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REVIEW ARTICLE

Front-Line and Salvage Therapies With Tyrosine Kinase Inhibitors and Other Treatments in Chronic Myeloid Leukemia

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ABSTRACT

Chronic myeloid leukemia (CML) has been a model disease in the development of targeted therapies. After nearly 40 years of the recognition of the chromosomal abnormality that defines CML, specific therapy was developed, initially with imatinib mesylate, which has transformed our treatment algorithms and has changed the natural history of the disease. Today, most patients have the expectation of a favorable outcome when treated with standard-dose imatinib. However, a significant proportion of patients do not achieve the optimal desirable outcome. Effective salvage therapy followed the recognition of some of the most common mechanisms of resistance. More recently, the focus has turned to new areas of research and medical need, such as improving the front-line therapy to minimize the risk of resistance, to fight the most resistant mutant forms of *BCR-ABL*, and to eliminate minimal residual disease with the goal of achieving total elimination of the disease and treatment discontinuation. In this review, we analyze the current status of therapy of CML, and we discuss some of the most relevant clinical questions that we face today.

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INTRODUCTION

The evolution in the understanding of the biology of chronic myeloid leukemia (CML) that eventually translated into the development of specific, highly effective therapy is unparalleled in cancer medicine. This fascinating story started in 1960, when a minute chromosome was identified in patients with CML.[1] Later, this abnormality was identified as a balanced translocation between chromosomes 9 and 22, now known as the Philadelphia chromosome,[2] with the formation of a chimeric gene, *BCR-ABL*,[3] that translates into a protein with increased tyrosine kinase activity.[4] The realization of the critical role this protein plays in the pathogenesis of CML[5] led to a search for specific inhibitors. This efforts came to fruition when imatinib was introduced.[6] After a rapid succession of clinical trials, imatinib became standard therapy in CML. The IRIS (International Randomized Study of Interferon and ST1571) trial, in which patients with CML in chronic phase (CP) were randomly assigned to receive imatinib or interferon alfa (IFN-α) plus cytarabine (Ara-C) established imatinib as the standard therapy.[7] With 8 years of follow-up on this study, the results are outstanding. A complete cytogenetic response (CCyR) was achieved in 83% of patients, with a projected 8-year event-free survival (EFS) of 81% and a projected overall survival of 85%.[8] Still, some patients do not have the favorable outcome for which we would hope. In this trial, 17% of patients never achieved CCyR, approximately 15% achieved CCyR but eventually lost it, and, nearly 5% were intolerant to imatinib. Thus, at least one third of all patients did not have an acceptable outcome.

By following the lead of imatinib development, a second generation of tyrosine kinase inhibitors (TKIs) was developed shortly after imatinib failure was identified. An initial important step was the identification of mutations in the tyrosine kinase domain as the most common mechanism of resistance.[9] This was soon followed by the development of new agents with higher binding affinity to *BCR-ABL*, even in the presence of most known mutants. Two of these agents, dasatinib and nilotinib, have been most extensively studied and have received regulatory approval for use as second-line therapy among patients with resistance or intolerance to imatinib. Both agents have significant clinical efficacy and a favorable toxicity profile in this setting. With dasatinib, a CCyR occurs in 51% of patients, with a 24-month progression-free survival (PFS) of 81%.[10] These results were obtained with what was initially the standard dose, 70 mg twice daily, proposed because of the short half-life of dasatinib of approximately 5 hours.[11] A subsequent randomized

trial established that intermittent kinase inhibition with a dose of 100 mg once daily was equally effective (CCyR, 50%; 24-month PFS, 80%) and was better tolerated than 70 mg twice daily, which decreased the frequency of some of the most troublesome adverse events, particularly pleural effusions and myelosuppression.[12] Nilotinib induced CCyR in 44%, with a 24-month PFS of 64%.[13] Interestingly, despite the much longer median half-life of nilotinib (approximately 15 hours), it is currently administered twice daily, as a standard dose of 400 mg twice per day. Bosutinib, another second-generation TKI under development, appears to have also significant clinical activity and a reported CCyR of 50%.[14]

The excellent results obtained with imatinib when used as initial therapy, and the availability of effective salvage therapy, redefined the CML treatment algorithm. Nearly all patients are offered therapy with imatinib at diagnosis, and for those who experience failure to therapy,[15] a second-generation TKI is indicated. With this approach, the median survival for CML patients will probably exceed 20 years. Still, as we better understand the disease and improve the outcome of patients, we have uncovered new challenges and important questions that demand attention.

WHAT SHOULD THE GOAL OF THERAPY BE?

IFN-α was for many years the standard therapy for CML, because it induced cytogenetic remissions in a significant number of patients. Most important, it was established that patients who achieved CCyR had a significant improvement in survival, with 78% alive after 10 years.[16] Thus, CCyR became the goal of therapy. With imatinib, not only did we have the means to achieve CCyR in many more patients, but also the tools to monitor patients have evolved considerably. The value of achieving an improved molecular response had been suggested for patients treated with IFN-α. Among patients who achieved CCyR, those with the least disease detectable by polymerase chain reaction had the best probability of a sustained response.[16,17] The definition of molecular response has evolved. Today, we consider major molecular response (MMR) a decrease in tumor load equivalent to a 3-log reduction from a standardized baseline determined in each laboratory for patients at the time of diagnosis. Because of the variability that this entails, this is better expressed in terms of an international scale (IS), which is implemented throughout the world by standardizing results so that an MMR corresponds to *BCR-ABL*–to–control gene ratio of $\leq 0.1\%$.[18] Definition of complete molecular response (CMR) depends on the quality of the samples analyzed. Thus, the sensitivity of the assay should be provided when CMR is provided. CMR may be considered when transcripts are undetectable in an assay with sensitivity of ≥ 4.5 log (ie, $CMR^{4.5}$).

It is important to consider whether achieving an MMR improves long-term outcome relative to achieving CCyR with no MMR. Considering that greater than 80% of patients achieve CCyR with imatinib, that we have highly effective salvage therapy for patients who experience imatinib failure, and that follow-up for imatinib-treated patients is relatively short, it is not surprising there is no evidence of improved survival for patients with MMR or CMR. Initial reports from the IRIS trial suggested that, among patients with CCyR, patients who achieved MMR by 12 months had a significantly better EFS probability than those without MMR.[19] With additional data, this difference was no longer detectable according to the 12-month response, but patients who had MMR had an improved EFS probability at 72 months (95%) compared with those who had CCyR but no MMR (86%) when response was measured at 18 months,.[20] The difference in probability of survival without transformation to accelerated phase or blast phase (AP/BP), although significant, was considerably smaller.[20] Achieving CMR may additionally decrease the probability of relapse.[21,22] Perhaps more important, achieving a CMR offers the possibility of discontinuing imatinib. In preliminary results from the STIM (Stop Imatinib) trial in 69 patients who discontinued imatinib after having a sustained CMR for greater than 2 years, 59% experienced relapse.[23] All relapses occurred within 7 months of discontinuation, were molecular relapses (ie, no cytogenetic or hematologic relapses), and always responded again to imatinib.[23] Thus, it appears desirable to achieve MMR and even CMR, as these responses may predict for more durable responses, particularly if we can additionally improve the ability to stop therapy without relapse. However, a patient who has persistent detectable disease in the setting of MMR and perhaps even CCyR should not be considered to have experienced failure to therapy. Current recommendations by the European LeukemiaNet do not include inability to achieve MMR or loss of MMR as a criterion of treatment failure,[15] and there are no studies showing that any intervention (eg, dose increase, change to new TKI) in this setting improves the long-term outcome.

CAN WE, AND SHOULD WE, IMPROVE FRONT-LINE THERAPY?

Despite the excellent results achieved with standard-dose imatinib, at least one third of patients do not achieve the desired outcome. Therefore, there is a need to improve these results. Among the early strategies to improve the outcome was the use of high-dose imatinib. Several single-arm, phase II trials (Table 1) suggested that patients treated with imatinib 600 to 800 mg rapidly achieved CCyR and MMR at higher rates than expected with imatinib 400 mg/d.[31-34] However, one randomized trial of standard- versus high-dose imatinib suggested that the difference eventually disappeared, resulting in no benefit in EFS or survival without transformation to AP/BP despite early suggestions of decreased rate of events in the first 12 months.[25] This was true even when only patients with high-risk Sokal status were selected.[35] The lack of overall benefit with higher dose may be due in part to the frequent dose-reductions and treatment interruptions when starting with higher doses in this multicenter trial. In fact, among patients able to maintain higher doses, and among those with minimal treatment interruptions, there was a significant improvement in the rate of MMR.[33,36] In another randomized trial, CML IV, patients received imatinib 400 mg, imatinib 800 mg, or imatinib plus IFN-α. The 5-year PFS was better for patients treated with high-dose imatinib (94%) than with standard-dose imatinib (87%). Importantly, the actual median dose for patients treated with high-dose was 646 mg/d, probably accounting for the superior results.[37] The effect of dose intensity might be modulated by the efficiency of the OCT-1 transporter. Patients with a less active transporter derived significant benefit from higher initial imatinib dose, whereas those with a more active transporter showed equivalent outcome with any dose.[38] Currently, higher starting doses of imatinib are not recommended outside of a clinical trial. However, these results suggested that a therapy that could deliver higher potency with less toxicity (and fewer interruptions and reductions) might improve the long-term outcome.

Another approach is to use imatinib-based combinations. Because of the established clinical benefit of IFN-α, combining imatinib

Table 1. Summary of Results With Tyrosine Kinase Inhibitors As Initial Therapy for CML

Outcome in First 12 Months	IRIS[7,24] Imatinib 400 mg (n = 553)	TOPS[25] Imatinib 400 mg (n = 157)	TOPS[25] Imatinib 800 mg (n = 319)	MDACC[26] Dasatinib (n = 62)	MDACC[27] Nilotinib (n = 61)	GIMEMA[28] Nilotinib (n = 73)	DASISION†[29] Dasatinib (n = 259)	DASISION†[29] Imatinib (n = 260)	ENESTnd†[30] Nilotinib 300 mg Twice Daily (n = 282)	ENESTnd†[30] Nilotinib 400 mg Twice Daily (n = 281)	ENESTnd†[30] Imatinib 400 mg (n = 283)
CCyR	65*	66	70	98	97	96	83	72	80	78	65
MMR	39*	40	46	71	81	85	46	28	55	51	27
Events	3.3	2.5	1.9	1.6	8.1	NR	NR	NR	2.1	0.3	4.6
Transformation	1.5	1.9	0.9	0	1.6	NR	1.9	3.5	0.7	0.3	3.8
Discontinued therapy	14	8	10	NR	NR	1	15.5	18.6	16	18	21

NOTE. Definitions and methodologies for the different end points vary from study to study. Some important differences include whether results are presented by 12 months (ie, cumulative incidence) or at 12 months, whether fluorescent in situ hybridization was acceptable for assessment of CCyR, whether results were presented on intention-to-treat populations, the definitions of events, and the criteria set for treatment discontinuation in the different studies. Thus, this table is meant as a summary of data and not as a comparison between studies.

Abbreviations: CML, chronic myeloid leukemia; IRIS, International Randomized Study of Interferon and STI571, TOPS, Tyrosine Kinase Inhibitor Optimization and Selectivity; MDACC, MD Anderson Cancer Center; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; DASISION, Dasatinib versus Imatinib Study in Treatment-Naive CML Patients; ENESTnd, Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Ph+ CML Patients; CCyR, complete cytogenetic response; MMR, major molecular response; NR, no response.

*Estimated.

†Rate of events and transformation reported with a median follow-up of 14 months.

with IFN-α became attractive (Table 2). Early attempts with these combinations established their feasibility, albeit with the expected IFN-α–related toxicity.[41] Results of at least three randomized trials that used imatinib with or without IFN-α as initial therapy in CP CML have been reported. In one study patients were randomly assigned to four treatment arms: standard-dose imatinib, high-dose imatinib (600 mg/d), imatinib plus cytarabine, and imatinib plus pegylated IFN-α-2a. Patients treated with imatinib and IFN-α had a higher rate of MMR (71%) and CMR (22%) at 24 months compared with patients treated with standard-dose (MMR, 48%; CMR, 10%) or high-dose imatinib (62%, and 11%, respectively). Patients treated with imatinib and cytarabine had similar outcome as those treated with high-dose imatinib. However, there was no advantage in the 4-year EFS for any group.[40] On another trial, patients were randomly assigned into three arms: standard-dose imatinib, high-dose imatinib (800 mg/d), or imatinib plus IFN-α. The 12-month rate of MMR was highest for patients treated with high-dose imatinib (61%) compared with standard dose (42%) or imatinib with IFN-α (45%). The 5-year PFS with IFN-α was 91%.[37] In the third study, 94 patients received imatinib 800 mg/d for the first 6 months, then randomly assigned to continue high-dose imatinib alone or with PEG-IFN-α-2b. After a median of 54 months, there were no differences in response rate, EFS, PFS, or survival between the two arms.[39] From these results, it appears that the addition of IFN-α to imatinib may have little benefit in prolonging EFS. However, these studies may still be too young to fully judge any possible effect. It is possible that any improvement in outcome may not bee seen for many years, because the early results with imatinib are already excellent. Also, a possible beneficial effect might not be reflected in the response rate or EFS but rather in the ability to maintain responses, particularly if imatinib is discontinued.

On the basis of the higher in vitro potency of the second-generation TKI, with lesser propensity to trigger development of mutations,[42] and the efficacy and adequate toxicity profile as second-line therapy, these agents became attractive candidates for front-line therapy. Three phase II, single-arm studies have been reported that use nilotinib or dasatinib as initial therapy. All three suggested that cytogenetic and molecular responses can be achieved rapidly, with CCyR reported in greater than 90% at 6 months.[26-28] MMR occurred at 12 months in 71% of patients treated with dasatinib[26] and in 81% to 85% treated with nilotinib.[27,28] To confirm these results, randomized trials

Table 2. Summary of Results of Randomized Studies Exploring Dose and Combination Therapy

Response	MDACC[39] Imatinib 800 mg (n = 49)	MDACC[39] Imatinib 800 mg + Interferon (n = 45)	German CML-Study IV[37] Imatinib 400 mg (n = 326)	German CML-Study IV[37] Imatinib 800 mg (n = 338)	German CML-Study IV[37] Imatinib 400 mg + Interferon (n = 351)	French SPIRIT[40] Imatinib 400 mg (n = 176)	French SPIRIT[40] Imatinib 600 mg (n = 171)	French SPIRIT[40] Imatinib 400 mg + Cytarabine (n = 172)	French SPIRIT[40] Imatinib 400 mg + Interferon (n = 176)
12-month CCyR	87	90	NR	NR	NR	57	65	66	71
12-month MMR	77	77	42	61	45	40	52	51	61
CMR	11	13	NR	NR	NR	11*	11*	12*	22*
PFS†	95	97	87	94	91	92	93	90	91
OS†	95	96	90	96	93	NR	NR	NR	NR

NOTE. Definitions and methodologies for the different end points vary from study to study.

Abbreviations: MDACC, MD Anderson Cancer Center; CML, chronic myeloid leukemia; SPIRIT, STI571 Prospective Randomized Trial; CCyR, complete cytogenetic response; NR, not reported; MMR, major molecular response; CMR, complete molecular response; PFS, progression-free survival; OS, overall survival.

*At 12 months for MDACC; at 24 months for French study.

†At 5 years in MDACC and German studies; at 4 years in French study.

were designed to compare imatinib with nilotinib, dasatinib, or bosutinib. In one study, patients received standard-dose imatinib or nilotinib at either 400 mg twice per day or 300 mg twice per day.[30] By 12 months of therapy, the rate of MMR (the primary end point of this study) was 43% with nilotinib 400 mg twice daily, 44% with nilotinib 300 mg twice daily, and 22% with imatinib ($P < .001$). More important, with a follow-up of 14 months, patients treated with nilotinib had a significantly lower rate of transformation (< 1% for each schedule) compared with patients treated with imatinib (4%).[30] Similarly, results of a study of dasatinib versus imatinib showed the rate of CCyR after 12 months was better with dasatinib (83%) than with imatinib (72%), with a similar advantage in the rate of MMR (46% *v* 28%). There was a higher rate of transformation to AP/BP with imatinib (3.5%) than with dasatinib (1.9%).[29] Evidently, longer follow-up is needed to fully assess the possible benefit of these agents beyond what is expected with imatinib. However, these results suggest that nilotinib and dasatinib may help reduce the percentage of patients who have unacceptable outcome with imatinib, at least at the earlier timepoints. Results of a trial of imatinib versus bosutinib are expected soon.

WHAT IS THE BEST STRATEGY?

With the excellent results using second-generation TKI as initial therapy, one important question is how these results may change the way we approach newly diagnosed patients. We have on one end excellent results with imatinib, with an 8-year follow-up that confirms the durability of responses and good tolerance for most patients, with no unanticipated adverse events with long-term use. On the other end, we have one third of patients treated with imatinib who do not have the minimally accepted outcome and the encouraging early results of studies that used second-generation TKI as initial therapy. Thus, we could envision two possible strategies to manage newly diagnosed patients with CML. The first option is to use imatinib for all patients and only change therapy for those with resistance (and, possibly, suboptimal response) or intolerance. The second option is to start all patients with a second-generation TKI.

Unfortunately, the available data only present results for one intervention at a time (ie, imatinib as front-line, or second-generation TKI after imatinib failure). The effect of sequential use of different treatment strategies is difficult to assess from the available literature. On the basis of IRIS data, 30% to 35% of patients would need to change therapy at some point. Approximately 50% of patients who develop imatinib resistance will achieve CCyR with a second-generation TKI, and the 2-year PFS rate after therapy with these agents is 64% to 81%.[10,13] Thus, approximately 30% to 40% of patients who experience failure on imatinib might be successfully rescued. When taken in isolation, the EFS rate after imatinib is 81%. However, accounting for patients successfully treated with a subsequent TKI, nearly 90% of patients would be expected to be alive and in CCyR.[43] Whether initial therapy with second-generation TKI will provide a long-term outcome superior to what would be expected with sequential TKI therapy requires additional study and longer follow-up.

At the heart of this debate is the significance of achieving earlier responses. The most obvious benefit yet from using new agents as initial therapy is that, very early, most patients achieve CCyR. Although some analyses have suggested that, for patients who achieve CCyR the time to response has little impact on EFS,[44] it is clear that a patient who has not achieved an early response faces the competing probabilities of improvement to the desired response, or eventually to disease progression. It has been suggested that, the longer it takes to achieve a CCyR, the lower the probability of achieving this response and the higher the probability of experiencing progression.[45] The early results from the randomized trial of imatinib versus nilotinib or dasatinib might support the benefits of an earlier response, as higher early response rates has been associated with a lower risk of transformation. In addition, population-based analysis have suggested that the rate of imatinib failure might be higher than reported in IRIS,[45,46] with a 5-year EFS of 63%.[46] With these results, the possible benefit of earlier responses could be magnified, provided these results can be reproduced in similar population-based analysis.

TREATMENT DISCONTINUATION AND THE POSSIBILITY OF CURE

Among the most intriguing clinical questions remaining in the management of CML is whether patients could eventually discontinue therapy and be cured. The current recommendation is to continue therapy indefinitely. Early attempts at treatment discontinuation among patients with CMR have suggested that most patients experienced relapse.[48-50] However, some patients remained in remission, and it was suggested that prior IFN-α use could contribute to a sustained response.[48] As mentioned in What Should the Goal of Therapy Be? in the STIM trial, 59% of patients experienced relapse after treatment discontinuation.[23] Although longer follow-up is needed, the approximately 40% of patients who had not experienced relapse is promising. An important task is to identify what characteristics make these patients remain in remission.

In aiming for treatment discontinuation and cure for all patients, two goals should be accomplished. One is to make treatment discontinuation available to all patients. Only patients who had sustained CMR for $\geq$ 2 years were eligible for the STIM trial. How often patients treated with imatinib reach this milestone is unclear. A recent analysis suggested that, after a median follow-up of 79 months, only 32% of all imatinib-treated patients achieved sustained CMR,[22] but other studies have suggested that approximately two thirds of patients may reach this hallmark.[20] One approach to increase the number of patient achieving CMR is the use of peptides or cells to trigger an anti-CML immune response. Several approaches have been reported, including a junction BCR-ABL peptide,[51-54] a proteinase-3-derived peptide (PR1[55]), heat-shock protein,[56] or granulocyte-macrophage colony-stimulating factor–transfected K562 cells.[57] Although immune responses have been reported with all of them, the clinical results have been mixed. One study that used the BCR-ABL junction peptide reported that 41% of patients achieved CMR after vaccination.[54]

The second important element is to develop approaches that decrease the probability of relapse after treatment discontinuation. In one study, patients received IFN-α as they discontinued imatinib. Three patients achieved CMR after imatinib discontinuation, and, after greater than 2 years of follow-up, 75% of patients remained in remission.[58] Intriguingly, some patients did not experience relapse despite the persistence of low levels of *BCR-ABL* transcripts. Although preliminary, these results suggest that IFN-α might aid in maintaining responses. Alternative strategies are looking at targets directed to the leukemic stem cell, such as inhibition of the smoothened/Hedgehog pathway.[59] Trials with these agents are being initiated. However, for the

Table 3. Results With Second-Generation TKI After Imatinib Failure: Imatinib Resistance

Outcome	START-C + R[60] Dasatinib 70 mg Twice Daily (n = 389)	Study 034[12] Dasatinib 100 mg Once Daily (n = 124)	Study 034[12] Dasatinib 70 mg Twice Daily (n = 126)	Nilotinib[13] Nilotinib 400 mg Twice Daily (n = 226)	Bosutinib[14] Bosutinib 500 mg Once Daily (n = 202)*
MCyR, %	55†	59	57	56	60
CCyR, %	44†	44	48	41	46
MMR, %					
24-month PFS, %	78	80‡	76‡	64‡	77
24-month OS, %	NR	91‡	88‡	87‡	92
Follow-up, months	24	Minimum 24		18	14

NOTE. Definitions and methodologies for the different endpoints vary from study to study.
Abbreviations: TKI, tyrosine kinase inhibitor; START, START-C + R, SRC/ABL Tyrosine kinase inhibition Activity Research Trial Chronic Phase + Randomized Dasatinib versus High-Dose Imatinib; MCyR, major cytogenic response; CCyR, complete cytogenic response; PFS, progression-free survival; OS, overall survival.
*Evaluable patients.
†Projected at 24 months.
‡Includes both intolerant and resistant.

moment, all patients should continue therapy indefinitely unless they are enrolled on clinical trials that explore treatment discontinuation.

WHEN IMATINIB FAILS: WHEN TO CHANGE THERAPY AND TO WHAT

For patients who have resistance or intolerance to imatinib, two TKIs (ie, dasatinib and nilotinib) have received regulatory approval, and others are under investigation. The efficacy of these agents in this setting has been previously described, and the indication to change therapy is unquestionable (Tables 3 and 4). Importantly, the indication to change therapy is for patients who meet criteria for treatment failure as defined by the European LeukemiaNet.[15] In these instances, changing therapy as soon as failure is recognized is important, because the outcome appears to be better for patients who are treated as soon as criteria for cytogenetic failure are met rather than waiting until hematologic response is also lost.[62] For patients who have a suboptimal response, the management is less well defined. According to the European LeukemiaNet, the management of these patients includes continuation of therapy unchanged, use of high-dose imatinib, or change to dasatinib or nilotinib.[15] The ambiguity of this recommendation results from the lack of data on the benefit of any of these interventions. Patients who have a suboptimal response to therapy have, indeed, an inferior long-term outcome.[63,64] However, this category encompasses a heterogeneous group of patients who have variable expectations. For example, the long-term outcome for patients who have suboptimal response at 6 months is significantly worse than that of patients who have suboptimal response at 12 months and, particularly, 18 months.[64] Because of this, it is reasonable to consider therapeutic interventions for patients who have early suboptimal responses (ie, at 6 months). A dose increase is sensible and is usually recommended as the initial strategy, but there is no evidence that either a dose increase or a change to a second-generation TKI changes the long-term outcome, even if they improve the immediate response. It is also important to underscore that a change on therapy (eg, to second-generation TKI and particularly to stem-cell transplantation) on the basis of persistent polymerase chain reaction positivity is not indicated outside of a clinical trial.

Once the indication for treatment change is established, one should choose which agent to use. The presence of a mutation can provide guidance, because some mutants have greater sensitivity to one agent than to the other.[65,66] The in vitro sensitivity of the mutations correlates well with the probability of response and EFS with dasatinib or nilotinib for patients in CP[67-69] but not for those in AP/BP.[69] Thus, for example, for a patient who has a *F317L* mutant, nilotinib is a better choice than dasatinib, whereas for a patient who has *F359V* or *Y253H/F*, dasatinib is preferable. However, mutations

Table 4. Results With Second-Generation TKI After Imatinib Failure: Imatinib Intolerance

Outcome	START-C + R[60] Dasatinib 70 mg Twice Daily (n = 99)	Study 034[12] Dasatinib 100 mg Once Daily (n = 43)	Study 034[12] Dasatinib 70 mg Twice Daily (n = 42)	Nilotinib[13] Nilotinib 400 mg Twice Daily (n = 95)	Bosutinib[61] Bosutinib 500 mg Once Daily (n = 92)*
MCyR, %	82†	77	74	66	73
CCyR, %	78†	67	69	51	59
MMR, %					
24-month PFS, %	94	80‡	76‡	64‡	86
24-month OS, %	NR	91‡	88‡	87‡	99
Follow-up, months	24	Minimum 24		18	14

NOTE. Definitions and methodologies for the different endpoints vary from study to study.
Abbreviations: TKI, tyrosine kinase inhibitor; START-C + R, SRC/ABL Tyrosine kinase inhibition Activity Research Trial Chronic Phase + Randomized Dasatinib versus High-Dose Imatinib; MCyR, major cytogenic response; CCyR, complete cytogenic response; MMR, major molecular response; PFS, progression-free survival; OS, overall survival; NR, no response.
*Evaluable patients.
†Projected at 24 months.
‡Includes both intolerant and resistant.

are only present in approximately 50% to 60% of patients who have resistance to imatinib, and, for most mutations, there is either no obvious difference between the two agents or there is no available information. In these instances, the choice of therapy may sometimes be guided by comorbidities and known toxicity profile of the different drugs. For example, for patients with pulmonary problems or hypertension, possible risk factors for pleural effusion,[70] or those who have a history of gastrointestinal bleeding[71] or who receive nonsteroidal anti-inflammatory agents,[72] nilotinib might be preferable. In contrast, dasatinib might be preferable for patients who have a history of pancreatitis. However, for most patients, there is no clear indication to choose one agent instead of the other. In those instances, the selection has to be made between two generally excellent treatment options, and issues such as familiarity with each agent, schedule preferences, and others may guide the choice.

BEYOND SECOND-LINE THERAPY

Patients who have experienced failure after two or more TKIs have limited options. Patients who have received two TKIs could receive the alternative TKI they have not yet used. When the reason for failure was intolerance, this is a good alternative. However, although approximately 25% of patients with resistance to two TKIs may achieve MCyR, responses are not durable, with median time to failure of 20 months in CP and shorter in advanced stages.[73] These patients should be considered for stem-cell transplantation when eligible, or for clinical trials. The use of the third available second-generation TKI can be justified for patients who do not have access to any of these options, with clear understanding and discussion of the expectations. It is also acceptable as a bridging approach for patients being evaluated for stem-cell transplantation.

Patients who develop T315I have a poor prognosis, mostly determined by the lack of available treatment, although variable expected survival has been reported; one study recorded a 2-year probability of 87% for those in CP,[74] whereas another series reported a median of only 22.4 months.[75] Stem-cell transplantation is recommended for these patients. Although the available data on the outcome in this setting are limited, stem-cell transplantation, when performed in CP, can induce durable responses.[76,77] Unfortunately, few patients (15% in one series) receive a transplantation because of lack of donors, age, comorbidities, and other reasons.[77] Several new agents are being developed with activity against T315I, including novel TKIs, such as ponatinib (AP24534), DCC2036, PHA739358, and XL228, and others that have different mechanism of action (eg, omacetaxine [homoharringtonine]). A detailed description of the results achieved with these agents is beyond the scope of this article. However, a patient who is in adequate condition and has a suitable donor should be offered stem-cell transplantation. For all others, it has been recommended to discontinue TKI, an intervention that has been associated with a reduction of the T315I-mutated clone, sometimes to the level of becoming undetectable. However, few instances for which a response to a TKI can be maintained for several months with continued therapy have been reported, which highlights the complexity of this condition. Inclusion in a clinical trial with agents that have activity against T315I is recommended.

The evolution in the understanding of the biology and management of CML has been rapid and hefty. Over the last 50 years, we have gone from identifying a common cytogenetic abnormality to translating this finding into treatment strategies that have changed the natural history of the disease. With improved treatment options and monitoring tools, the need for adequate management of patients, including proper use of the different treatment options and adequate monitoring and follow-up, is crucial to optimize outcome. Important questions still remain to lead us to the promise of cure for all patients. The success in the recent past should not be reason for a decline in our research efforts if we are to complete this task.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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