Sequencing Treatment in Chronic Myeloid Leukemia: The First Choice May Be the Hardest

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Abstract: The advent of tyrosine kinase inhibitors (TKIs) as primary treatment in chronic myeloid leukemia (CML) has greatly changed expectations of both physicians and patients. The use of imatinib has led not only to reliable cytogenetic responses, but also to deeper "molecular" responses that have brought long-term survival to a disease that was generally lethal in patients who were not candidates for stem cell transplantation. The more recent entrée of second-generation TKIs—nilotinib, dasatinib, bosutinib, and ponatinib—as well as the protein synthesis inhibitor omacetaxine, has provided access to more potent agents. These new drugs provide a safety net for patients whose disease does not respond to imatinib, but also create dilemmas for physicians treating CML patients. This review examines the evidence that informs choice of initial therapy, and discusses management options in the context of new goals of care, emerging toxicities, and the possibility of discontinuing treatment.

Keywords
Bosutinib, chronic myeloid leukemia, dasatinib, early molecular response, imatinib, major molecular response, nilotinib, ponatinib, tyrosine kinase inhibitor

Introduction

It can seem incredible that half a generation ago, chronic myeloid leukemia (CML) was generally a fatal disease with a median survival of 4 years.[1] The introduction of imatinib (Gleevec, Novartis) into the treatment armamentarium was a significant first step toward changing expectations for both patients and physicians. With the introduction of second-generation tyrosine kinase inhibitors (TKIs), patients whose treatment with imatinib failed—owing to either toxicity or lack of effectiveness—had the possibility of continuing treatment and maintaining or achieving a rescue response. The astounding clinical results of the past 15 years have changed the complexion of CML management to the degree that clinicians almost presume that patients will have control (and now, possibly cure) of their disease with 1 or a few pills each day and minimal side effects. The fulfillment of that presumption in the majority of patients, however, belies the challenges that physicians now face in identifying the treatment (or treatments) that is most likely to lead to the best outcome for the patient, not only in controlling the CML but also in minimizing toxicity. The emergence of new

adverse effects adds to the difficulty in choosing the best treatment. This review will weigh the therapeutic options for initial treatment, and discuss approaches to changing agents when necessary.

Initial Treatment of CML

Randomized trials of nilotinib (Tasigna, Novartis) and dasatinib (Sprycel, Bristol-Myers Squibb) versus imatinib have shown that second-generation TKIs have greater efficacy against CML than first-generation TKIs, as measured by achievement of a 3-log reduction in *BCR-ABL* transcript levels (a major molecular response [MMR]). There is also some evidence that the incidence of progression to accelerated- or blast-phase CML may be reduced by using the more potent agents as first-line therapy. This approach has been validated by the US Food and Drug Administration (FDA), which approved nilotinib and dasatinib in patients with previously untreated CML after first approving these agents in patients who had failed to respond to imatinib. Although the approach of using the most effective agent in the upfront setting has gained significant traction, the clinical experience with imatinib is longer. Furthermore, to date the overall survival (OS) with imatinib has been equivalent to that with second-generation drugs.

Imatinib

Imatinib demonstrated remarkable clinical activity against chronic-phase CML in initial phase 1 testing,[2] which was first reported in 2001. The efficacy and safety of imatinib have stood the test of time in the years since then. The IRIS (International Randomized Study of Interferon vs STI571) trial, which compared imatinib with interferon and cytarabine, found that at 8 years, the OS was 85% and the disease-free survival was 93% for patients on imatinib.[3] Although inducing cytogenetic remission had been the goal with interferon-based therapies, the depth of response to imatinib was greater, and none of the patients who achieved an MMR by 18 months had progression to accelerated- or blast-phase disease, vs 5% of those who did not.[4,5] This finding highlighted the importance of monitoring *BCR-ABL* transcript levels by quantitative reverse transcription-polymerase chain reaction (qRT-PCR or qPCR), and has been incorporated into the major practice guidelines for CML by the National Comprehensive Cancer Network and the European LeukemiaNet.[6,7] Molecular monitoring has been facilitated by the increasing adoption of the International Scale (IS), which permits standardization of the assay.[8] At 8 years of follow-up, the rate of MMR with imatinib was 86%.[3] Further analysis of the IRIS data also found that incidence of progression to accelerated- or blast-phase disease declined substantially after the first 3 years of treatment, suggesting that the major incidence of progression to accelerated- or blast-phase CML occurs relatively early in TKI therapy.[3,9]

Imatinib is well tolerated, and phase 1 tests of up to 1600 mg daily have failed to identify a maximally tolerated dose. Long-term testing has found major side effects of edema, muscle cramps, and rash without finding new safety concerns over time.[2] However, 38% of patients initially randomized to imatinib in the IRIS study had discontinued treatment by 7 years owing to inadequate efficacy (16%), toxicity (6%), stem cell transplantation (3%), and death (3%).[9]

Nilotinib

Nilotinib is a rationally designed second-generation TKI that was designed to target ABL more selectively than does imatinib.[10] As such, nilotinib is approximately 20 times more potent than imatinib in inhibiting ABL kinase activity, and is even more potent at killing cells that are dependent on ABL signaling. Nilotinib was first approved by the FDA in 2007 for CML patients who failed initial therapy. It was subsequently approved as first-line therapy in 2010 on the basis of the ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Ph+ CML Patients) trial, which compared imatinib at the standard dose of 400 mg daily with 2 different doses of nilotinib: 300 mg every 12 hours and 400 mg every 12 hours.[11] At 12-month follow-up, 79% of patients in the combined nilotinib arms achieved a complete cytogenetic response, compared with 65% of patients in the imatinib arm. Deeper responses manifested by MMR were obtained in 43.5% of patients in the combined nilotinib arms and 22% of patients in the imatinib arm. Somewhat surprisingly, at the early 12-month point, patients treated with nilotinib had a significantly lower rate of progression to accelerated- or blast-phase disease than patients treated with imatinib.

Landmark analysis at 4-year follow-up of the ENESTnd trial demonstrated continued superiority in regard to therapeutic efficacy of nilotinib compared with imatinib.[12] The rate of MMR was 74.5% in patients treated with nilotinib, compared with 56% in imatinib-treated patients. Each of the nilotinib arms was associated with a statistically significant reduction in risk of progression to accelerated- or blast-phase disease (96.7% for nilotinib 300 mg, 97.8% for nilotinib 400 mg) compared with standard dose imatinib (93.3%).

Dasatinib

Dasatinib is a dual SRC and ABL kinase inhibitor that is up to 325 times more potent than imatinib in killing cells dependent on *BCR-ABL*.[13] The DASISION (Dasatinib vs Imatinib Study in Treatment-Naive CML Patients) trial compared response in previously untreated CML patients

randomized to either dasatinib 100 mg daily or imatinib 400 mg daily.[14] At the initial 12-month report, dasatinib treatment resulted in a higher rate of complete cytogenetic response (77%) than imatinib (66%), as well as a higher rate of MMR (46% vs 28%). Although the difference in progression to accelerated- or blast-phase disease was not statistically lower in the dasatinib arm, progression occurred in fewer dasatinib-treated patients (5/259 or 1.9%) than imatinib-treated patients (9/260 or 3.5%).

Now with 3 years of follow-up, the differences between dasatinib and imatinib—like nilotinib and imatinib—have persisted.[15] While rates of MMR have increased in both arms of the trial, 66% of patients treated with dasatinib gained this milestone compared with 55% of patients treated with imatinib. Similarly, 3% of patients treated with dasatinib had progressed to accelerated- or blast-phase disease compared with 5% of patients treated with imatinib. This difference—although again, not statistically significant—continued the trend of the earlier point and is consistent with the findings with nilotinib in the ENESTnd trial.

The Value of Early Molecular Response

Analysis of the IRIS trial indicated that at 7-year follow-up, patients who achieved an early molecular response (EMR)—manifested by a 1-log reduction in *BCR-ABL* transcript levels as measured by an IS value of 10% or less by 6 months of therapy—had an event-free survival (EFS) of at least 85%. By contrast, patients with IS ratios greater than 10% had an EFS of 56%.[9] In addition, patients who achieved an MMR by 12 months had an EFS of 91%, compared with 78% for patients who did not attain this milestone. The results indicated that the speed of initial response matters.

The benchmark of EMR has since been revised to achieving a *BCR-ABL* IS level less than 10%, the approximate equivalent of a partial cytogenetic response, at 3 months and has been validated with other TKIs.[16] In patients treated with imatinib as initial therapy, achieving a *BCR-ABL* IS level less than 10% was the most significant indicator of OS, with an advantage of 93.3% vs 56.9% for patients with inferior responses with 8 years of follow-up.[17] Similarly, landmark analysis of the ENESTnd trial at 4 years of follow-up showed that patients who had an EMR had superior OS in all arms of the study.[12] Although nilotinib has not yet demonstrated superiority in OS compared with imatinib, a significantly higher percentage of patients treated with nilotinib achieved an EMR. The DASISION trial comparing dasatinib with imatinib also showed that patients who had an EMR had superior PFS in both treatment arms.[15] As with nilotinib, a significantly higher percentage of patients achieved an EMR with dasatinib compared with imatinib (84% vs 64%). Again, it should be noted that this difference has not yet translated to a survival advantage for dasatinib-treated patients. Nonetheless, these data taken together suggest that nilotinib and dasatinib offer patients a higher probability of attaining an EMR and that with longer follow-up of the ENESTnd and DASISION trials, the more potent TKIs will show a more definitive advantage in survival. These data have also led the National Comprehensive Cancer Center Network to endorse an EMR as a critical element in choosing to continue or alter initial treatment.[6]

The Value of Deep Molecular Response

The STIM (Stop Imatinib) and CML8 trials have suggested that patients who achieve and maintain a deep molecular response of at least a 4.5-log reduction in *BCR-ABL* transcript levels on the IS (MR[4.5], which was formerly termed complete molecular response), may be able to discontinue imatinib.[18,19] The STIM trial found that 39% of patients were able to maintain stable MR(4.5) after discontinuing imatinib, and the CML 8 trial found that 42% of patients could discontinue imatinib without needing treatment. Speed and depth of response also seem to be related because EMR was predictive of patients who were able to attain the landmark MR(4.5).[20]

Although patients treated with imatinib are able to achieve MR(4.5), both nilotinib and dasatinib are superior to imatinib. In the ENESTnd trial, 38.5% of the patients treated in the combined arms of nilotinib achieved MR(4.5) compared with 23% in the imatinib arm at 4 years of follow-up.[12] In the DASISION trial, the rate of attaining MR(4.5) was 22% in patients in the dasatinib arm and 12% in the imatinib arm after 3 years.[15] Thus, nilotinib and dasatinib both appear to be able to place a higher percentage of treated patients in a position to discontinue treatment than does imatinib.

Just as the speed of initial response appears to play a role in determining ultimate response, the depth of remission is also prognostic. The German CML Study IV compared initial treatment with imatinib 400 mg daily and 800 mg daily with adaption of the dose for toxicity (other arms including cytarabine and interferon alfa were terminated early).[21] With a median follow-up of more than 5.5 years, patients treated with the higher dose of imatinib had a higher rate of achieving MR(4.5). Further, independent of treatment arm, patients who attained MR(4.5) at 4 years had improved OS compared with patients who attained 2 to 3 log reductions in *BCR-ABL* transcript levels (MR[2] to MR[3] [MMR]), a degree of response that is at least equivalent to complete cytogenetic remission. In addition, no patient who achieved MR(4.5) experienced disease progression, suggesting that MR(4.5) is another important prognostic standard.[22]

Toxicity Considerations

Although nilotinib and dasatinib appear to be more efficacious than imatinib in the first-line treatment setting, the long-term safety profile of imatinib may be better than that of the second-generation TKIs with regard to uncommon, but late treatment-emergent side effects. The ENESTnd trial found that overall safety profiles of nilotinib and imatinib were similar, with low incidences of grade 3 and 4 toxicities at the 12-month mark.[11] Among grade 1 and 2 toxicities, nilotinib resulted in more headache and rash, whereas imatinib caused more nausea and edema. With 4 years of follow-up, no new safety signals were reported.[12] Nonetheless, recent reports suggest that nilotinib may cause a higher incidence of severe peripheral artery occlusive disease, including stroke and Raynaud syndrome, compared with imatinib.[23,24] This observation has contributed to an added caution in the FDA prescribing information.[25]

In the DASISION trial, dasatinib also had a low rate of toxicity compared with imatinib at the 12-month point, with less overall fluid retention and nausea.[14] Dasatinib, however, has been associated with an increased incidence of pleural effusion. In addition, 3-year follow-up of the DASISION trial found that 8 of 258 patients in the dasatinib arm (3.1%) developed pulmonary artery hypertension, compared with none in the imatinib arm.[15] Pulmonary artery hypertension had previously been identified in a retrospective review of dasatinib-treated patients, although preclinical models of pulmonary artery hypertension had suggested a potential beneficial therapeutic effect of dasatinib in this condition.[26-28]

Together with the possibility of new side effects, physicians caring for patients with CML must contend with coprescription of drugs that may alter TKI blood levels. A review of the Medco Health Solutions database showed that 43% of patients receiving imatinib had coprescription of drugs that had the potential to decrease efficacy and 68% of patients had coprescription of drugs with the potential to increase imatinib levels and thus increase the risk of side effects.[29] Similarly, 26% of patients receiving dasatinib had coprescription of drugs that might reduce dasatinib levels, and 46% of patients had coprescription of drugs that might increase dasatinib levels. These results indicate that some patients receive prescriptions that both reduce *and* increase TKI levels. The high prevalence of coprescription of drugs that might increase the blood levels of potent TKIs such as dasatinib also raises concern that the likelihood of side effects could be higher in these patients. The new treatment-emergent adverse events of nilotinib and imatinib, coupled with recently appreciated toxicities of ponatinib (see below), has led some to consider that the more potent TKIs may carry more side effects than imatinib and has contributed to some uncertainty regarding the balance between safety and efficacy.[30]

Management in the Setting of Initial Treatment Failure

Failure of initial treatment of CML can come in several guises. Although the TKIs are generally well tolerated, the introduction of alternative agents has presented treatment options for patients who are unable to tolerate initial therapy. In the period when imatinib was the only available TKI, and alternatives included stem cell transplant and interferon, patients and physicians were more willing to manage side effects. Now, however, a switch in therapy may help to enhance quality of life. A recent review of 57 patients who achieved a complete cytogenetic response to imatinib as first-line therapy and changed treatments owing to minor persistent side effects found that none of the patients had disease progression.[31] In fact, 17 patients (30%) subsequently switched to a third-line treatment and 2 (3.5%) advanced to a fourth TKI. Although the change in treatment was to a more potent TKI, this approach suggests that treatment changes due to side effects, even minor ones, may not endanger subsequent response.

Failure of initial treatment due to lack of efficacy can be a more challenging problem. Careful monitoring includes evaluation of *BCR-ABL* transcript levels by qRT-PCR standardized to the IS, because early treatment decisions may hinge on this analysis.[6,7] Notwithstanding the attention that has been focused on the development of resistance mutations, causes of failure also include: interaction with medications that lower TKI levels, especially those that activate the CYP34A enzymes (see above); compromised gastrointestinal absorption; polymorphisms in the multidrug resistance gene (MDR-1); and expression of the human organic cation transporter (OCT-1).[32-35] Surprisingly, adherence has emerged as an important determinant of failure, highlighting the importance of monitoring side effects carefully.[36,37] Many in the medical community are also concerned about the high cost of TKI treatment, which runs in excess of $50,000 per year in the United States. The cost can make access to effective treatment difficult, even with generous safety net programs available.[38] In sum, the emergence of *ABL* kinase domain mutations (discussed below) may account for only 20% of clinical failures and points to the necessity of paying close attention to all aspects of the patient's medical, psychological, and social conditions.[39]

Treatment Alternatives in the Setting of Treatment Failure

The enhanced potency of nilotinib and dasatinib—supported by data showing more rapid response and a lower incidence of accelerated- or blast-phase CML—has persuaded many physicians to use these second-generation

TKIs as initial therapy. The long-term safety profile of imatinib, and OS rates with strategies employing imatinib as first-line treatment, have yet to be surpassed by nilotinib and dasatinib, however. These findings support the ongoing use of imatinib as initial therapy. In addition, many CML patients who began treatment prior to FDA approval of dasatinib and nilotinib in the first-line setting began taking imatinib and have continued to take it. Thus, for this population, nilotinib and dasatinib remain important second-line agents. Supplementing these agents, the TKIs bosutinib and ponatinib have FDA approval in the setting of treatment failure (with special warnings associated with ponatinib, as noted below) as does the protein synthesis inhibitor omacetaxine (Synribo, Teva). Considerations in choosing a second-line agent may include side effect profile and dosing considerations, but for patients who fail to achieve treatment milestones, the possibility of resistance mutations should be evaluated by sequencing the *ABL* kinase domain. Since some TKIs have better efficacy with certain kinase domain mutations, this information can be used to guide TKI selection.[6,40] The *ABL* T315I mutation, in particular, is resistant to imatinib, nilotinib, dasatinib, and bosutinib, so only ponatinib and omacetaxine are viable treatments in this setting.[41-43]

Data regarding molecular response in second-line therapy is not as robust as in initial therapy, but there are emerging data suggesting that EMR is also predictive of ultimate response. In 119 patients initially treated with imatinib who failed to meet the targeted response criteria of the European LeukemiaNet at that time, those who achieved an EMR had an OS advantage of 91.3% vs 72.1%, and an EFS advantage of 49.3% vs 13%, at 4 years of follow-up.[44,45] It should be noted that 52% of the patients switched to a third-line TKI owing to resistance or intolerance, but initial treatment sensitivity at the time of the first switch seemed to identify patients with more sensitive disease. These results suggest that close molecular follow-up and early therapeutic changes might provide a reasonable rationale to use imatinib as initial therapy. However, subanalysis of this study found that patients who failed to achieve an EMR with imatinib had a low rate of achieving MR(4.5) (2 of 52) despite an early switch to nilotinib, and leave open the possibility that with the lower rates of EMR achieved with imatinib compared with nilotinib and dasatinib, some patients may lose the opportunity to have optimal response with an imatinib first strategy.[46] For patients treated with nilotinib in the second-line setting, 4-year follow-up of imatinib failures found that 45% achieved a complete cytogenetic response and the OS was 78%.[47] For patients treated with second-line dasatinib, 42% of patients who were imatinib resistant and 53% of patients who were imatinib intolerant achieved an MMR at 5 year and OS was 77% in the imatinib-resistant and 82% in the imatinib-intolerant cohorts.[48]

Bosutinib

Bosutinib is a dual inhibitor of SRC and ABL kinases that is orally administered on a daily schedule.[49] A phase 1/2 trial of bosutinib in patients who failed imatinib found that at 2 years, 41% had achieved a complete cytogenetic response and 26% had achieved an MMR.[50] Mainly in the third-line setting, 24% of patients with chronic phase CML attained a complete cytogenetic response at a median of 28 months of follow-up.[51] Gastrointestinal side effects—including diarrhea, nausea, and vomiting—were common, but grade 3 and 4 severity were modest.[52] Thus, bosutinib has therapeutic activity in the setting of second-generation TKI failures with what appears to be a toxicity profile that is distinct from other TKIs.

Ponatinib

Ponatinib is a potent ABL kinase inhibitor that has the potential to inhibit all known *ABL* mutations.[53] Clinical efficacy has been promising, and the phase 2 PACE trial produced complete cytogenetic remissions in 40% of patients who were resistant to nilotinib and/or dasatinib and in 66% of patients with the *BCR-ABL* T315I mutation.[43] Responses appeared to be durable, but FDA adverse event review found a rate of arterial and venous thrombosis as high as 27% that prompted temporary withdrawal of ponatinib from the United States market and a subsequent restriction in labeled indications.[30,54,55] Evaluation of patients in the PACE trial who had vascular occlusive events found that OS appeared to be similar to patients who did not have thrombosis, suggesting that some of the ponatinib-related toxicities may be manageable and that there may be patient populations in whom the risk of CML progression warrants the potential therapeutic risks.[56]

Omacetaxine

Omacetaxine is a reversible protein translation inhibitor that selectively reduces *BCR-ABL* levels in CML cells.[57] A phase 2 study of omacetaxine in patients who had failed imatinib or who had the *BCR-ABL* T315I mutation found that 16% achieved a complete cytogenetic response and that median PFS was 7.7 months. The principal adverse events were related to myelosuppression, and other severe adverse events were rare. The practical use of omacetaxine is complicated by the mode of administration (subcutaneously twice daily for 14 days every 28 days until hematologic remission, and subcutaneously twice daily for 7 days every 28 days thereafter), but omacetaxine in the relapsed setting has more activity than any non-TKI and may help to facilitate disease management, especially as a bridge to stem cell transplant.

Discussion

With the availability of imatinib and second-generation TKIs, the management of patients with CML has become more complex. The choice of initial therapy has become especially challenging. The ENESTnd and DASISION trials have provided compelling evidence that nilotinib and dasatinib, respectively, offer therapeutic benefits over imatinib in the first-line setting.[12,15] Follow-up in these trials thus far has not shown an advantage in OS, but the increased rate of EMR and MR(4.5) with the second-generation TKIs and the strong correlation of these endpoints with survival suggest that survival differences with imatinib may just be a matter of longer follow-up. The lower rates of progression to accelerated- and blast-phase CML, a difference that reached statistical significance with nilotinib, also provide support for using second-generation TKIs as first treatment. The finding that this difference was evident in the first 12 months of treatment is another indication that early treatment with more potent TKIs may prevent progression in patients whose disease might otherwise progress with imatinib.[11] In the ENESTnd trial, patients treated in the nilotinib arm had approximately half the *ABL* kinase domain mutations as patients treated with imatinib, implying that early suppression of resistance mutations with more-potent TKIs is clinically important.[58]

Toxicity and potential cost savings, however, may favor initial use of imatinib. Ponatinib, dasatinib, and nilotinib have had the emergence of significant toxicities, usually in a minority (in some instances, a small minority) of patients, whereas the long-term safety of imatinib has been outstanding.[3,9,15,23,26,54] It is also important to remember that the safety of all of the TKIs, including imatinib, remains untested in important patient populations who were excluded from clinical trials, such as patients who are HIV-positive, patients who have had solid organ transplants, and patients with significant medical comorbidities, including renal failure and severe heart disease. Since many patients in this category require management by other specialists, the importance of coordinated care cannot be overemphasized, considering that many of the drugs used to manage other conditions have the potential to have interactions with TKIs that could affect efficacy and/or toxicity.[29] Nonetheless, the favorable toxicity profile of imatinib could provide a rationale for use in medically challenging patients. As a counterweight, it should be noted that CML still has the potential to be a deadly disease and that many TKI side effects can be managed medically, so that possible toxicity considerations must be balanced with therapeutic efficacy.

With regard to the financial aspect of treatment, it is expected that generic versions of imatinib may be available as early as 2015; these have the potential to reduce costs dramatically.[38] If the cost differences are significant, payers may favor imatinib over other TKIs given the absence of a proven survival advantage. Despite potential savings, there may be a clear advantage of the more-potent TKIs among some CML subpopulations. For example, in ENESTnd, patients who fell into intermediate- and high-risk groups using the Sokal criteria had the same rate of EMR with nilotinib, whereas patients with high-risk Sokal scores had inferior rates of EMR in the imatinib arm.[9] Sokal high-risk patients are also more likely to have an *ABL* kinase domain mutation, which adds to the argument to use more-potent TKIs as initial therapy in this population.[58] Close molecular monitoring in conjunction with imatinib as initial therapy might also provide a basis for cost-effective therapy using EMR and other milestones as a basis to switch treatment.[6,7] However, analysis of trials employing early switch approaches shows that some patients progress. It remains unclear whether an early switch approach with imatinib as first-line therapy provides optimal salvage compared with initial use of a more potent TKI.[20,46]

The challenges to physicians trying to provide the best treatment for their CML patients are substantial. The considerations in this decision require integration of emerging scientific data regarding efficacy and toxicity, and information on underlying medical conditions in the individual patient. An additional factor is psychosocial barriers, including financial status, that may affect adherence. These decisions, made on a daily basis, also occur within the subtext of the high cost of medical care. These challenges will continue to require study to meet the expectations of patients and physicians so that deaths due to CML will remain rare and become rarer, with treatment having little impact on quality of life.

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