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Significance of Suboptimal Response to Imatinib, as Defined by the European LeukemiaNet, in the Long-Term Outcome of Patients With Early Chronic Myeloid Leukemia in Chronic Phase

Yesid Alvarado, MD, **Hagop Kantarjian, MD**, **Susan O'Brien, MD**, **Stefan Faderl, MD**, **Gautam Borthakur, MD**, **Jan Burger, MD**, **William Wierda, MD**, **Guillermo Garcia-Manero, MD**, **Jianqin Shan, MD**, and **Jorge Cortes, MD**

Department of Leukemia, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Abstract

BACKGROUND—The European LeukemiaNet recommendations for chronic myeloid leukemia (CML) defined a group of patients with suboptimal response to imatinib. The significance of this response was not well defined.

METHODS—The significance of having had a suboptimal response during imatinib therapy among 281 patients with CML treated with standard-dose (n = 73) or high-dose (n = 208) imatinib was investigated.

RESULTS—Rates of suboptimal response at 6, 12, and 18 months were 4%, 8%, and 40%, respectively, and were not influenced by Sokal risk score. Patients with a suboptimal response at 6 months had a significantly lower probability of eventually achieving a complete cytogenetic response (CCyR) compared with those with an optimal response (30% vs 97%; $P < .001$), and their event-free survival (EFS) and transformation-free survival (TFS) were found to be similar to those with criteria for failure at this time point. Suboptimal response at 12 months defined a group with a similar TFS as those with optimal response, but with worse EFS. In contrast, patients with a suboptimal response at 18 months had outcomes that were similar to those patients with an optimal response. A multivariate analysis confirmed the significance of response category after adjusting for pretreatment characteristics and imatinib dose.

CONCLUSIONS—The results of the current study suggested that suboptimal response was a heterogeneous category, and some patients had an outcome that mirrored that of patients with failed therapy. Interventions aimed at improving this outcome are required.

Keywords

chronic myeloid leukemia; imatinib; suboptimal response; chronic phase

Corresponding author: Jorge Cortes, MD, Department of Leukemia, The University of Texas M. D. Anderson Cancer Center, Unit 428, 1515 Holcombe Boulevard, Houston, TX 77030; Fax: (713) 794-4297; jcortes@mdanderson.org.

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Imatinib is currently standard therapy for patients with chronic myeloid leukemia (CML) in early chronic phase. The most recent update of the International Randomized Study of Interferon and STI571 (IRIS) trial demonstrated that 82% of patients achieve a complete cytogenetic response (CCyR), with most responses being durable.[1] After 6 years of follow-up, the event-free survival rate is 83%, and that for survival free from transformation is 93%. Despite these favorable results, there is a subset of patients who do not achieve the optimal response and may eventually require additional therapy. A panel of experts, on behalf of the European LeukemiaNet (ELN), recently proposed definitions for the criteria of what is considered failure to therapy.[2] These definitions became particularly relevant as new tyrosine kinase inhibitors were developed for the treatment of patients with resistance or intolerance to imatinib therapy. Two of these agents, nilotinib and dasatinib, have demonstrated efficacy in the management of patients who meet these definitions of failure after imatinib therapy.[3,4] In addition, the ELN recognized the presence of a group of patients with a response that the group considered suboptimal. Similar to the definition for failure, the definition for suboptimal response was based on the level of response achieved at different time points. Patients with suboptimal response were described as a group of patients who could still derive substantial benefit from continuing therapy with imatinib, but it was noted that the long-term outcome of such treatment was not likely to be as favorable as in responders at the same time point.[2] However, the long-term outcome of patients who meet these definitions of suboptimal response is not yet well known.

Thus, we conducted an analysis of patients receiving imatinib as initial therapy for early chronic-phase CML to determine the frequency with which suboptimal response occurs and the long-term outcome of patients with such response.

MATERIALS AND METHODS

From July, 2000 through July, 2005, 281 patients with Philadelphia (Ph)-chromosome positive CML were included in 4 consecutive clinical trials for the treatment of early chronic-phase CML with imatinib. Among these, 73 were treated with a starting dose of 400 mg daily, including 23 patients who were treated as part of a larger multicenter trial (IRIS)[5] and 50 patients who were treated in a single-institution phase 2, single-arm study.[6] An additional 208 patients received imatinib at a starting daily dose of 800 mg as part of 2 consecutive trials: 114 were treated in a single-institution, phase 2 trial[7] and 94 were treated in a randomized phase 2 trial in which all patients were treated with a starting daily dose of imatinib of 800 mg; after 6 months, patients were randomized to continue high-dose imatinib alone or in combination with pegylated interferon-α and sargramostim.[8] The preliminary results of the latter study suggested no difference in overall response, event-free survival (EFS), transformation-free survival (TFS), or overall survival (OS), and therefore both arms were included in this analysis together with patients treated with high-dose imatinib alone.

The eligibility criteria for all these studies were similar and included chronic-phase CML within 12 months from the time of the initial diagnosis and no prior therapy for CML (a maximum of 30 days of prior therapy with interferon-α, or imatinib for patients treated with high-dose imatinib, was allowed in the 3 single-institution trials). In addition, patients were

required to be aged >15 years, have an Eastern Cooperative Oncology Group performance status of 0 to 2, and normal organ function. All patients were enrolled in protocols approved by the institutional review board (IRB) and registered in clinical-trials.gov, and signed an informed consent approved by the IRB.

Follow-up was similar in all studies and included a history and physical examination, complete blood counts and blood chemistry at the initiation of therapy and every month for the first 3 months, then every 3 months until 12 months from the start of therapy, and then every 12 months. Cytogenetic response was assessed by G-banding karyotype assessed in the bone marrow with at least 20 metaphases counted. Molecular response was assessed by real-time quantitative polymerase chain reaction (RT-PCR). Both the cytogenetic and molecular response assessments were performed at baseline, every 3 months for the first 12 months, and then every 6 months.

Response criteria were as previously described.[7] A complete hematologic response (CHR) was defined as a white blood cell count $<10 \times 10^9$/L, a platelet count $<450 \times 10^9$/L, no immature cells (blasts, promyelocytes, or myelocytes) in the peripheral blood, and the disappearance of all signs and symptoms related to leukemia (including palpable splenomegaly). CHR was further categorized by the best cytogenetic response as CCyR (0% Ph positive), partial (PCyR; 1%–35% Ph positive), and minor (36%–90% Ph positive). A major cytogenetic response (MCyR) included CCyR plus PCyR (ie, ≤35% Ph positive). A major molecular response (MMR) was defined as a 3-log reduction in transcript levels from the baseline value established for untreated patients at our institution by real-time, TaqMan-based, quantitative PCR performed in peripheral blood samples. A complete molecular response (CMR) was defined as undetectable levels of *BCR-ABL* with a level of detection of at least 4.5 logs.[9]

Patients were classified as having failure or having a suboptimal response according to the definitions proposed by the ELN.[2] We identified no patients with a suboptimal response at 3 months; therefore, we considered only responses at 6, 12, and 18 months. Briefly, a suboptimal response is defined when there is less than a PCyR 6 months from the time of the initiation of therapy, less than a CCyR at 12 months, and less than an MMR at 18 months from the initiation of therapy. Failure is defined as less than a CHR or no cytogenetic response at 6 months, less than a PCyR at 12 months, and less than a CCyR at 18 months (Table 1). For the purposes of this analysis, patients not having failure or a suboptimal response were classified as having an `optimal' response.

Statistical Analysis

The rates of suboptimal response and failure at each time point were calculated among evaluable patients, that is, 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. EFS was measured from the initiation of imatinib therapy (overall) or from the time response was assessed (landmark analysis for responses at 3, 6, and 12 months) until loss of CHR or MCyR, progression to the accelerated or blastic phases of CML, or death from any cause during treatment. TFS was measured from the initiation of therapy (overall) or from the times of interest (landmark

analysis) until progression to the accelerated or blast phases of CML or death from any cause during treatment. OS was defined from the initiation of therapy (overall) or from the times of interest (landmark analysis) to the date of death or last follow-up. Survival probabilities were estimated with the Kaplan-Meier method and compared using the log-rank test.[10] Cox multivariate analysis was used to adjust for differences in baseline characteristics to define the independent impact of suboptimal response at any time on EFS and TFS. Differences among variables were evaluated using the chi-square test and Mann-Whitney *U* test for categorical and continuous variables, respectively.[11]

RESULTS

A total of 281 patients were treated and followed for a median of 52 months (range, 2 months-90 months). Approximately 7% of patients had received prior interferon (n = 4) or imatinib (n = 16) for <30 days as allowed per inclusion criteria. The majority (65%) of patients were in the Sokal low-risk category (Table 2). Patient characteristics were found to be similar between the cohorts treated with standard or high-dose imatinib. Overall, 261 (93%) patients achieved a MCyR, including 246 (88%) who achieved a CCyR. Among the 246 patients who achieved a CCyR at any time, 19 (8%) had lost such a response at the time of last follow-up. In addition, among 270 patients who had PCR testing performed after the initiation of treatment, 188 (70%) achieved an MMR including 103 (38%) with CMR. A total of 42 (15%) patients experienced events as defined for EFS, with 21 (7%) experiencing transformation to accelerated (n = 9) or blast (n = 5) phase, and 7 dying of a non-CML–related cause. The 4-year EFS, TFS, and OS rates for the whole group were 88%, 93%, and 98%, respectively.

At 6 months from the initiation of therapy, 10 (4%; 6 with low-risk Sokal score, 3 with an intermediate score, and 1 with a high-risk score) of 261 evaluable patients met the definition of suboptimal response (ie, less than a MCyR) and 9 (3%) had failure (ie, no CHR or no cytogenetic response). By 12 months, 19 (8%; 13 with a low-risk Sokal score, 5 with an intermediate score, and 1 with a high-risk score) of 247 evaluable patients had a suboptimal response (ie, less than a CCyR) and 14 (6%) met the definition for failure (ie, less than MCyR). By 18 months, the percentage of patients with a suboptimal response (ie, less than MMR) increased to 40% (61 patients with a low-risk Sokal score, 26 with an intermediate score, and 4 with a high-risk score), and 9% met criteria for failure (ie, less than CCyR). At both the 6-month and 12-month marks, the probability of having either a suboptimal response or failure was greater for patients treated with standard-dose imatinib (Table 3). However, it is interesting to note that by 18 months there was a trend toward a higher rate of suboptimal responses noted among evaluable patients treated with the 800-mg dose of imatinib but a significantly lower rate of failures among this cohort. However, by this time, 21 (29%) patients in the standard-dose group had already discontinued imatinib therapy because of resistance or intolerance compared with 42 (20%) in the high-dose imatinib cohort (including 7 [3%] patients who died due to non-CML causes). The probability of having suboptimal response at any given time was similar for all Sokal risk groups.

We also analyzed the EFS and TFS rates according to the response at each time point. For this purpose, we grouped patients from the standard-dose and high-dose cohorts together.

According to the response at 6 months, as expected, patients meeting the definition of failure were found to have a significantly worse EFS than those with an optimal response (4-year EFS rate of 27% vs 93%; $P < .0001$) (Fig. 1a). Of interest, the EFS for patients with a suboptimal response (4-year probability 45%) was found to be more similar to that of patients with failure than patients with an optimal response. Similarly, the 4-year TFS for patients with either failure (78%) or a suboptimal response (60%) was significantly worse than that of patients with an optimal response (95%) ($P < .0001$) (Fig. 1b). According to the response at 12 months, patients with failure have significantly worse EFS (4-year rate of 29%) and TFS (4-year rate of 62%) compared with patients with an optimal response (4-year EFS rate of 96%, and 4-year TFS rate of 96%). In contrast, patients with a suboptimal response have demonstrated a trend toward inferior EFS (4-year rate of 87%) compared with patients with an optimal response, but a similar TFS (4-year rate of 93%) (Figs. 2a and 2b). A similar distribution was observed based on the response by 18 months (Figs. 3a and 3b).

The population analyzed in the current study was heterogeneous with regard to their pretreatment characteristics and the dose used. We thus performed a multivariate analysis to investigate whether the significance of suboptimal response was independent of these factors. According to response at 6 months, multivariate analysis confirmed that patients with a suboptimal response had a similar inferior outcome as those with failure compared with those with an optimal response (hazards ratio [HR], 3.2 and 3.4, respectively; $P < .001$ for both). At 12 months, patients with a suboptimal response had a significantly worse EFS than patients with an optimal response (HR, 2.1; $P = .005$) but better than patients with failure (HR failure vs optimal response, 4.1; $P < .001$). According to response by 18 months, patients with a suboptimal response had a similar outcome as those with an optimal response ($P = .13$), whereas those with failure had a significantly worse EFS (HR, 4.0; $P < .001$).

Table 4 summarizes the probability of eventually achieving a CCyR or MMR (when applicable) according to the response category at each time point, as well as the probability of eventually having an event or transforming to the accelerated or blast phase. None of the patients with a suboptimal response at 6 months eventually achieved an MMR, and only 30% obtained a CCyR. This, as well as the probability of eventually having an event or transforming to the accelerated or blast phase, mirrors the prognosis of patients with failure at 6 months. According to the response at 12 months, although 72% of patients with a suboptimal response at this time eventually achieved a CCyR, only 39% eventually achieved an MMR (compared with 82% for patients with an optimal response but no MMR yet for patients with failure). This results in a rate of transformation that is similarly low as that for patients with an optimal response, but a higher probability of events. Based on the response at 18 months, patients with a suboptimal response still had a 66% probability of eventually achieving an MMR compared with 10% for patients with failure. Patients with suboptimal response had lower rates of transformation (5%) and events (10%) than those with failure.

We then analyzed the probability of patients with a suboptimal response be reclassified to a different category (optimal or suboptimal) at subsequent time points. As shown in Figure 4a, none of the 10 patients with a suboptimal response at 6 months had a therapeutic intervention at the time. None of these patients improved to an optimal response 6 months later (ie, at 12 months from the initiation of therapy), whereas 3 maintained a suboptimal

response and 6 worsened to failure by 12 months (1 was not evaluable for response at 12 months). Similarly (Fig. 4b), of the 19 patients with a suboptimal response at 12 months, 4 improved to optimal by 18 months, 5 maintained a suboptimal response, 8 worsened to failure by 18 months, 1 was not evaluable, and 1 was lost to follow-up. There were no treatment changes in any of these patients during this period (ie, from 12 months to 18 months). Of the 5 patients still with suboptimal response at 18 months, 2 remained in CCyR with no MMR, 2 improved to MMR (n = 1) or CMR (n = 1), and 1 failed because of noncompliance. Of the 8 patients catalogued as failure at 18 months, 3 lost a PCyR and regained it after a dose increase, 1 later achieved CCyR (at 33 months), and 4 patients changed therapy because of failure.

DISCUSSION

The recommendations from the ELN have been very useful in harmonizing the definitions and treatment patterns for patients with CML. With the advent of new treatment options for patients who may develop resistance or intolerance to initial therapy with imatinib, 1 important need was to establish clear and uniform definitions of what constitutes failure to therapy in which a change of therapy may be indicated. In doing so, the ELN also proposed definitions for a group of patients considered to have a suboptimal response. In the words of this group of experts, suboptimal response indicates that the patient still may receive substantial benefit from continuing therapy with imatinib but, because the long-term outcome is not likely to be optimal, the patient is eligible for other treatments. These definitions were based on the available information at the time, mostly from the IRIS study. Because the ELN recommendation is widely used throughout the world in guiding the management of patients with CML, we explored the prognostic significance of having a suboptimal response and how this may differ from having an optimal response or a failure.

The results of the current study suggest that indeed, patients with a suboptimal response represent a distinct category of patents with an outcome that is different (generally worse) than that of patients with an optimal response. However, we also demonstrated that patients with a suboptimal response represent a heterogeneous group of patients in whom the prognostic implications are different, depending on the time when a suboptimal response is determined. Thus, patients determined to have a suboptimal response at 6 months have a poor prognosis that is more similar to that of patients who already met criteria for failure than to patients with an optimal response. For example, the probability of transformation at any time in the future was 30% for patients with a suboptimal response at 6 months, compared with 22% for patients with failure and 6% for those with an optimal response. In contrast, patients deemed to have a suboptimal response based on the 12-month assessment have an outcome that is closer to that of patients with an optimal response, with a similar TFS, although with a lower probability of MMR and an increased probability of developing an event over the course of therapy. By 18 months, patients categorized as having a suboptimal response have an outcome that nearly overlaps with that of patients with an optimal response, similar to what has been reported from the IRIS study.[12]

The current analysis also suggests that the use of higher dose imatinib as initial therapy may decrease the probability of having a suboptimal response or failure at 6 months and 12

months. This is in accordance with the more rapid responses reported with high-dose imatinib in several studies.[7,13–16] Reducing the rate of suboptimal responses at the earliest time points, when they appear to have the most adverse prognostic implications (eg, from 11% with standard dose therapy to 1% with high dose therapy at 6 months in this analysis), could potentially result in an improved long-term outcome. Comparison with historical controls suggests that this might be the case,[17] but ongoing randomized trials comparing standard-dose versus high-dose imatinib will more definitively answer this question.

There are some important considerations that need to be taken into account in interpreting the results of the current study. First, they constitute a retrospective analysis of patients treated prospectively in clinical trials. In addition, patients who had received up to a maximum of 30 days of therapy with interferon or imatinib were allowed in these trials. Thus, the timing of the response may be off with respect to those used in the ELN recommendations and the rate of suboptimal responses might be underestimated. However, exposure to prior therapy (particularly imatinib) was minimal and occurred in only a minority of patients. Finally, we included patients treated with either standard-dose or high-dose imatinib. The definitions from the ELN were specifically designed for patients treated with standard-dose imatinib. Other than the difference in the rate of suboptimal responses and failures at some time points, we identified no differences in the significance of such responses by the dose used. In a multivariate analysis, the significance of response was maintained after adjusting for dose as well as pretreatment characteristics such as Sokal score. As new treatment modalities are being investigated as initial therapy for CML in early chronic phase (such as high-dose imatinib,[7,14] nilotinib,[18] and dasatinib[19]) it becomes important to consider these definitions beyond standard-dose imatinib. The results of the current study suggest these definitions apply (with acknowledgment of the heterogeneity mentioned earlier) to patients treated with both standard-dose and high-dose imatinib.

An important implication of recognizing a group of patients with a different outcome is the possibility of therapeutic interventions for these patients. The ELN recommended that, for these patients, dose escalation may be an appropriate first step. Unfortunately, to our knowledge there are no data regarding the efficacy of this approach in this setting. There has also been interest in examining the use of new tyrosine kinase inhibitors for patients with suboptimal response. However, to our knowledge, there are currently no data available regarding the benefit of these agents in this setting and how this may compare with dose escalation.

We conclude that patients with a suboptimal response as defined by the ELN recommendations constitute a distinct category of patients with an outcome that may be different (usually worse) from that of patients with optimal response. However, the category of suboptimal response includes a heterogeneous group of patients with different outcomes, depending on the time when a suboptimal response is determined. Therapeutic interventions aimed at improving the outcome of patients with this response need to consider this heterogeneity.

After submission of this article, a report by Marin et al has been published on this topic.[20] In this study, 224 patients with CML treated with standard dose imatinib were analyzed to

examine the value of suboptimal responses and failure. These investigators found that criteria for failure identify patients with significantly worse cytogenetic response, progression-free survival, and overall survival than other patients. Patients with suboptimal response according to their response at 6 and 12 months had a worse outcome, but those with suboptimal response at 18 months had a similar outcome to those with no failure or suboptimal response. Overall, the results of both studies suggest the validity but also the heterogeneity of the criteria for suboptimal response.

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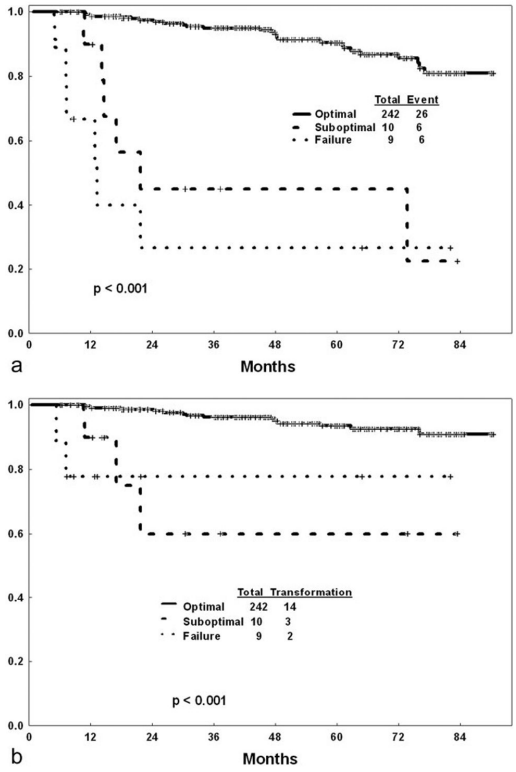

Figure 1.

Outcome according to response at 6 months by landmark analysis is shown according to (a) event-free survival and (b) transformation-free survival.

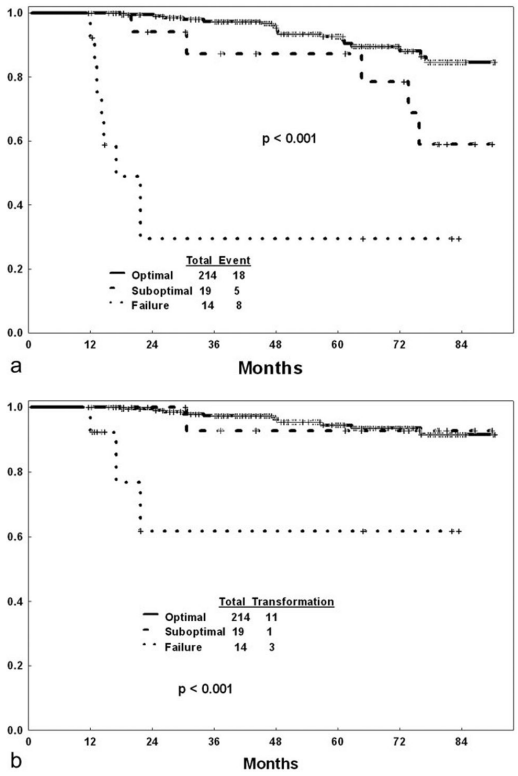

Figure 2.

Outcome according to response at 12 months by landmark analysis is shown according to (a) event-free survival and (b) transformation-free survival.

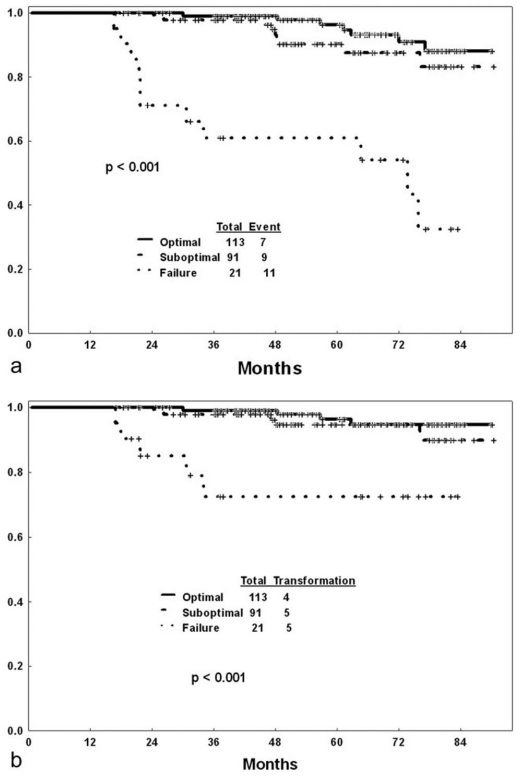

Figure 3.

Outcome according to response at 18 months by landmark analysis is shown according to (a) event-free survival and (b) transformation-free survival.

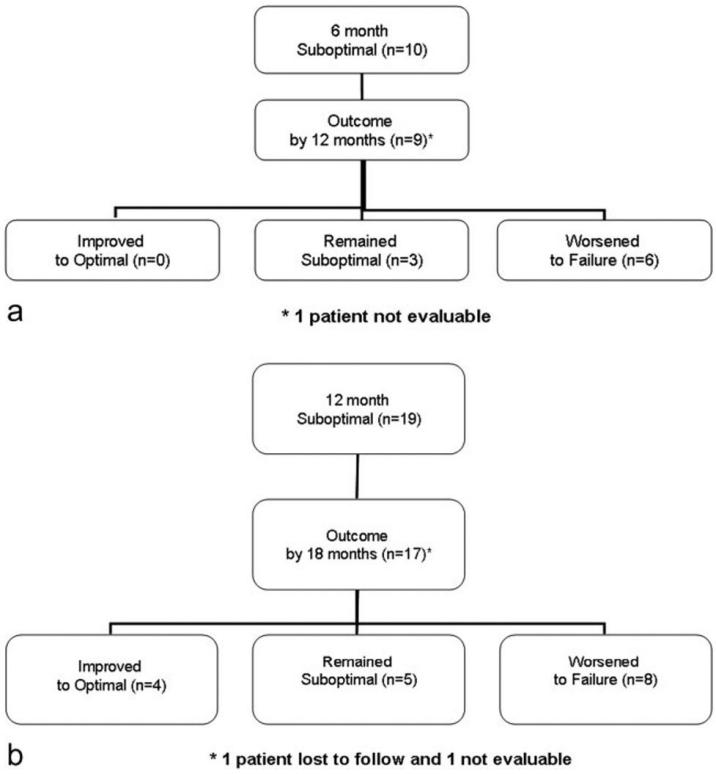

Figure 4.

Evolution of response from the evaluation at (a) 6 months and (b) 12 months to the next landmark analysis is shown.

Table 1

Definitions of Suboptimal and Failure Response at 3, 6,12, and 18 Months

Months of Treatment	Suboptimal Response	Failure Response
3	<CHR	No HR
6	<PCyR	<CHR
12	<CCyR	<PCyR
18	<MMR	<CCyR

CHR indicates complete hematologic response; HR, hematologic response; PCyR, partial cytogenetic response; CCyR, complete cytogenetic response; MMR, major molecular response.

Table 2

Patient Characteristics

	Median (Range) or No. (%)			
	400 mg (n=73)	**800 mg (n=208)**	**Total**	***P*** *
Age, y	48 (15–78)	48 (17–84)	48 (15–84)	0.52
Time from diagnosis to treatment, mo	2 (0–12)	1 (0–6)	1 (0–12)	<.001
Platelets, $\times 10^9$/L	367 (103–1043)	352 (58–1476)	250(58–1476)	.77
Hemoglobin, g/dL	12.7 (7.9–15.7)	12.4(6.2–16.7)	12.4(6.2–16.7)	.21
WBC, $\times 10^9$/L	20.5 (1.6–277)	27.8 (2.2–283)	25.5(1.6–283)	.009
PB blast, %	0 (0–2)	0 (0–12)	0 (0–12)	.03
PB basophils, %	3 (0–16)	3 (0–19)	3 (0–19)	.24
BM blast, %	1 (0–6)	2 (0–14)	2 (0–14)	.03
BM basophils, %	2 (0–9)	3 (0–15)	2 (0–15)	.08
Splenomegaly	16 (22)	59 (28)	75 (27)	.28
Prior therapy				
Imatinib	0	16(8)	16(6)	.3*
Interferon	3(4)	1 (<1)	4(1)	
Clonal evolution	2(3)	7(3)	9(3)	1.0
Ph% >90	67 (93)	193 (93)	260 (92)	.94
Sokal risk group				
Low	50 (68)	132 (63)	183 (65)	.08
Intermediate	22 (30)	57 (27)	79 (28)	
High	1 (2)	19(9)	19(7)	
Del der(9)	0/48 (0)	22/201 (11)	22/249 (9)	-
Variant Ph translocations	5(7)	8(4)	13(5)	.33
Response				
CCyR	59 (81)	187 (90)	246 (88)	.06
MMR	42/68 (62)	146/202(72)	188/270(70)	.10
4-y outcome				
EFS	85%	89%	88%	.60
TFS	87%	95%	93%	.34

WBC indicates white blood cell count; PB, peripheral blood; BM, bone marrow; Ph, Philadelphia chromosome; Del der(9), deletion of derivative chromosome 9; CCyR, complete cytogenetic response; MMR, major molecular response; EFS, event-free survival; TFS, transformation-free survival.

* *P* value for 400-mg versus 800-mg groups.

Table 3

Frequency of Suboptimal Response and Failure by Dose of Imatinib

Months on Therapy	Response	No. (%)			*P* *
		400 mg	800 mg	Total	
3	Optimal	70 (100)	199 (98)	269 (99)	NS
	Suboptimal	0	0	0	
	Failure	0	4(2)	4(1)	
6	Optimal	58 (83)	184 (96)	242 (93)	<.001
	Suboptimal	8(11)	2(1)	10(4)	
	Failure	4(6)	5(3)	9(3)	
12	Optimal	45 (70)	169 (92)	214 (87)	<.001
	Suboptimal	11 (17)	8(4)	19(8)	
	Failure	8(13)	6(3)	14(6)	
18	Optimal	24 (45)	89 (52)	113 (50)	<.001
	Suboptimal	17 (32)	74 (43)	91 (40)	
	Failure	12 (23)	9 (5)	21 (9)	

NS indicates not significant.

* *P* value for patients treated at a dose of 400 mg/day versus patients treated at a dose of 800 mg/day.

Table 4

Long-Term Outcome According to the Response Criteria at 6,12, and 18 Months

Months on Therapy	Response	Percent Probability of Event (*P*)							
		CCyR			MMR			Transformation	Event
		24 Months	48 Months	Ever	24 Months	48 Months	Ever		
6	Optimal	92 (<.001)	89(<.001)	97(<.001)	60(<.001)	64 (<.001)	80 (<.001)	6 (.003)	11 (<.001)
	Suboptimal	0	29	30	0	0	0	30	60
	Failure	0	13	13	0	0	0	22	67
12	Optimal	NA	NA	NA	63(<.001)	68 (<.001)	82 (<.001)	5 (.05)	8(<.001)
	Suboptimal	56 (.003)	69 (.02)	72 (.008)	25	38	39	5	26
	Failure	0	18	18	0	0	0	21	57
18	Optimal	NA	NA	NA	NA	NA	NA	4 (.002)	6(<.001)
	Suboptimal	NA	NA	NA	38(<.001)	54 (<.001)	66 (<.001)	5	10
	Failure	15	35	45	0	6	10	24	52

CCyR indicates complete cytogenetic response; MMR, major molecular response; NA, not applicable.