Front-Line Therapy With Second-Generation Tyrosine Kinase Inhibitors in Patients With Early Chronic Phase Chronic Myeloid Leukemia: What Is the Optimal Response?

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ABSTRACT

Purpose

The response definitions proposed by the European LeukemiaNet (ELN) are defined on the basis of imatinib front-line therapy. It is unknown whether these definitions apply to patients treated with second-generation tyrosine kinase inhibitors (TKIs).

Patients and Methods

One hundred sixty-seven patients with newly diagnosed chronic myelogenous leukemia (CML) in chronic phase were treated with second-generation TKIs in phase II trials (nilotinib, 81; dasatinib, 86). Median follow-up was 33 months. Event-free survival (EFS) was measured from the start of treatment to the date of loss of complete hematologic response, loss of complete or major cytogenetic response, discontinuation of therapy for toxicity or lack of efficacy, progression to accelerated or blastic phases, or death at any time.

Results

Overall, 155 patients (93%) achieved complete cytogenetic response (CCyR), including 146 (87%) with major molecular response (MMR; complete in 46 patients [28%]). According to the ELN definitions, the rates of suboptimal response were 0%, 2%, 1%, and 12% at 3, 6, 12, and 18 months of therapy, respectively. There was no difference in EFS and CCyR duration between patients who achieved CCyR with and without MMR across all the landmark times of 3, 6, 12, and 18 months.

Conclusion

The use of second-generation TKIs as initial therapy in CML induces high rates of CCyR at early time points. The ELN definitions of response proposed for imatinib therapy are not applicable in this setting. We propose that achievement of CCyR and partial cytogenetic response at 3 months should be considered optimal and suboptimal responses, respectively. The achievement of MMR offered no advantage over CCyR in defining long-term outcome in patients with newly diagnosed CML treated with second-generation TKIs.

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INTRODUCTION

The European LeukemiaNet (ELN) recommendations were proposed during the era of imatinib front-line therapy,¹ a treatment that produced complete cytogenetic responses (CCyRs) in 83% of patients with Philadelphia chromosome (Ph)⁺-positive chronic myelogenous leukemia (CML), with most responses being durable.²⁻⁴ Achieving a CCyR correlated with survival.²⁻⁴

According to the ELN definitions, the overall response to imatinib can be defined as optimal, suboptimal, and failure. Optimal means that there is no indication that a change of therapy may improve a

survival that is currently projected as being close to 100% after 6 to 7 years. Suboptimal response means that the patient may still have a substantial long-term benefit from continuing a specific treatment, but the chances of an optimal outcome are reduced, so that suboptimal responders may be eligible for alternative approaches. Failure means that a favorable outcome is unlikely and that the patient should receive a different treatment whenever available and applicable.

Second-generation tyrosine kinase inhibitors (TKIs), such as dasatinib and nilotinib, are more potent *BCR-ABL* TKIs with demonstrated efficacy in patients resistant to or intolerant of imatinib.⁵⁻⁷

Dasatinib and nilotinib were first approved for patients resistant to or intolerant of prior imatinib therapy, are active against most BCR-ABL mutations with the exception of T315I, and have well-established safety profiles.^{2,8} Single-arm phase II studies⁹⁻¹¹ first suggested, and phase III randomized trials later confirmed that dasatinib and nilotinib were superior to imatinib, inducing faster and higher rates of CCyRs and molecular responses. Therefore, both drugs were granted approval by the US Food and Drug Administration to be used in patients with newly diagnosed CML in chronic phase (CML-CP).^{12,13}

The application of the ELN definitions—optimal, suboptimal, and failure—in patients receiving front-line therapy with second-generation TKIs may not be relevant since most patients will achieve early CCyRs. To determine the significance of ELN response criteria for patients receiving dasatinib or nilotinib as initial therapy for CML-CP, we conducted an analysis of patients receiving second-generation TKIs in early CML-CP to determine the frequency with which optimal and suboptimal responses occur and the long-term impact of such responses.

PATIENTS AND METHODS

One hundred and sixty-seven patients with newly diagnosed CML-CP were treated with second-generation TKIs in two simultaneous phase II trials (partially reported previously in Cortes et al¹⁰ and Rosti et al¹¹): one trial used nilotinib 400 mg twice daily and the other used dasatinib 100 mg once daily. Entry criteria were similar for both trials. CML-CP was defined as the presence in the peripheral blood of less than 15% blasts, less than 20% basophils, less than 30% blasts and promyelocytes, and platelets at more than $100 \times 10^9/L$.¹⁴ Patients were treated on protocols approved by institutional review boards, and informed consent was obtained in accordance with the Declaration of Helsinki. Response criteria were as previously described.² A complete hematologic response (CHR) was defined as a WBC count of less than $10 \times 10^9/L$, a platelet count of less than $450 \times 10^9/L$, no immature cells (blasts, promyelocytes, myelocytes) in the peripheral blood, and disappearance of all signs and symptoms related to leukemia (including palpable splenomegaly). This was further categorized by the best cytogenetic response as CCyR (0% Ph-positive metaphases), partial cytogenetic response (PCyR; 1% to 35% Ph-positive), or minor (36% to 95% Ph-positive). A major cytogenetic response (MCyR) included CCyR plus PCyR (ie, < 35% Ph-positive). Cytogenetic response was judged by standard cytogenetic analysis in 20 metaphases performed on bone marrow aspirates. Fluorescent in situ hybridization on peripheral blood was used only when routine cytogenetic analysis was not successful (ie, insufficient metaphases). Major molecular response (MMR) was defined as a *BCR-ABL/ABL* transcript ratio of $\leq 0.1\%$ (international scale). A complete molecular response (CMR) was defined as undetectable transcripts by using an assay with sensitivity of at least 4.5-log.¹⁴

The rates of suboptimal response and failure at each time point were calculated among evaluable patients (those patients still receiving therapy and with an evaluable hematologic, cytogenetic, and/or molecular result, as appropriate) to determine the response at the specified time point to be classified according to the ELN. Differences among variables were evaluated by the χ^2 test and Mann-Whitney *U* test for categorical and continuous variables, respectively. Event-free survival (EFS) was measured from the start of treatment to the date of any of the following events while on therapy: loss of CHR, loss of CCyR or MCyR, discontinuation of therapy for toxicity or lack of efficacy, progression to accelerated or blastic phases, or death from any cause at any time. Survival was measured from the time treatment was started to the date of death from any cause at any time or date of last follow-up. Transformation-free survival was measured from the start of therapy to the date of transformation to accelerated or blastic phases while on therapy or to the date of last follow-up. Survival probabilities were estimated by the Kaplan-Meier method and compared by the log-rank test.

RESULTS

A total of 167 patients were treated. The median follow-up time was 33 months (range, 3 to 66 months). Patients' characteristics are provided in Table 1. Eighty-six patients (52%) received dasatinib and 81 (48%) received nilotinib. The median time from diagnosis to therapy was 1 month (range, 0 to 8 months). The majority of patients (76%) were in the Sokal low-risk category.

Overall, 155 patients (93%) achieved a CCyR, including 146 (87%) who achieved an MMR (complete in 46 [28%]). Among the

Table 1. Patient and Disease Characteristics When Second-Generation TKI Therapy Was Initiated and Overall Outcome

Characteristic	No.	%
Age, years		
Median	46	
Range	18-85	
Time from diagnosis to treatment, months		
Median	1	
Range	0-8	
Platelets $\times 10^9/L$		
Median	296	
Range	73-2,000	
Hemoglobin, g/dL		
Median	12.2	
Range	6.7-15.8	
WBC $\times 10^9/L$		
Median	31.6	
Range	0.8-342.5	
Peripheral blood blasts		
Median	0	
Range	0-7	
Peripheral blood basophils		
Median	3	
Range	0-19	
Marrow blasts		
Median	2	
Range	0-8	
Marrow basophils		
Median	2	
Range	0-12	
Splenomegaly	44	26
Clonal evolution	10	6
% Patients Ph+ > 90	144	86
Sokal risk group		
Low	127	76
Intermediate	31	19
High	9	5
Second-generation TKI		
Dasatinib	86	52
Nilotinib	81	48
Response		
CCyR	155	93
MMR	146	87
4-year outcome		
EFS		89
TFS		97
OS		99

Abbreviations: CCyR, complete cytogenetic response; EFS, event-free survival; MMR, major molecular response; OS, overall survival; Ph+, Philadelphia chromosome-positive metaphase; TFS, transformation-free survival; TKI, tyrosine kinase inhibitor.

Table 2. Frequency of Suboptimal Response and Failure at 3, 6, 12, and 18 Months of Therapy

Months of Therapy	Response	Total	
		No.	%
3 (n = 160)	Optimal	160	100
	Suboptimal	0	
	Failure	0	
6 (n = 155)	Optimal	152	98
	Suboptimal	3	2
	Failure	0	
12 (n = 129)	Optimal	128	99
	Suboptimal	1	1
	Failure	0	
18 (n = 119*)	Optimal	99	84
	Suboptimal	14	12
	Failure	5	4

*One patient achieved a complete cytogenetic response, but no molecular test was performed at that time point; thus, we gave neither optimal nor suboptimal.

155 patients who achieved a CCyR at any time, five (3%) had lost such a response at the time of last follow-up, one of whom (20%; one of five) was taken off study because of adverse events. A total of 17 patients (10%) experienced events as defined for EFS, with three (2%) experiencing transformation to accelerated (n = 2) or blastic (n = 1) phase. The 4-year EFS, transformation-free survival, and overall survival (OS) rates for the whole group were 89%, 97%, and 99%, respectively.

The incidence of optimal and suboptimal responses and failure at 3, 6, 12, and 18 months is provided in Table 2. At 3 months from the initiation of therapy, all patients who had been evaluated for response (n = 160) achieved CHR (ie, optimal response); at 6 months, 152 (98%) of the 155 evaluable patients achieved an optimal response (MCyR), and three patients (2%) met the definition of suboptimal response (ie, less than an MCyR). By 12 months, 128 (99%) of 129 evaluable patients had an optimal response (CCyR), and one (1%) met the definition for suboptimal response (ie, less than CCyR). By 18 months, the percentage of patients with a suboptimal response (ie, less than MMR) increased to 12% (14 of 118 evaluable patients), and 84%

achieved an optimal response. Criteria for failure were met by 0%, 0%, 0%, and 4% at 3, 6, 12, and 18 months, respectively. Best responses and events by time on therapy are summarized in Table 3.

Overall, according to the ELN definitions, the rates of suboptimal response were low and were 2%, 1%, and 12%, at 6, 12, and 18 months of therapy, respectively. No patients met the criteria of suboptimal response at 3 months. The EFS from 3, 6, 12, and 18 months by cytogenetic and molecular response at these time points is shown in Figures 1A to 1D. At 3 months, patients with PCyR had a higher rate of events compared with patients with at least CCyR; patients who did not achieve a CHR had a poor outcome. At 6 months, patients with PCyR had a worse EFS compared with those who achieved a CCyR. At 12 months, all evaluable patients had achieved at least a CCyR, and outcome was similar, regardless of achievement of a molecular response; although not statistically significant, patients with a CMR had no events throughout their follow-up. At 18 months, patients with at least a CCyR (regardless of the molecular response) had a better prognosis than patients with PCyR or worse. Overall, patients with less than CCyR at any time points have a higher rate of events with a worse EFS. Importantly, there was no difference in EFS between patients who achieved a CCyR without molecular response and those who achieved an MMR or a CMR across all landmark time points of 3, 6, 12, and 18 months. In addition, CCyRs were durable, with no statistical difference, whether or not patients had achieved an MMR or a CMR in addition to CCyR at any time points (Figs 2A to 2D).

DISCUSSION

The recommendations from the ELN have been useful in harmonizing the definitions and treatment patterns for patients with CML treated with imatinib. According to the ELN definitions, the overall response to imatinib can be defined as optimal, suboptimal, and failure. These definitions were based on the information available at the time, mostly from the International Randomized Study of Interferon and STI571 (IRIS) study. With the advent of new treatment options with second-generation TKIs for patients with newly diagnosed early CML-CP, we explored whether the prognostic significance of these definitions is applicable for these populations.

Table 3. Adverse Events According to Cytogenetic and Molecular Response at 3, 6, 12, and 18 Months

Response	Months to Response											
	3 (n = 160)			6 (n = 155)			12 (n = 129)			18 (n = 119)		
	No.	%	IRIS/MDACC Events	No.	%	IRIS/MDACC Events	No.	%	IRIS/MDACC Events	No.	%	IRIS/MDACC Events
Molecular	52	32	0/3	109	70	0/6	102	79	1/5	99	83	0/3
Complete	1	< 1	0/0	11	7	0/1	11	9	0/0	17	14	0/0
Major	51	32	0/3	98	63	0/5	91	70	1/5	82	69	0/3
Cytogenetic	104	65	4/11	46	30	3/7	27	21	2/3	18	15	1/3
Complete	76	48	1/5	39	25	2/4	26	20	2/3	15	13	0/1
Partial	24	15	2/4	4	3	1/2	1	< 1	0/0	3	2	1/2
Minor	4	2	2/2	3	2	0/1	0		N/A	0		N/A
Others (CHR)	4*	3	0/1	0		N/A	0		N/A	2	2	2/2

Abbreviations: CHR, complete hematologic response; IRIS, International Randomized Study of Interferon and STI571; MDACC, MD Anderson Cancer Center; N/A, not applicable.

*Two patients achieved CHR, but no information on cytogenetic response was available because of insufficient metaphases.

Fig 1. The University of Texas MD Anderson Cancer Center event-free by response at (A) 3 months, (B) 6 months, (C) 12 months, and (D) 18 months. (*) One patient with partial cytogenetic response (PCyR) had no adverse events and was excluded. CCyR, complete cytogenetic response; CHR, complete hematologic response; CMR, complete molecular response; MinCyR, minor cytogenetic response; Resist, resistant.

Our study of homogeneous patients with early CML-CP treated with second-generation TKIs has confirmed that second-generation TKIs used in the front-line setting are highly efficacious and induced higher rates of CCyRs, with the majority of these responses occurring within 3 months of starting therapy. This is in line with what has been previously reported with the use of second-generation TKIs in the salvage and front-line setting.^{3,4,9,10} This is in contrast with the results obtained with imatinib therapy in which the CCyR rates peak around 12 to 18 months.¹⁵ Thus, with the majority of patients (99%) achieving an optimal response within 3 months, the ELN definitions of response may not be applicable in patients with newly diagnosed CML treated with second-generation TKIs.

At 3 months of therapy, patients with less than a CCyR had a poor outcome, and patients achieving a PCyR had an intermediate outcome. Therefore, it is important to closely monitor, from the earliest time points, all patients treated with second-generation TKIs with a goal of achieving a CCyR at 3 months of therapy since this was associated with the best long-term outcome. Patients with a PCyR, although they cannot be considered to have experienced a treatment failure, have a higher likelihood of adverse events (17%),

and therefore should be considered suboptimal. These patients should be reassessed at 6 months of therapy, because by that time, they should have achieved a CCyR; otherwise, they would be considered as having experienced treatment failure. Therefore, after 6 months of therapy, patients were either in CCyR or they experienced treatment failure (Fig 1B). Thus a redefinition of response at 3 months is proposed, with an optimal response defined by at least a CCyR, a suboptimal response defined by a PCyR, and treatment failure defined as less than a PCyR. A validation of these responses in independent cohorts is needed, particularly because only a small minority of our patients (5%) were in the Sokal high-risk category compared with a quarter of the patients enrolled in the randomized trials.^{12,13}

The broadly used IRIS definitions of events did not take into consideration intolerance and adverse effects that would lead to switching therapy regardless of efficacy. In our analysis, we used a broader definition of adverse events than what is traditionally used as introduced in the IRIS trial. However, by repeating the analysis with more restricted criteria like those of IRIS (Table 3), the findings were similar: patients achieving less than a CCyR at 3 months did have a worse outcome.

Fig 2. Complete cytogenetic response (CCyR) duration by response at (A) 3 months (mo), (B) 6 months, (C) 12 months, and (D) 18 months. CMR, complete molecular response; MMR, major molecular response.

We and others¹⁶⁻²⁰ have shown that the achievement of an early CCyR remains the major surrogate end point for long-term outcome in patients with CML treated with imatinib as well as with second-generation TKIs. The long-term implications of achieving an additional MMR on outcome of patients with CML remains controversial. Our study has failed to show any advantage in EFS and response duration in favor of patients who achieved an MMR compared with those who achieved only a CCyR at all time points. This is in line with our historical experience with imatinib in patients with newly diagnosed CML.¹⁹ Similarly, Marin et al²⁰ previously reported that the achievement of an MMR at 12 or 18 months of therapy with imatinib failed to confer any benefit in 5-year progression-free survival or OS. A recent update of the IRIS results has shown no significant impact on EFS or OS, whether a patient has or has not achieved an MMR by 12 months, provided a CCyR was achieved, and a modest but statistically significant benefit in EFS but not OS when assessed by 18 months.²¹ This observation may have important practical consequences. Recent trends in CML have emphasized the importance of close monitoring of minimal molecular residual disease, advocating molecular studies every 3 months.² Our analysis suggests that in a patient treated with second-generation TKIs in stable durable CCyR, the depth of mo-

lecular response (MMR *v* less than MMR but with CCyR) may not be a significant prognostic factor for outcome. That said, regular molecular monitoring may allow physicians to identify in less invasive ways those patients achieving a CCyR (ratio below 1% on the international scale)²¹ and, more importantly, to identify patients achieving a CMR. These last patients may be potential candidates for stopping therapy in the context of a clinical trial.²²

In summary, second-generation TKIs used in front-line therapy induce high and fast rates of CCyR that could translate into better outcome. The ELN definitions of response are not applicable in this setting, which should prompt a discussion of what the definitions should be for patients treated with second-generation TKIs. Therefore, we propose that for patients treated with second-generation TKIs as initial therapy for CML, achieving a CCyR by 3 months of therapy should be considered an optimal response, and achieving a PCyR should be considered a suboptimal response. Patients with less than a CCyR at 3 months might be considered for alternative treatment options, provided those options can realistically be expected to offer a better long-term outcome. Finally, the achievement of an MMR offered no advantage over CCyR on midterm outcome in patients with newly diagnosed CML treated with second-generation TKIs; a longer follow-up is needed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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