COUNTERPOINTS

Current Controversies in Hematology and Oncology

What Should Frontline Treatment Be in Chronic Myeloid Leukemia?

The US Food and Drug Administration has approved 3 tyrosine kinase inhibitors (TKIs) for use as frontline treatment in chronic myeloid leukemia (CML): imatinib, dasatinib (Sprycel, Bristol-Myers Squibb), and nilotinib (Tasigna, Novartis). In this month's Counterpoints, Drs Stephanie Glancy Lee and Jeffrey H. Lipton make the case that imatinib should be used as frontline therapy in CML, whereas Drs Carmen Fava and Giuseppe Saglio argue that the second-generation TKIs—dasatinib and nilotinib—are preferred.

Everything Old Is New Again: The Case for Imatinib as Frontline Therapy in 2017

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TKIs have revolutionized the treatment of CML. Imatinib, which was the first TKI to receive regulatory approval, has shown remarkable efficacy and long-term outcomes.[1,2] More recently, second-generation TKIs, specifically dasatinib and nilotinib, have been approved as frontline treatment of CML. The choice of which TKI to start at the outset—imatinib, dasatinib, or nilotinib—is at the discretion of the physician.[3]

Dasatinib and nilotinib have been shown to reduce progression to the accelerated phase and blast phase, as well as to generate faster and deeper treatment responses than those achieved with imatinib.[4-7] Despite these data, excellent reasons exist to prescribe imatinib as frontline treatment in patients with chronic-phase CML (CML-CP).

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The Biology of CML Supports Second-Generation TKIs as Frontline Treatment

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Imatinib not only has revolutionized the treatment of CML but also represents a cornerstone in the history of medicine. It was one of the first TKIs to be developed, and its clinical use marks the start of molecularly targeted therapy. To this day, imatinib remains the most notable example of a molecularly targeted treatment.[1]

Imatinib has its place as a first-line treatment of CML in the current era, but only in specific situations or for economic reasons. The reason is that dasatinib and nilotinib, the more potent second-generation TKIs, have been shown to provide superior efficacy.[2,3] This finding, which is based on data from clinical studies, is further supported by what we know about the biology of CML.

In CML, the winning strategy for therapy always has been to prevent progression and attempt early eradication of disease.[4] In the past, eradication was possible only with

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Everything Old Is New Again: The Case for Imatinib as Frontline Therapy in 2017 *(cont)*

Herein, we discuss disease-based factors, patient factors, physician factors, and socioeconomic factors that support the ongoing use of imatinib as frontline therapy in these patients.

Disease-Based Factors

Two major clinical endpoints in the treatment of CML are survival outcomes and treatment-free remission (TFR). To date, no studies have shown a statistically significant difference between the survival outcomes of patients treated with imatinib and those treated with dasatinib, or between the outcomes of patients treated imatinib and those treated with nilotinib.[4-7]

The 5-year follow-up of DASISION (A Phase III Study of Dasatinib vs Imatinib in Patients With Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia), the phase 3 randomized control trial that compared dasatinib vs imatinib in patients who had newly diagnosed CML-CP, showed a 5-year progression-free survival (PFS) rate of 85% for dasatinib and 86% for imatinib (HR, 1.06; 95% CI, 0.68-1.66).[6] More imatinib-treated patients than dasatinib-treated patients died of CML-related causes, but the related difference in 5-year overall survival (OS) did not achieve statistical significance (HR, 0.53; 95% CI, 0.24-1.19; *P*=.1192).[6] Furthermore, the age-adjusted life expectancy for patients with CML-CP in both arms of DASISION approached that of patients in an external, non-CML population.[6]

ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Ph+ CML Patients) was a phase 3 randomized controlled trial that compared nilotinib (300 or 400 mg twice daily) with imatinib in patients who had newly diagnosed CML-CP. The 5-year results of this study showed on-study 5-year PFS rates of 92.2%, 95.8%, and 91%, and 5-year OS rates of 93.7%, 96.2%, and 91.7% in the arms treated with nilotinib 300 mg twice a day, nilotinib 400 mg twice a day, and imatinib, respectively.[7] Although PFS and OS were slightly improved in the nilotinib arms, neither difference met statistical significance.[7]

One argument for the use of dasatinib and nilotinib as frontline therapy is based on evidence that these TKIs induce deeper and faster treatment responses, thus increasing the number of patients eligible for treatment discontinuation.[4-7] Despite this evidence, we maintain that imatinib is a reasonable frontline treatment option if TFR is the clinical endpoint. The interim analysis of DASFREE (Open-Label Study Evaluating Dasatinib Therapy Discontinuation in Patients With Chronic Phase Chronic Myeloid Leukemia With Stable Complete Molecular Response), an ongoing trial evaluating TFR in patients receiving dasatinib as first-line therapy and dasatinib as second-line or subsequent therapy, showed that the 12-month major molecular response rates in the first-line dasatinib arm and the second-line or subsequent dasatinib arm were 71% and 56%, respectively.[8] Furthermore, subgroup analysis of ENESTop (Treatment-Free Remission After Achieving Sustained MR4.5 on Nilotinib), a phase 2 study evaluating TFR in patients who achieved a sustained deep molecular response following a switch from imatinib to nilotinib, evaluated data on the basis of the reason for switching from imatinib to nilotinib, classified as "intolerance," "resistance," or "physician preference." At 48 weeks, the TFR rates in the imatinib-intolerant, imatinib-resistant, and physician preference for nilotinib groups were 58%, 53%, and 61%, respectively.[9]

> It is imperative that physicians select therapy that causes minimal adverse effects and can easily be incorporated into a patient's lifestyle.

An additional reason to consider imatinib as frontline therapy is the evidence that dasatinib and nilotinib can be effective as salvage therapy if imatinib treatment fails. In contrast, there is limited evidence that imatinib, nilotinib, or dasatinib will be effective as salvage therapy if dasatinib or nilotinib is used as frontline therapy.[10] In the 7-year follow-up of the phase 3 trial of dasatinib for patients with imatinib-resistant CML-CP or imatinib intolerance, the major molecular response, PFS, and OS rates were 46%, 42%, and 65%, respectively.[11] In the case of nilotinib, the 24-month update of the phase 2 study of nilotinib in patients with imatinib-resistant CML-CP or imatinib intolerance showed that a major

cytogenetic response and a complete cytogenetic response were achieved in 56% and 41% of patients with imatinib-resistant CML-CP, respectively, and in 66% and 51% of patients with imatinib intolerance, respectively.[12] The 24-month PFS and OS rates in this study were 64% and 87%, respectively.[12]

In summary, imatinib offers the same survival benefit as dasatinib and nilotinib in the frontline treatment of CML-CP. Furthermore, an imatinib-first approach allows better evidence-based options for subsequent TKI therapy in the event of treatment failure, generating good clinical outcomes as well as a greater than 50% chance of achieving TFR.

Patient Factors

TKIs have transformed CML into a chronic condition in which most patients require daily, lifelong TKI treatment. The adherence of many patients to CML treatment, however, is poor owing to medication-associated adverse events and treatment restrictions.[13] A major advantage of imatinib as frontline therapy is its favorable side effect profile in the aging population, which is especially relevant given that the prevalence of CML increases with age.

In the 5-year follow-up of DASISION, drug-related pleural effusions occurred in 28% of patients on dasatinib therapy and 0.8% of patients on imatinib therapy.[6] (Hypertension, a prior history of cardiac disease, underlying lung disease, and older age all have been identified as risk factors for dasatinib-associated pleural effusions.)[14] The 5-year follow-up of ENESTnd revealed that grade 3 or 4 cardiovascular events occurred in 4.7%, 8.7%, and 1.8% of patients treated with nilotinib 300 mg twice a day, nilotinib 400 mg twice a day, and imatinib, respectively.[7] Furthermore, greater elevations in blood cholesterol and glucose levels were observed in the patients receiving nilotinib than in those receiving imatinib.[7]

Nilotinib has the most complex dosing schedule of the 3 frontline TKIs, and treatment difficulties have been reported to be higher among patients taking nilotinib (63.3%) than among those taking dasatinib (2.6%) or imatinib (19.2%; $P<.0001$ for both).[13] Moreover, in comparison with patients on imatinib, those on nilotinib reported more missed doses ($P<.05$) and less treatment satisfaction.[13]

Given that treatment adherence is essential to favorable long-term therapeutic outcomes in CML, it is imperative that physicians select therapy that causes minimal adverse effects and can be easily incorporated into a patient's lifestyle. This cautionary principle supports the use of imatinib as frontline therapy in patients of advanced age (≥65 years) and those with underlying risk factors for pulmonary or vascular disease.

Physician Factors

Retrospective evidence indicates that physician adherence to clinical practice guidelines improves outcomes in patients with CML.[15] Unfortunately, like patient adherence, physician adherence is imperfect.[16] Approximately 20% of physicians reported a lack of time to search guidelines as a barrier to implementing clinical practice recommendations in CML.[16] Given that imatinib has been on the market since 2001, and that dasatinib and nilotinib have been on the market only since 2010, physicians may be more comfortable and familiar with imatinib treatment recommendations and adverse event monitoring.

Socioeconomic Factors

The life expectancy of patients of all ages with CML has increased dramatically and now approaches that of the general population.[17] In parallel, the cost of treating CML has been rising consistently.[18] As patients with CML continue to live longer, costs to both them and the health care system will increase. Imatinib is the only frontline TKI that is available in generic form, and it has been proposed that the introduction of generic imatinib in the United States will lead to a 70% to 90% decrease in the price of this drug.[19] A recent cost analysis study hypothesized that an "imatinib-first" approach (using generic imatinib in CML-CP and switching to dasatinib or nilotinib if intolerance or lack of effectiveness developed) would be more cost-effective and would generate savings of up to $9.12 million in US dollars over 5 years.[19] Furthermore, the cost of the supplementary tests needed to evaluate and monitor for the comorbidities associated with dasatinib and nilotinib is another reason to use of imatinib as frontline therapy.[20] Approximately 30% of physicians have reported that the high cost of TKI medications, which drains patient resources, is a barrier to guideline adherence.[16] The financial burden of treating CML—to both patients and the health care system—supports the use of imatinib as initial therapy for CML-CP.

Conclusion

The introduction of TKIs has transformed CML from a fatal disease to a manageable, chronic one, with the survival of affected individuals nearly identical to that of the general population.[17] Most patients remain on TKI treatment indefinitely. Given that no statistically significant differences in survival have been found among patients treated with the 3 approved frontline TKIs, the choice of

therapy should be individualized on the basis of disease-related factors, patient safety and quality-of-life measures, physician experience, and socioeconomic considerations. Overall, excellent evidence exists to support the ongoing use of imatinib as frontline therapy for CML-CP.

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The Biology of CML Supports the Choice of Second-Generation TKIs as Frontline Treatment *(cont)*

allogeneic stem cell transplant, which carries a high risk for toxicity and mortality. Thanks to TKI therapy, definitive cure—which we think should remain the main goal of CML therapy—is now possible for a clinically significant percentage of patients. Imatinib can reduce the risk for progression and death from CML, and second-generation TKIs are even more effective in reaching these goals.

Efficacy of Second-Generation TKIs

CML is one of the few neoplastic processes in which a single hit—the formation of the *BCR-ABL1* oncogenic hybrid gene and the constitutive tyrosine kinase activity of the corresponding protein—is responsible not only for the onset of chronic-phase leukemia but also for its subsequent evolution into advanced-phase leukemia. The advanced phase—which encompasses the accelerated phase and the blast phase—is the final step in the natural evolution of the leukemic process. To this day, advanced-phase CML remains incurable and fatal in most cases.[5]

Imatinib dramatically alters this natural evolution because the inhibition of BCR-ABL1 tyrosine kinase activity blocks the progression of CML from the chronic phase to the advanced phase.[6] However, 7% to 8% of cases of CML treated with imatinib still progress. Thus, despite the great improvement in the OS of patients with CML, progression of CML is still the major cause of death in these patients for the first 10 years after diagnosis.[7]

> The number of cases of progression and death due to CML in patients treated with first-line nilotinib or dasatinib is approximately half the number in patients who receive first-line imatinib.

Progression is caused by the genetic instability introduced by the tyrosine kinase activity of BCR-ABL1. It arises from the expansion of subclones, which frequently are undetectable at diagnosis with current techniques, that are resistant to imatinib because of the presence of *BCR-ABL1* mutations or the activation of oncogenic pathways that can partially or completely replace BCR-ABL1 oncogenic activity.[8]

We know from clinical studies in which dasatinib or nilotinib was used as second-line therapy after imatinib failure that approximately 50% of these subclones are sensitive to a second-generation TKI, which can overcome the resistance to imatinib.[9,10] Purging resistant and potentially dangerous subclones with second-generation TKIs at the beginning of treatment instead of waiting for them to manifest clinically delays the progression of events.[11,12]

Molecular response, particularly early molecular response, to TKI therapy is the best surrogate marker for predicting CML outcomes in terms of PFS, event-free survival, and OS.[13] Approximately 30% of patients treated with first-line imatinib do not reach the target molecular milestones established by the international recommendations for CML treatment. They are likely to switch eventually to treatment with other TKIs, mainly dasatinib or nilotinib. The percentage of these patients is lower (10%-15%) if we use second-generation TKIs at diagnosis, so that the need to change treatment because of inadequate response is reduced.[11,12] These differences in molecular response can explain why the number of cases of progression and death due to CML in patients treated with first-line nilotinib or dasatinib is approximately half the number in patients who receive first-line imatinib.[11,12] Although imatinib has not been shown to improve OS, it is relevant to reduce patients' risk for dying of the disease, particularly if they are considered to be at intermediate risk or high risk on the basis of their Sokal score (10%-15% of cases).[12]

Problems Related to Toxicity

Although second-generation TKIs are generally well tolerated, the incidence of adverse events (AEs) and long-term toxicities is higher with these agents than with imatinib.[11,12] Of particular concern, the long-term use of nilotinib has been linked to an increased number of cases of cardiovascular AEs, and long-term dasatinib has been linked to an increased number of cases of pleural effusion and pulmonary arterial hypertension. In most instances, however, these AEs affect patients who have specific risk factors. Therefore, the patient's profile should be considered when a first-line treatment is chosen.

Furthermore, there is increasing evidence that most AEs are dose-dependent. Planned and ongoing clinical trials are investigating whether lower dosages

of second-generation TKIs can have the same level of efficacy as currently approved dosages.[14] In particular, we do not know whether the initial dosage of a second-generation TKI is still needed once specific molecular milestones have been obtained.[14] This issue, of course, is also important for second-line treatment; we know that approximately 40% to 50% of patients originally treated with imatinib must switch to a second-generation TKI because of intolerance or resistance, and they may therefore face the same problem.

Achievement of Treatment-Free Remission

TFR, which is the maintenance of a deep molecular response (DMR) despite discontinuation of therapy, is becoming the new treatment goal for patients with CML.[15] After the STIM (Stop Imatinib) trial, several other trials investigated TKI discontinuation in patients with a sustained DMR. The majority of these trials involved patients on long-term imatinib therapy.[16] The findings of other, ongoing trials, which are specifically investigating TFR following treatment with second-generation TKIs, are expected to allow TFR in a higher percentage of patients.[17] This is not only because the percentage of patients who achieve a DMR is increased (to almost double that seen with imatinib) but also because the DMR can be obtained in a shorter period of time.[11,12] The results of the phase 2 ENESTfreedom study (Nilotinib Treatment-Free Remission Study in CML Patients), the first trial to assess specifically whether patients who have been treated with frontline nilotinib and who have a sustained DMR can stop treatment, seems to confirm these expectations, showing a TFR in 51% of patients at 12 months after a median treatment time of 3.7 years and a median duration of sustained DMR of 1.5 years.[18]

Conclusions

The availability of at least 5 different TKIs for CML therapy, 3 of them registered as frontline therapy, makes it possible to tailor treatment according to each patient's profile and treatment goal. The efficacy of the second-generation TKIs is certainly greater than that of imatinib, although their toxicity profiles limit their use in patients at elevated risk for specific AEs. Clinical trials exploring more flexible schemes of treatment (eg, a second-generation TKI at full dosage followed by a decrease in dosage or a switch to imatinib as soon as specific molecular endpoints have been achieved) are needed to optimize the treatment of CML with TKIs. The goal is to combine maximum efficacy—leading to increased OS and therapy discontinuation—with a minimal risk for AEs.

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