PERSPECTIVE

CHRONIC MYELOGENOUS LEUKEMIA

Are there new relevant therapeutic endpoints in the modern era of the *BCR::ABL1* tyrosine kinase inhibitors in chronic myeloid leukemia?

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INTRODUCTION

The availability and affordability of multiple *BCR::ABL1* tyrosine kinase inhibitors (TKIs) beginning in 2000 have changed the prognosis and treatment dynamics in Philadelphia-chromosome (Ph)-positive (or *BCR::ABL1*-positive) chronic myeloid leukemia (CML) [1–3]. Evolving discussions relate to the optimal biologic (lower) dose schedules; frontline versus later-line therapies; management of toxicities versus resistance; the benefit-risk of changing TKIs in patients in good molecular response in order to achieve treatment-free remission (TFR) status; and, with the availability of generic formulations, the cost or treatment value. These issues have been detailed elsewhere [4–6].

In the early days, with multiple unanswered questions, the main aims of TKI therapy were borrowed from the experience with interferon alpha. These focused on the achievement of hematologic response and cytogenetic response/complete cytogenetic response (CCyR). The latter endpoint, which required a bone marrow evaluation, was later replaced by its equivalent molecular endpoint, *BCR::ABL1* transcripts on the International Scale (IS) of ≤1% (2-log reduction of *BCR::ABL1* transcripts, or MR2). The achievement of major molecular response (MMR; *BCR::ABL1* transcripts [IS] ≤0.1%), a deeper response than MR2, was later found to correlate with event-free survival (EFS) and has been used as an early surrogate endpoint for EFS improvement in clinical trials.

The correlation between MMR at 12 or 18 months and EFS or progression-free survival (PFS) has been debated extensively and reviewed elsewhere [7]. Also, the association of 12-month MMR with survival was embedded in the association of CCyR or MR2 with survival. For example, in the IRIS trial, the long-term follow-up showed that achieving MMR at 12 months did not impact survival. Among patients in CCyR at 12 months, those obtaining a 12-month MMR had a 7-year EFS rate of 92%, compared to 91% in those who did not ($P = 0.25$) [8, 9]. The 18-month MMR rate correlated with EFS but not with overall survival (OS) or transformation-free survival (TFS). In a randomized study comparing imatinib 800 mg/day versus 400 mg/day versus 400 mg/day plus interferon-alpha, no survival differences were observed between patients with *BCR::ABL1* transcripts (IS) ≤ 0.1% (MMR) and those with levels of ≤0.1% to 1% (CCyR): the 3-year PFS rates were 99% versus 97%; the 3-year OS rates were 99% and 98%, respectively [10]. An analysis from M.D. Anderson Cancer Center showed that among patients in CCyR, achieving MMR did not predict better OS. Additionally, although MMR correlated with a trend for higher rates of PFS, such differences may not be clinically relevant [11].

USE OF EARLY SURROGATE ENDPOINTS TO PREDICT LONG-TERM OUTCOMES IN CML

The long-term follow-up in randomized trials showed that treatment with second-generation TKIs did not improve survival in frontline CML therapy (already near that of an age-matched normal population with imatinib), even though they improved the early surrogate endpoints of CCyR, MMR, and deep molecular response (DMR or MR4; *BCR::ABL1* transcripts [IS] ≤0.01%) [12–16]. With imatinib therapy at the 10-year mark, the relative survival rate was 90%, the annual CML-related mortality was 1% or less, the resistance rate was 10%, and the incidence of blast phase CML was 5.8% [16]. Among patients who developed resistance or intolerance to imatinib, newer-generation TKIs were highly effective, thus rebalancing the survival benefit with salvage therapy.

In cancer, experience indicates that true research often begins, and certainly expands drastically, after a drug is approved. This is true for almost every drug approved in leukemia, in other hematologic malignancies, and in most solid tumors. Therefore, when more drugs are approved, cancer research and patient care improve concordantly, as long as there is a clear indication for safety and relative efficacy. Research conducted post regulatory approval will almost always refine the role and treatment value of the drug in the tumor indication, and frequently results in additional often successful explorations in other cancers.

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In the case of CML, after imatinib resulted in a major clinical benefit and near-normalization of survival, another important question was raised: How can newer *BCR::ABL1* TKIs receive approval from the Food and Drug Administration (FDA) and other regulatory authorities sooner rather than later? In regulatory consideration of new TKIs for use as standard of care following frontline TKI failure, it was reasonable to continue using major cytogenetic response (MCyR; Ph-positive metaphases <35%) or CCyR (at 1 year) as surrogate endpoints for EFS or OS. But what about the approval of newer-generation TKIs for the frontline setting?

A BRIEF SUMMARY OF THE REGULATORY APPROVALS OF THE BCR::ABL1 TKIS IN CML

The four FDA-approved TKIs for the frontline treatment of chronic phase CML (CML-CP) are imatinib (first generation), and dasatinib, nilotinib, and bosutinib (second generation) [17–24].

The frontline approval of imatinib was based on the IRIS trial, which randomized 1106 patients (1:1) with newly diagnosed CML-CP to imatinib 400 mg daily or interferon plus low-dose cytarabine. The primary endpoint was disease progression defined as any of the following: death from any cause during therapy; development of accelerated or blast phase; loss of complete hematologic response; or loss of MCyR. This later became a generally accepted definition of PFS or EFS in CML (the same definition used interchangeably in different studies). At 12 months, there was no disease progression in 96.6% of patients on imatinib therapy versus 79.9% of patients on interferon and low dose cytarabine ($P < 0.001$). The 18-month rate of MCyR was 87.1% versus 34.7% ($P < 0.001$), and of CCyR 76.2% versus 14.5% ($P < 0.001$). Since the primary endpoint of the trial was met, all patients in the control arm were allowed to cross over (within a median time of 0.8 year) to imatinib therapy, as it was judged unethical to continue treating them with less effective and more toxic interferon-based therapy [17]. The long-term follow-up results did not show a significant survival benefit with imatinib therapy: the 10-year OS rate was 83.3% versus 78.8% [7]. This was attributed to the benefit of the cross-over treatment. Historical comparisons clearly confirmed a survival benefit with imatinib therapy [18, 19]. Also, the achievement of CCyR at 12 months correlated with a significant survival benefit, making it a surrogate endpoint for survival [20]. Patients achieving MMR by 18 months of therapy showed no disease progression to accelerated or blastic phase and a 7-year EFS rate of 95% [20].

The frontline approval of dasatinib was based on the DASISION trial, which randomized 519 patients (1:1) to dasatinib 100 mg daily or imatinib 400 mg daily. The primary endpoint was the rate of CCyR at 12 months, which was 77% with dasatinib versus 66% with imatinib ($P = 0.007$). This resulted in the FDA approval of dasatinib 100 mg daily as frontline therapy for CML [21].

The ENEST-nd trial randomized 846 patients (1:1:1) to one of two dose schedules of nilotinib, 300 mg twice daily or 400 mg twice daily (the approved dose-schedule in salvage therapy), or imatinib 400 mg daily. The primary endpoint was the rate of MMR at 12 months (a deeper molecular response than MR2), and results were 43–44% with nilotinib versus 22% with imatinib ($P < 0.001$). The 300 mg twice daily dose was safer, and the FDA approved it as a new standard of care in frontline CML therapy [22].

The frontline bosutinib trials had a tougher regulatory path. The original design of the BELA trial compared bosutinib 500 mg daily (the approved dose in salvage therapy) to imatinib 400 mg daily. The 12-month CCyR rate, the primary endpoint, was 70% versus 68% ($P = 0.60$), respectively. The primary endpoint was not met because of the higher-than-expected drop-out rate on the bosutinib arm due to side-effects (at that time, reducing a TKI dose was considered potentially to reduce efficacy), and because a significant proportion of patients did not have bone marrow evaluations at the 12 months mark. Interestingly, the 12-month MMR rate (accepted as an approvable regulatory endpoint) was higher with bosutinib (41% versus 27%; $P < 0.001$) [23]. This highlights that accepted regulatory endpoints should be interpreted cautiously, and that they may not be relevant to the true efficacy of the drug in CML (or cancer in general). A subsequent frontline trial (BFORE) randomized 536 patients (1:1) to bosutinib 400 mg daily or imatinib 400 mg daily. The MMR rate at 12 months, the primary endpoint, was 47.2% versus 36.9% ($P = 0.02$), which resulted in the approval of bosutinib 400 mg daily as frontline therapy for CML [24].

In this discussion, we omitted the details of the earlier *BCR::ABL1* TKI approval strategies and endpoints in CML later-line therapies because they differed according to the time the research was conducted, the evolving concepts, and the available TKIs. In general, OS was not a primary endpoint, but rather EFS, PFS, and the incidences of hematologic response (for accelerated phase CML), partial cytogenetic response, CCyR and MMR. These exciting research times resulted in the regulatory approval of multiple *BCR::ABL1* TKIs that have helped improve the outcomes in CML.

The recent experience with the approval of a third generation TKI, asciminib, in CML third-line therapy, is instructive. In the ASCEMBL pivotal trial, 223 patients (excluding those with T315I- or V299L-mutated CML) who failed 2 prior TKI therapies were randomized (2:1) to receive asciminib 40 mg twice daily or bosutinib 500 mg daily. The primary endpoint, the 6-month MMR rate, was met: 25.0% with asciminib versus 11.9% with bosutinib [25]. This resulted in the regulatory approval of asciminib as third-line therapy in CML, and for the treatment of T315I-mutated disease at a dose of 200 mg twice daily, based on the supportive data from a separate single-arm trial for those patients [26]. Several observations warrant discussion. First, the longer-term follow-up of the pivotal trial confirmed the persistence of the improved asciminib MMR rates: 38% with asciminib at 2 years versus 16% with bosutinib. However, the 2-year survival rates were similar, 97% and 99%, respectively [27]. Thus, the early MMR endpoint that led to the approval has not yet translated into a longer-term benefit at this early stage of follow-up, even in a heavily pretreated patient population. Second is the marked difference between the results with bosutinib on the control arm of the ASCEMBL trial and those in the BYOND trial using it as third-line therapy [28]. In the latter study, the 1-year CCyR rate was 68%, and the 2-year MMR rate was 64% (2-year survival rate of 95%). Thus, the worse results on the ASCEMBL control arm of the trial are puzzling, and may be due to the strict use of bosutinib 500 mg daily (the FDA-approved dose) and consequent high early drop-out rate, or to different patient and disease characteristics [26–28]. Third is the treatment value of asciminib when used in T315I-mutated CML; the cost is $1.45 million/year in the US for a dose of 200 mg twice daily (compared with the cost of ponatinib, about $270,000/year in the US) [6]. This indication has not been approved in Europe, Japan and other parts of the world.

A final important point is the recent announcement (January 8, 2024) that the frontline randomized trial of asciminib versus TKI of choice met the primary endpoint, the MMR rate at 12 months. This may result in the regulatory approval of asciminib as frontline therapy of CML.

AIMS OF THERAPY IN CML, AND HOW THEY INFLUENCE RESEARCH AND THE CHOICE OF TKI

In early 2000, the primary aim of CML therapy was to improve survival. Researchers did not even envision the therapeutic miracle of normalization of survival with the *BCR::ABL1* TKIs, thinking that cancer cells (CML cells in particular) would be smart and would develop resistance mechanisms [29]. This was partially true, as CML became the model of a cancer developing mutations that cause resistance to therapy, ABL1 kinase domain mutations in the case of CML (as well as other mechanisms). But the true CML resistance rate was only 10% in 10 years [16].

Once survival was significantly improved, the attention turned to a second important endpoint: Can CML be cured? The surrogate endpoint for this was the possibility of inducing a durable DMR, or durable MR4, and no CML relapse after discontinuation of TKI therapy. For this discussion, DMR refers to *BCR::ABL1* transcripts (IS) ≤ 0.01% (i.e., MR4). A durable MR4 of 2+ years is associated with a TFR rate of 40-50% [30]. Its durability for 5+ years is associated with a TFR rate of 80+% [31]. The preclinical models suggested that this might not be possible because there was a niche of dormant CML stem cells resistant to the *BCR::ABL1* TKIs that would invariably cause relapse [29]. Fortunately, this was not borne out by the clinical experience. The French pilot trials indicated that patients in durable DMR for at least 2 years who stopped TKI therapy could remain in a TFR status at a rate of 40-50% [32]. This was supported by subsequent studies in Europe and elsewhere. While the CML experts continue to use the term TFR cautiously, it is similar to a "molecular cure," or potential clinical cure in CML.

The achievement of TFR has been increasingly emphasized by CML experts and by patients as an important milestone. It was also publicized and encouraged in educational meetings, symposia, reviews, and by the drug companies developing novel *BCR::ABL1* TKIs, in hopes that patients with good disease responses, but not MMR or MR4, would change TKI therapy to achieve a durable MR4 and possibly a TFR. This was also thought to be perhaps more important among younger patients (e.g., those who may not want to continue a lifetime of TKI therapy).

Two additional endpoints in CML therapy that are increasingly important are: 1) the side effects of TKIs; and 2) the need for available and affordable TKIs to 100% of patients with CML, hence the treatment value of a TKI.

Concerning the TKI side effects, recent studies have addressed the issue of the optimal biologic dose of a TKI, and the possibility of reducing the dose for side effects or even preemptively to avoid them in a patient with a good response (e.g., CCyR or MMR) without losing efficacy [4–6].

With regard to the treatment value, it is important to emphasize that in countries where health care is universal and TKIs are available to all patients with CML, the 10-year relative survival rates have improved to 90% [16]. In contrast, in the SEER data in the US, where health care is not universal, the 5-year survival rates since 2000 have plateaued at about 70% [33]. This suggests that 20+% of patients with CML in the US do not have access to, or cannot afford, optimal TKI therapy. This was before the availability of generic imatinib at a price of only $500/year from Cost Plus.

HOW THE REGULATORY APPROVAL PROCESS AND ENDPOINTS MAY NOT ALIGN WITH THE AIMS OF RESEARCH AND ENDPOINTS POST APPROVAL

Several exciting and important novel TKIs are currently being explored in CML, with early encouraging results. As CML researchers, we believe it is important to facilitate the regulatory approvals of TKIs for CML in both later-line and frontline therapy. The current primary endpoints used for regulatory approval, such as the 6-month or 12-month MMR rates or CCyR (or *BCR::ABL1* transcripts {IS} <1%) rate in CML salvage, and the 12-month MMR rate in CML frontline, are reasonable.

However, once the new TKIs are approved, research can begin to address clinically relevant endpoints: survival, PFS, TFR, long-term toxicities, and treatment value. With frontline therapy, the cost of the TKI becomes critical with the availability of the inexpensive generic imatinib and dasatinib worldwide (generic dasatinib in the US in 2024), and of generic formulations of nilotinib, bosutinib and ponatinib by 2027. Of note, the price of generic and patented TKIs and their availability can vary by country; hence, the choice of the best frontline TKI may be at times country specific. For example, in France, generic imatinib costs 9600 euros/year (surprisingly, in the US, the Cost Plus generic is less, only $500/year), generic dasatinib 18,000 euros/year, and patented second- and third generation TKIs about 54,000 euros/year. Thus, generic imatinib or generic second generation TKIs may be the better frontline TKI, depending on the therapeutic aim and their cost in a particular geography.

For a new TKI to be used as frontline therapy, CML experts should ask the following questions: 1) Does the new drug demonstrate equivalent or superior survival compared to the existing TKIs? This will be almost impossible to prove. 2) Will the new TKI result in an equivalent or superior rate of TFR compared to the existing TKIs? For this, we need to agree on a new endpoint of "durable deep molecular response," or durable MR4, rather than TFR, to be included as an important treatment endpoint in frontline therapy (more objective; not dependent on the decisions/choices of the tumor expert and the patient), and also identify reproducibly earlier surrogate endpoints for durable MR4 (perhaps the rates of MMR at 18 or 24 months). 3) Is the long-term side-effect profile of the new TKI as safe or safer than existing TKIs? This has become a critical issue considering that the concerning safely issues with nilotinib were not reported until the 10-year update showed a 10-year cumulative incidence of arterio/vaso-occlusive events (AOEs/VOEs) of 25%, even with the lower dose schedule of 300 mg twice daily [34]. The 5-year update mentioned the possible numerical increase of the incidence of AOEs/VOEs, but concluded that there were no significant concerning safety issues [35]. 4) How much treatment value would the new TKI offer? Generic imatinib now may cost <$500/year, and generic dasatinib may cost <$3000–5000/year [36]. 5) What is the benefit of starting the most expensive drug first versus escalating to it only for those who might need it? 6) What is the quality of life of patients on the new TKI compared with imatinib or second-generation TKIs? Thus, we propose that any new frontline TKI would not provide a good treatment value if priced at > $30,000–40,000/year, regardless of the impact on TFR (which is not proven) or considering the long-term drug safety (also requiring at least 5 to 10 years of follow-up).

CONCLUSION

The availability of TKI generics affordable to all patients with CML highlights the importance of considering the treatment value of frontline TKI therapy. The benefit, cost, and potential long-term toxicity of any novel TKI evaluated for frontline therapy should be compared to imatinib if survival is the endpoint, and to generic dasatinib (50–100 mg daily) if durable MR4 is an additional endpoint. And current and future trials should include as an endpoint the incidence of a time dependent durable MR4 (for 2 years) in the comparative analyses, and should search for earlier correlative endpoints (such as the incidence of MMR at 18 months, or others) [37].

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AUTHOR CONTRIBUTIONS

All authors contributed equally to the concert and design of the perspective, writing and approving the final manuscript.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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