therapeutic strategy.

The report of Michel *et al.* recalls an interesting observation made several years ago in the OpTKima study. There, some older subjects receiving imatinib 400 mg/d, but who stopped therapy every 3rd month maintained a MMR and sometimes even improved the depth of molecular response.[12] However, unlike the uniformly stable MMRs reported by Michel *et al.*, approximately 25% of subjects in the OpTKima study lost their MMR. The studies differ, of course, in the fact that, in the OpTKima study, subjects completely stopped imatinib while in the CML-Study IV subjects had an imatinib dose reduction.

What do these data suggest? A reasonable conclusion is that the best strategy is to optimize initial imatinib dose based on the rapidity, depth and stability of a subject's molecular response rather than using the same dose and schedule for everyone. Alternatively, some subjects who could benefit by starting off directly on a 2nd generation TKI,[13] could be moved to lower (and less toxic) dosages of the same drug once they achieved a good molecular response, or eventually, in specific cases, switch to imatinib for maintenance. Studies testing the feasibility and the value of this approach are needed and, indeed, some are already ongoing or planned.[14]

The regulatory approved dose of imatinib and other TKIs often evolves from results of phase I safety studies designed to determine the maximum tolerated dose (MTD) followed by phase II and III studies of efficacy.[15] This developmental scheme assumes the MTD is the maximally effective dose (MED). But is this assumption correct? In the case of CML, the MED is the dose associated with maximal inhibition of $P210^{BCRABL1}$ that is also safe, especially when given over a long period of time. Given these considerations, it is easy to see why the MTD and MED might differ for a TKI.[15]

Another issue is why different subjects respond differently to the same dose of a TKI like imatinib. Many factors could explain this heterogeneity but the most obvious is *BCRABL1* mutations.[16] Other variables include pharmaco-kinetic and pharmaco-dynamic variables related to TKI absorption and metabolism, susceptibility to AEs, and compliance.[17] Also, some subjects in chronic phase CML have subclones with additional mutations in genes other than *BCR-ABL1* reflecting the genomic instability typical of CML.[18] These subclones are not detected by routine diagnostic procedures and may be important in determining response to TKI-therapy and likelihood of CML progression, obviously confounded outcomes. In this context, it is important to remember that there is a substantial interval between when *BCRABL1* is acquired to when CML is diagnosed, leaving ample time for clonal evolution. For example, in the atom bomb survivors, who likely acquired *BCRABL1* when the atom bomb exploded, median latency to CML diagnosis was 10 years with a possible range of from <2 to >30 years.[19]

How can we best reconcile the goal of reducing the risk and severity of AEs with the need to control or eradicate undetected CML subclones that may require a higher TKI dose, different TKIs, or both? One strategy might be to start with what might be called an 'induction phase' with a high-dose of a 2nd or even a 3rd generation TKI, or high-dose imatinib, followed by switching to a lower dose in a 'maintenance phase' in responders. It might also be reasonable to begin with a 2nd or 3rd generation TKI and then switch to imatinib.

The next question is when to transition from the 'induction' to the 'maintenance' phase. The decision could be based on surrogate end points such as MMR or MR4, but it is also important to remember that end points like MMR or MR4 are predictive rather than prognostic surrogate end points.[20]

Which TKI is best? Should we reduce the approved dose of newer TKIs or switch to imatinib 400 mg/d? This could depend on the therapeutic goal and this may differ in different subjects. Is it to improve EFS, PFS or survival, achieve TFR, decrease AEs and costs, increase compliance, something else, or a combination of different goals? When the therapeutic goal is TFR, the rapidity of achieving a deep molecular response (DMR) and its stability and duration are crucial.[21] As such, a more intensive initial therapy strategy may be preferable. However, this may not be the goal in other subjects in whom survival is the goal and where less 'induction' therapy may be appropriate.

Another way to consider revising TKI therapeutic strategy is to make treatment decisions based on time-to-event end points with the possibility of continually revising strategy according to outcomes using statistical techniques such as Markov or Bayesian adaptive models.[22] This can be considered an extension of current European LeukemiaNet recommendations,[23] while also considering additional variables, such as TKI, dose, schedule, therapeutic goal, AEs, pharmaco-kinetic and pharmaco-dynamics, and others, such as the kinetics of decline of *BCRABL1* transcripts. It is even conceivable that one might consider potency of suppression of $P210^{BCRABL1}$ kinase activity in different subjects, and even activity in CML leukemia stem cells.

The bottom line is that it is time to re-think our strategy of using TKIs to treat CML. We suggest testing an individualized, precision-based approach that considers disease, patient and therapeutic goal heterogeneities, and modifying therapy according to the rate, depth, duration and stability of molecular response while acknowledging poor correlations with EFS, PFS and survival. Much work remains to clarify these issues, and this needs to be tested in randomized trials.

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Mogamulizumab *versus* investigator choice in relapsed/refractory adult T-cell leukemia/lymphoma: all four one or none for all?

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The human T-cell lymphotropic (or leukemia) virus type-1 (HTLV-1) was isolated by Poiesz *et al.* in 1980 from the T-cell line Hut-102, established from a patient thought to have cutaneous T-cell lymphoma.[1] HTLV-1 causes adult T-cell leukemia/lymphoma (ATL), HTLV-1 associated myelopathy/tropical spastic paresis (HAM/TSP), and other inflammatory disorders.[2] ATL is a clinically heterogeneous but often very aggressive mature T-cell neoplasm with dismal survival rates and limited therapeutic options, particularly in the relapsed/refractory (R/R) setting.[3] Most cohort studies and clinical trials in ATL come from Japan where the virus is highly endemic in certain regions. Here, investigators have led efforts to define diagnostic criteria, clinical subtypes, prognostic models, and the value of new therapies, including the anti-CCR4 antibody mogamulizumab (KW-0761), approved in Japan for both R/R and chemotherapy-naïve CCR4-positive ATL.[4,5] Data on subtype frequency, natural history, and outcome in ATL from non-Japanese endemic regions and from non-endemic regions (North America, Europe) remain very limited, although recent studies have begun to shed some light on this, showing that North American ATL patients present with more aggressive disease and have a worse prognosis (median survival approx. 7 months) compared to Japanese patients.[6,7] The availability of mogamulizumab for ATL in Japan provided the impetus to explore its activity in other ATL populations. In this issue of *Haematologica*, an important study by Phillips *et al.*[8] significantly advances our understanding of the global therapeutic impact of mogamulizumab in ATL, by reporting results of an international randomized Phase II trial (KW-0761-009) assessing the safety and efficacy of mogamulizumab *versus* investigator choice of chemotherapy in patients with R/R ATL.

HTLV-1 belongs to a group of T-lymphotropic deltaretroviruses, which includes four types of Simian T-lymphotropic viruses (STLV). HTLV-1 is believed to have originated from interspecies transmission between STLV-1-infected Old-World monkeys and humans. HTLV-1 is highly endemic in Southwestern Japan, the Caribbean, Northern Iran, and in Aboriginal populations in central Australia.[9] HTLV-1 RNA is reverse-transcribed into a