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ORIGINAL REPORT

Adherence Is the Critical Factor for Achieving Molecular Responses in Patients With Chronic Myeloid Leukemia Who Achieve Complete Cytogenetic Responses on Imatinib

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ABSTRACT

Purpose
There is a considerable variability in the level of molecular responses achieved with imatinib therapy in patients with chronic myeloid leukemia (CML). These differences could result from variable therapy adherence.

Methods
Eighty-seven patients with chronic-phase CML treated with imatinib 400 mg/d for a median of 59.7 months (range, 25 to 104 months) who had achieved complete cytogenetic response had adherence monitored during a 3-month period by using a microelectronic monitoring device. Adherence was correlated with levels of molecular response. Other factors that could influence outcome were also analyzed.

Results
Median adherence rate was 98% (range, 24% to 104%). Twenty-three patients (26.4%) had adherence ≤ 90%; in 12 of these patients (14%), adherence was ≤ 80%. There was a strong correlation between adherence rate (≤ 90% or > 90%) and the 6-year probability of a 3-log reduction (also known as major molecular response [MMR]) in *BCR-ABL1* transcripts (28.4% *v* 94.5%; $P < .001$) and also complete molecular response (CMR; 0% *v* 43.8%; $P = .002$). Multivariate analysis identified adherence (relative risk [RR], 11.7; $P = .001$) and expression of the molecular human organic cation transporter-1 (RR, 1.79; $P = .038$) as the only independent predictors for MMR. Adherence was the only independent predictor for CMR. No molecular responses were observed when adherence was ≤ 80% ($P < .001$). Patients whose imatinib doses were increased had poor adherence (86.4%). In this latter population, adherence was the only independent predictor for inability to achieve an MMR (RR, 17.66; $P = .006$).

Conclusion
In patients with CML treated with imatinib for some years, poor adherence may be the predominant reason for inability to obtain adequate molecular responses.

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INTRODUCTION

Chronic myeloid leukemia (CML) is characterized by a consistent chromosomal abnormality (the Philadelphia [Ph] chromosome), which carries a unique fusion gene, termed *BCR-ABL1*.[1] In the absence of treatment, CML is inexorably fatal. Imatinib is an adenosine triphosphate analog that selectively inhibits the enhanced tyrosine kinase activity of the Bcr-Abl1 oncoprotein and induces durable cytogenetic responses in the majority of patients with a relatively benign adverse effect profile.[1] In approximately 75% of patients, the Ph chromosome is no longer detectable after 2 years of therapy (for a status referred to as complete cytogenetic response [CCyR]).[2,3] The achievement of CCyR is the major objective of therapy, because it is associated with prolonged survival.[2,3] In patients who achieve CCyR, *BCR-ABL1* transcript levels may be monitored to assess the quantity of residual leukemia, and results are often expressed as the $\log_{10}$ reduction from a standardized value for untreated patients. It is generally accepted that CCyR corresponds to an approximately 2-log reduction in transcript levels.[4] By 5 years, approximately 50% of patients will have achieved a 3-log reduction in transcript levels

(defined as a major molecular response [MMR])[3]; this confers additional clinical benefit,[5] and it is also considered an important therapeutic target.[6] With continued treatment, approximately 20% to 30% of patients eventually achieve a 4-log reduction; in at least 10% of patients, the transcripts will become undetectable (ie, complete molecular response [CMR]).[3] In some instances, durable CMR may be the equivalent of cure, as it is possible to discontinue the imatinib in some of these patients without subsequent relapse.[7] The reasons underlying the different responses in different patients are unclear, but they may be caused in part by the intrinsic heterogeneity of CML.[8,9]

The extent to which patients with cancer comply with prescribed oral anticancer therapy ranges between 16% and 100%, depending on the specific therapy and method used to measure adherence.[10] The methods used to monitor drug adherence include self reporting, frequency of repeat prescriptions, pill counts, drug plasma levels, and various microelectronic monitoring systems (MEMS). These systems consist of an electronic device fitted in the cap of a normal-looking medication bottle that automatically records each time the bottle is opened. Although, when using MEMS, one cannot be certain that the specified daily dose is actually taken each time the patient opens the bottle, MEMS are considered the gold standard for measuring adherence.[11-14] The other methods are less accurate, as people may be reluctant to admit bad behavior or may remove unused tablets before returning the bottle. As adherence declines, pill counts become even less accurate.[12,13] Moreover, patients who are persistently noncompliant tend to take their medication on the day before they visit their physician, thereby giving a false impression of adherence when drug levels are measured.[12-14] In two different studies performed in heterogeneous cohorts of patients with CML, adherence to imatinib was estimated at approximately 75%[15] (using refilling prescriptions) and 90%[16] (using pill counts). In the latter study, higher adherence rates were associated with better outcome.[16]

We designed a clinical study to determine whether imatinib adherence correlates with degree of molecular response in which adherence was monitored by using MEMS. We also considered clinical variables previously shown to predict response together with other factors identified more recently (ie, expression of human organic cation transporter-1 [hOCT1],[17,18] polymorphisms in multidrug resistance gene-1 [MDR1, or ABCB1],[19] mutations in the tyrosine kinase domain [KD] of *BCR-ABL1*,[20] and imatinib plasma levels).[21,22]

METHODS

Patient Variables and Treatment

Between April 2008 and February 2009, 99 consecutive adults with *BCR-ABL1*- positive CML in chronic phase who had received imatinib as first therapy for some years were offered enrollment on the study at Hammersmith Hospital. Three refused participation. Of the 96 patients enrolled, two were lost to follow-up, and seven others were excluded from the study because they could not be monitored with MEMS (because four patients were using dosing boxes and because the MEMS malfunctioned for three patients). Eighty-seven patients constituted the basis of this report. The study protocol was approved by the research ethics committee, and patients gave written informed consent. Patients were eligible if imatinib was started within 6 months of diagnosis while in first chronic phase.[2] Imatinib was prescribed initially as 400 mg daily to be taken in a single dose. Patients were eligible for the study if they had been treated with imatinib for 2 years or longer (median, 59.7 months; range, 25 to 104 months) and were able to tolerate at least 400 mg daily. All patients were in CCyR at the time of enrollment. Before inclusion on the study, patients had been monitored in our center, as described elsewhere.[3] For patients who failed to achieve MMR but who were tolerating the 400-mg dose well (ie, grade 1 or lower toxicity), the dose had been increased to 600 mg daily between 18 and 24 months after starting imatinib. Table 1 lists the patient characteristics.

Adherence Measures

Patients were monitored for a median of 91 days (range, 84 to 120 days) by using MEMS (Aardex, Zug, Switzerland). Patients were told that their adherence was going to be monitored by counting the number of imatinib tablets returned, but they were not told about the monitoring system in the bottle caps. Because the half-life of imatinib is long, the adherence rate for each patient was defined as the dose that was taken according to the MEMS reading expressed as a percentage of the dose prescribed during the total duration of the study.

Laboratory Assessments

BCR-ABL1 transcripts were measured in the blood at 6- to 12-week intervals from diagnosis and at the beginning and end of the monitoring period by using real-time quantitative polymerase chain reaction (Q-PCR).[3,23-25] Results were expressed as $\log_{10}$ reductions from a standardized baseline according to the international scale.[26] *BCR-ABL1* KD mutation analysis was performed as described elsewhere.[20]

Trough imatinib plasma levels were measured as previously reported.[21] Patients who took the imatinib in the evenings were instructed to take it in the mornings for the 3 days before the clinic visit. This was verified with the MEMS. The levels of hOCT1 transcripts were measured by Q-PCR in a peripheral-blood sample obtained at diagnosis. Briefly, primers and probes for quantitating hOCT1 were designed by using ABI Gene Express 1.5 software (ABI, Warrington, United Kingdom; Appendix Table A1, online only). Expression was measured in triplicate using the Taqman system on a 7,500 platform (ABI) with standard thermal cycling conditions, and β-glucuronidase (GUSB) was the endogenous control. The hOCT1 levels were expressed as the ratio of OCT1 to GUSB from the same sample. The polymorphism 1236C/T in ABCB1 was genotyped by using pyrosequencing.[20,27] Oligonucleotide primers for genotyping were designed with PSQ Assay Design software (Biotage, Uppsala, Sweden; Appendix Table A1). Results were analyzed by using PyroMark Q24 software (Biotage, Uppsala, Sweden).

Statistical Methods

The probabilities of molecular response were calculated with the Kaplan-Meier method. Univariate analyses to identify prognostic factors for molecular response were carried out with the log-rank test. Variables significant at $P < .20$ were entered into a proportional hazards regression analysis; a forward-stepping procedure was employed to find the best model. The proportional hazards assumption was confirmed by adding a time-dependent covariate for each covariate. Tests for interactions were carried out, but none was found to have statistical significance. The relation between the different prognostic factors and the response at 18 months was explored by using a logistic regression model. Groups were compared by using Fisher's exact test for categoric data and the Mann-Whitney Test for quantitative data. *P* values were two sided.

RESULTS

Long-Term Adherence to Imatinib

For the 87 evaluable patients, the median adherence measured by MEMS was 97.6% (range, 22.6% to 103.8%). Tables 2 and 3 show the proportion of patients with different adherence rates. The adherence rates did not differ significantly in patients who had been taking the imatinib for different lengths of time (always beyond the second year); for example, the median adherence rate for the 11 patients monitored during the third year of therapy was 98.8%, a value similar to the 99.4% for the 12 patients monitored during the eighth year (Data Supplement, online only).

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Patients (N = 87)
Age, years	
At diagnosis	
Median	45.4
Range	20.9-86.4
At enrollment	
Median	50.7
Range	25.5-89.0
Sex, %	
Male	56.3
Weight, kg	
Median	74.0
Range	40.0-119.7
Sokal risk group, %	
Low	37.9
Intermediate	36.8
High	25.3
Hemoglobin at diagnosis, g/L	
Median	116
Range	69-160
Leukocyte count at diagnosis, $\times 10^9$/L	
Median	139.5
Range	5.1-410.9
BCR-ABL1 transcript type, %	
e13a2	37.9
e14a2	46.0
e13a2 and e14a2	16.1
BCR-ABL1/*ABL1* ratio at diagnosis, %	
Median	73.2
Range	10.1-334.3
Tyrosine kinase domain mutations at enrollment*	1.2
Imatinib plasma level at end of trial, μg/mL	
On 400 mg daily	
Median	0.9
Range	0.4-1.6
On 600 mg daily	
Median	1.3
Range	0.6-3.5
MDR1 polymorphism, %	
C/C	86.2
T/C	13.8
hOCT1/GUSB transcript ratio at diagnosis	
Median	0.16
Range	0.013-3.5
Time from diagnosis to imatinib therapy, months	
Median	2.2
Range	0-5.1
Time from imatinib therapy to enrollment, months	
Median	59.7
Range	25-104
Patients with MMR	
%	65.5
Probability at 6 years	69.7
Time to MMR, months	
Median	20.4
Range	9-63
Patients with a 4-log reduction	
%	42.5
Probability at 6 years	55.0
Time to 4-log reduction, months	
Median	33
Range	9-63
Patients with CMR	
%	25.3
Probability at 6 years	32.1
Time to CMR, months	
Median	45.6
Range	9-69

Abbreviations: MMR, major molecular response; CMR, complete molecular response; MDR1, multidrug resistance gene-1; hOTC1, human organic cation transporter-1; GUS, glucuronidase.

*One patient had the kinase domain mutation Q252H at the beginning of the monitoring period. In a second patient, the mutation T315I was found at the end of the monitoring period. Both patients had a low adherence rate (87 and 79%, respectively).

Achievement of a Molecular Response Is Related to the Adherence to Imatinib Therapy

The adherence rate was strongly associated with prior achievement of MMR (RR, 1.093; $P < .001$), with achievement of 4-log reduction (RR, 1.104; $P = .002$) and with achievement of CMR (RR, 1.135; $P = .012$). Table 2 and Figure 1 show the 6-year probability of MMR, 4-log reduction, and CMR according to adherence rates. Similar results were found when patients taking imatinib 400 and 600 mg/d were considered separately. We also correlated adherence rates with the specific molecular responses achieved at the 18-month time point, as shown in Table 3.

Adherence to Therapy Is the Critical Factor for Achieving Molecular Responses

We studied the influence on achievement of MMR, 4-log reduction, and CMR of most of the important prognostic factors recognized to date. Tables 4 and 5 show results of the univariate analysis.

Table 2. Six-Year Probability of MMR, 4-Log Reduction in Transcript Levels, and CMR and Degree of Adherence

Adherence Rate (%)	No. of Patients	Six-Year Probability of Response					
		MMR		4-Log Reduction		CMR	
		%	*P*	%	*P*	%	*P*
≥100	36	91.1	.01	79.9	.02	46.7	.02
≤ 99	51	58.6		38.6		22.7	
> 95	57	94.5	< .001	77.2	< .001	45.2	.002
≤ 95	30	29.3		15.0		8.2	
> 90	64	93.7	< .001	76.0	< .001	43.8	.002
≤ 90	23	13.9		4.3		0	
> 85	69	85.8	< .001	69.2	.001	40.8	.007
≤ 85	18	11.8		5.6		0	
> 80	75	81.2	.001	63.8	.005	37.1	.04
≤ 80	12	0		0		0	

NOTE. The median adherence rates for patients with a rate of ≤ 99%, ≤ 95%, ≤ 90%, ≤ 85%, and ≤ 80% were 93.5%, 81.7%, 76.0%, 73.9%, and 63.1%, respectively.

Abbreviations: MMR, major molecular response; CMR, complete molecular response.

Table 3. Relation Between the 18-Month Responses and the Degree of Adherence

Adherence Rate (%)	No. of Patients	Patients With Responses at 18 Months					
		MMR			4-Log Reduction		
		No.	%	*P*	No.	%	*P*
≥ 100	36	20	55.5	.1	14	38.8	.4
≤ 99	51	19	37.2		15	29.4	
> 95	57	34	59.6	.002	25	43.9	.013
≤ 95	30	5	16.7		4	13.3	
> 90	64	37	57.8	< .001	28	43.7	.004
≤ 90	23	2	8.7		1	5.6	
> 85	69	38	55.1	< .001	28	40.6	.001
≤ 85	18	1	5.6		1	5.6	
> 80	75	39	52	< .001	29	38.7	.007
≤ 80	12	0	0		0	0	

NOTE. The median adherence rates for patients with a rate of ≤ 99%, ≤ 95%, ≤ 90%, ≤ 85%, and ≤ 80% were 93.5%, 81.7%, 76.0%, 73.9%, and 63.1%, respectively.
Abbreviation: MMR, major molecular response.

Imatinib plasma levels measured at the end of the study were significantly associated with prior MMRs (RR, 2.11; $P = .01$; Table 4). When we subclassified the patients according to the plasma level, as previously reported,[21] we found that patients with imatinib levels less than 1 μg/mL had a lower probability of being in MMR (Table 5). Similar results were found when we considered only the patients taking imatinib 400 mg (Table 5). Imatinib plasma levels were not correlated with outcome when we considered only the patients receiving imatinib 600 mg.

Higher levels of hOCT1 transcripts at diagnosis significantly predicted for the achievement of MMR (RR, 2.199; $P < .001$), 4-log reduction (RR, .69; $P = .001$), and CMR (RR, 1.665; $P = .045$). The patients with an hOCT1 transcript level less than the median value (ie, 0.16) had a lower probability of 6-year MMR, of 4-log reduction, and of CMR that the patients with higher levels (Table 4).

We analyzed the relative influence of the various factors in multivariate analysis. The degree of adherence to imatinib therapy (ie, greater or less than 90%) and hOCT1 transcript level (ie, greater or less than the median) were the only two independent factors for MMR in the multivariate analysis (RRs, 11.17 [$P = .001$] and 1.79 [$P = .038$], respectively). The degree of adherence to therapy and the hOCT1 transcript level were the only independent factors for the achievement of a 4-log reduction; RRs were 19.35 ($P < .001$) and 1.74 ($P = .048$), respectively. The degree of adherence to therapy was the only independent factor for achieving CMR (RR, 19.35; $P = .004$). Similar results were found when the variables were considered as continuous and when analysis was limited to patients receiving imatinib 400 mg daily (data not shown).

We also considered the prognostic influence of the achievement of an early molecular response (EMR), defined as having achieved a 1-log reduction (*BCR-ABL/ABL* ratio ≤ 10%) by 3 months.[28,29] The 32 patients with EMR had a superior probability of achieving MMR, a 4-log reduction in transcript levels, and CMR compared with the 55 patients without EMR (namely, 81.8% *v* 62% [$P < .001$]; 76.7% *v* 42.7% [$P = .001$], and 46.5% *v* 22.4% [$P = .006$]). When we included EMR in the multivariate model presented in the Methods, we found that adherence rate and EMR were the only independent factors for MMR (RR, 14.2 [$P < .001$] and 2.8 [$P < .001$], respectively) and a 4-log reduction in transcript levels (RR, 18.9 [$P < .001$] and 2.6 [$P = .004$], respectively), but the adherence rate remained the only independent factor for CMR. Patients with high hOCT1 expression

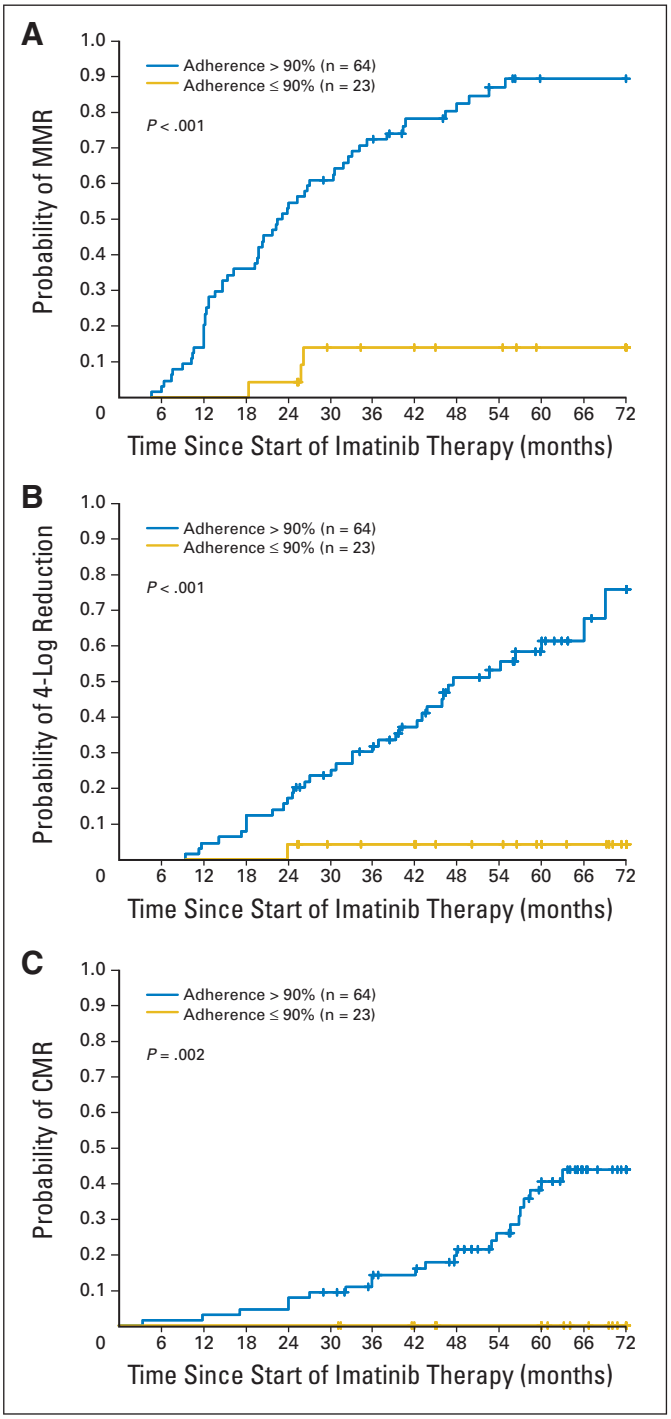

Fig 1. Six-year probability of major molecular response (MMR), 4-log reduction in transcript levels, and complete molecular response (CMR) in the 87 enrolled patients according to the measured adherence rate. The probability of MMR for the 23 patients with an adherence rate ≤ 90% was 13.9%, whereas the probability was 93.7% for the 64 patients with an adherence rate greater than 90% ($P < .001$). Similarly, the probability of a 4-log reduction was 4.3% versus 76% ($P < .001$), and the probability of CMR was 0% versus 43.8% ($P = .002$).

Table 4. Patient Characteristics and 6-Year Probability of MMR, 4-Log Reduction in Transcript Levels, and CMR at Diagnosis

Variable at Diagnosis	No. of Patients	Response: MMR %	MMR P	4-Log Reduction %	4-Log Reduction P	CMR %	CMR P
Sex							
Male	49	68.1	.45	53.8	.2	26.9	.29
Female	38	70.3		59.5		39.1	
Age, years							
≤ 45	42	66.4	.056	44.2	.07	21.0	.052
> 45	45	80.2		65.8		46.1	
RR		1.020	.06	1.013	.27	1.015	.15
Sokal risk group			.49		.98		.36
Low	33	77.8		67.8		54.1	
Intermediate	32	69.4		47.0		31.1	
High	22	61.3		47.1		24.8	
Hemoglobin, g/L							
≤ 115	40	59.2	.036	39.5	.03	14.7	.011
> 115	47	80.7		69.1		47.6	
RR		1.186	.012	1.323	.01	1.209	.07
Leukocytes, × 10^9/L							
≤ 140	44	78.8	.012	56.7	.022	35.4	.017
> 140	43	63.1		37.6		28.1	
RR		0.996	.008	0.996	.015	.996	.11
BCR-ABL1 transcript type							
e14a2	40	78.1	.05	56.9	.024	34.1	.29
e13a2	33	63.5		35.7		20.3	
e13a2 and e14a2	14	76.5		57.6		38.5	
BCR-ABL1/*ABL1* ratio, %							
≤ 100	44	71.4	.25	53.0	.038	32.7	.1
> 100	43	52.6		26.6		8.4	
RR		.996	.44	.971	.002	.979	.13
hOCT1 transcript level							
≤ 0.16	30	55.2	< .001	42.0	.01	16.6	.02
> 0.16	30	81.4		64.8		45.3	
RR		2.199	< .001	1.990	.001	1.665	.04
MDR1 polymorphism							
C/C	75	71.1	.9	57.8	.35	30.8	.8
T/C	12	68.7		36.5		37.1	

Abbreviations: MMR, major molecular response; CMR, complete molecular response; RR, relative risk; hOCT1, human organic cation transporter-1; MDR1, multidrug resistance gene-1.

*Samples were not available in 27 patients. For this reason, we repeated the multivariate analysis excluding this variable. The adherence rate and WBC were the only independent predictors for the achievement of MMR; adherence rate was the only independent predictor for the achievement of a 4-log reduction and CMR. In three patients, the trough plasma level was not available.

Table 5. Patient Characteristics and 6-Year Probability of MMR, 4-Log Reduction in Transcript Levels, and CMR While on Study

On-Study Variable	No. of Patients	Response: MMR %	MMR P	4-Log Reduction %	4-Log Reduction P	CMR %	CMR P
Age, years							
≤ 50	42	62.8	.03	45.5	.06	16.3	.01
> 50	45	82.7		63.3		49.9	
RR		1.021	.037	1.015	.23	1.021	.06
Weight, kg							
≤ 74	40	72.7	.45	53.6	.99	26.2	.49
> 74	47	68.2		56.4		43.9	
RR		.992	.34	1.000	.99	1.004	.76
Imatinib plasma level, μg/mL*†							
≤ 1	43	60.1	.02	53.0	.07	23.3	.14
> 1	41	83.2		68.0		44.4	
RR		2.11	.01	2.50	.06	2.25	.09
Adherence rate, %							
> 90	64	93.7	< .001	76.0	< .001	43.8	.002
≤ 90	23	13.9		4.3		0	
RR		1.093	< .001	1.104	.002	1.135	.012

NOTE. The relative risks and their *P* values are provided for quantitative variables.

Abbreviations: MMR, major molecular response; CMR, complete molecular response; RR, relative risk.

*In three patients, the trough plasma level was not available.

†When we considered only the patients receiving imatinib 400 mg/d, the RRs for MMR, 4-log reduction, and complete cytogenic response were 2.62 ($P = .01$), 2.83 ($P = .046$), and 2.38 ($P = .08$), respectively.

had a greater probability of EMR that patients with low expression (52.1% *v* 17.1; $P = .006$).

Adherence to Imatinib Is the Most Important Factor Contributing to Molecular Responses but Is Poor After Dose Increase

The median adherence rate in the 32 patients who had their dose of imatinib increased was 86% (range, 57.3% to 103.6%), which is significantly lower that that observed in the 55 patents who remained on imatinib 400 mg (98.8%; $P = .021$). Higher adherence rates were associated with achievement of MMR and a 4-log reduction (Fig 2).

We repeated the univariate analysis limited to the patients on imatinib 600 mg and included the variables listed in Tables 4 and 5 and included EMR (data not shown). The degree of adherence to imatinib (greater or less than 90%) and hOCT1 transcript levels (greater or less than the median) were the only two factors for MMR in the univariate analysis, and RRs were 17.66 ($P = .006$) and 1.89 ($P = .03$), respectively. Adherence was the only independent predictor for MMR. Similar results were found when the variables were considered continuous (data not shown).

Low Adherence Rate is More Frequent in Young Patients, in Patients With Adverse Effects, and in Patients With Unexplained Increases in BCR-ABL1 *Transcript Levels*

Younger patients were more likely to have a lower adherence rate. The median age for patients with an adherence rate ≤ 90% was 43.8 years compared with 53.8 years for patients with a rate greater than 90% ($P = .004$). We found significantly lower adherence rates in patients with asthenia, nausea, muscle cramps, and bone or joint pains and in patients who took imatinib independently of the meals (data not shown).

Unexplained five-fold increases in *BCR-ABL1* transcript levels at any time during follow-up were predictive for poor adherence. Ten (44%) of 23 patients with unexplained increases had adherence rates ≤ 90%, whereas only 10 (16%) of 64 patients with no significant change in transcript levels had an adherence rate ≤ 90% ($P = .01$).

DISCUSSION

Patients with CML vary greatly in their responses to therapy, as demonstrated originally by Sokal et al[9] in 1984, and the same variation is seen in patients treated with imatinib in the modern era. The basis for this variation is unknown, but it has been attributed to the intrinsic

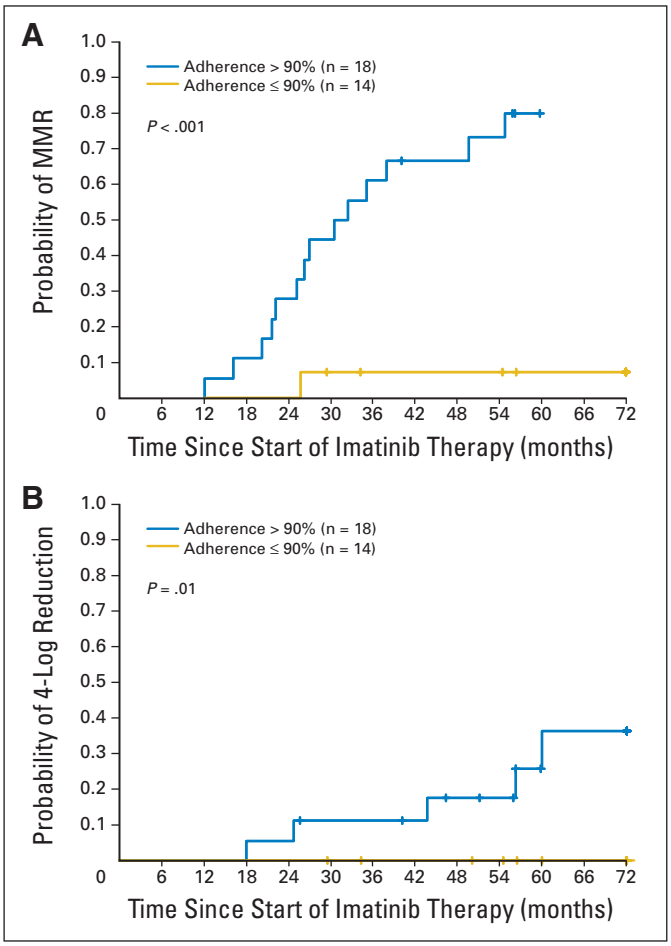

Fig 2. Six-year probability of major molecular response (MMR) and 4-log reduction in the transcript level in the 32 patients who had their dose of imatinib increased according to the measured adherence rate. Higher adherence rates were associated with achievement of MMR (relative risk [RR], 1.105; $P = .008$) and 4-log reduction (RR, 1.095; $P = .026$). Only three patients receiving imatinib 600 mg achieved complete molecular response (CMR), so we did not perform an analysis for this outcome. The 14 patients with an adherence rate ≤ 90% had a lower 6-year probability of MMR and 4-log reduction in transcript levels than the 18 patients with greater than 90% adherence (7.1% *v* 80% [$P = .002$] and 0% *v* 36.3% [$P = .01$]). Similar results were achieved when we considered other cutoff points for the adherence rate. The 6-year probabilities of MMR were 18.6% for the 17 patients with an adherence rate ≤ 95% versus 88.2% for the 15 patients with a rate greater than 95% ($P < .001$); 9.1% for the 11 patients with an adherence rate ≤ 85% versus 67.9% for the 21 patients with a rate greater than 85% ($P = .006$); and 0% for the seven patients with an adherence rate ≤ 80% versus 60.7% for the 25 patients with a rate greater than 80% ($P = .02$).

biologic heterogeneity of the leukemia. Lack of adherence to oral therapy for chronic diseases is a well-recognized problem,[10-12,30] and we have confirmed this, because 26.4% of patients with a potentially fatal disease fail to adhere to optimal dosing at a median of 5 years from diagnosis. Ideally, a study of the influence of adherence on prognosis would be performed in newly diagnosed patients and would require prolonged follow-up to ascertain the interactions between prognostic features, adherence, and overall outcome. To conduct such a study with the MEMS would be difficult, if not impossible. We therefore chose to conduct our study on a group of patients in stable CCyR in whom we could study drug behavior together with other known prognostic factors and could evaluate any possible effect on molecular responses. In doing so, we accepted that our study could not address the impact of adherence on early failure of imatinib, in which patients destined to experience progression early in the disease would do so irrespective of drug compliance. Conversely, it is quite possible that some of the patients who did not respond to imatinib in the first 2 years failed to respond or lost an initial response primarily because the adherence was poor; in that case, our study underestimates the overall level of adherence in a total population of patients who start treatment with imatinib. Although we accept these limitations, we have clearly shown that adherence to therapy at a median of 5 years from diagnosis is associated with the molecular response at 18 months and, indeed, is the most important factor influencing the depth of response in patients in CCyR. In practice, no CMRs were observed when adherence was ≤ 90%, and no MMRs were observed when adherence was ≤ 80%.

In this study, the only other factor influencing molecular responses was the level of expression of hOCT1 at diagnosis. The molecular transporter hOCT1 is responsible for the active intracellular intake of imatinib, and low levels have been associated with poor cytogenetic and molecular responses[17,18,31,32] Our study confirms these findings. We also showed that EMR was predictive for subsequent achievement of greater degrees of molecular response[28,29] and that patients with higher levels of hOCT1 were more likely to achieve EMR. We could not confirm the previously reported association between polymorphism in the MDR1 gene and achievement of MMR,[19] possibly because we only studied patients with chronic phase disease in CCyR. We found KD mutations in two patients (Table 1); in both instances, the patients had low adherence rates. However, this did not allow us to establish a clear relation between the degree of adherence and the development of KD mutations. We did confirm the previously reported association between imatinib plasma levels and achievement of MMR[21,22]; we also found a trend toward higher probability of 4-log reduction and CMR in patients with higher imatinib plasma levels, although the predictive value of imatinib levels disappeared when adherence was taken into account.

Adherence in patients who had their imatinib dose increased was significantly lower than in the patients who remained on 400 mg/d; in many patients on the higher dose, adherence was ≤ 85%. Adherence was the only independent factor associated with molecular response after the dose of imatinib was increased. Moreover, responses to dose increases were rare when the adherence rate was ≤ 90%. It is not clear from our study whether the low adherence behavior had developed before the dose of imatinib was increased (and had, therefore, been the cause of the initial poor response) or had developed thereafter.

We found lower adherence was associated with younger age. It was also associated with adverse effects, though many patients with mild adverse effects had good adherence rates. Psychological differences between patients or differing perceptions patients have about therapy may account for a significant proportion of nonadherence. It is unclear how adherence could be improved for patients on chronic medication, but various efforts have been reported.[33-35] Interestingly we found a significant association between unexplained increases in transcripts observed before enrollment and low adherence. This association is likely to be higher in practice, as some patients may have improved their adherence when they were told that their transcript levels were increasing.

In summary, a substantial proportion of patients with CML treated with imatinib for more than 2 years fail to take a drug that can unequivocally prolong their life and may, in some instances, cure their

leukemia. Unfortunately, the relatively poor adherence to imatinib that we have described in this article may apply equally to patients receiving second-generation tyrosine kinase inhibitors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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