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ORIGINAL ARTICLE

Impact of second decline rate of *BCR-ABL1* transcript on clinical outcome of chronic phase chronic myeloid leukemia patients on imatinib first-line

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Abstract

Early molecular response has been associated with clinical outcome in chronic myeloid leukemia (CML) patients treated with tyrosine kinase inhibitors. The *BCR-ABL1* transcript rate decline from baseline to 3 months has been demonstrated to be more predictive than a single *BCR-ABL1* level at 3 months (M3). However, it cannot be used routinely because *ABL1*, as an internal gene control, is not reliable for *BCR-ABL1* quantification above 10%. This study aimed to compare clinical outcome and molecular response of chronic phase CML patients, depending on the percentage of *BCR-ABL1* transcript decrease from month 3 to month 6 using *ABL1* as an internal control gene. Two hundred sixteen chronic phase CML patients treated with imatinib 400 mg for whom M3 and month 6 molecular data were available were included in the study. Associations with event-free (EFS), failure-free (FFS), progression-free (PFS), and overall survivals (OS) molecular response 4 log and 4.5 log were assessed. The percentage of *BCR-ABL1* decline from month 3 to month 6 was significantly linked to the EFS and the FFS ($p < 0.001$). A common cut-off of 67% of decline predicted the better risk of event. Patients with a decrease below 67% have worse EFS and FFS as compared to those having a higher decrease ($p < 0.001$). The impact was confirmed by multivariate analysis. Since the slope between diagnosis and 3 months cannot be reliable using *ABL1* as an internal gene control, the second decline rate of *BCR-ABL1* transcript between month 3 and month 6 could efficiently identify patients at higher risk of event.

Keywords Early molecular response (EMR) · Imatinib · Event-free survival (EFS) · Second slope · Failure-free survival (FFS)

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Introduction

Chronic myeloid leukemia (CML) is a unique disease model where a chromosomal translocation that produces the Philadelphia chromosome [1] results in the BCR-ABL1 chimeric tyrosine kinase with deregulated activity [2]. Tyrosine kinase inhibitors (TKI) have dramatically improved outcomes for patients with CML, and the overall survival of chronic phase CML patients is now very close to that of the normal population as it was well demonstrated in the Swedish registry [3, 4]. Despite the fact that nilotinib and dasatinib (second generation TKI) are also approved as front-line treatment, imatinib (IM) or its generics are still the most frequent front-line TKI proposed for de novo CML chronic phase (CP) patients. It is commonly admitted that 15–20% of the patients will present an event during the evolution of their disease [5] and that one sixth of the patients under IM will reach a sustained deep molecular response (DMR) allowing TKI discontinuation [3]. Quantification of *BCR-ABL1* transcripts aligned on the international scale (IS), at month 3 (M3) or month 6 (M6) of treatment, allows the assessment of the early molecular response (EMR). Several studies have reported the importance of obtaining M3 *BCR-ABL1* transcript level ≤ $10\%^{IS}$ or M6 *BCR-ABL1* transcript level ≤ $1\%^{IS}$ or ≤ $10\%^{IS}$ (depending of the studies) in order to reduce the risk of event, progression, and/or death [5–22] or to increase the probability of DMR achievement [5–8, 10–17, 19, 20, 22–25], after IM [5, 6, 11–17, 19, 22, 24, 25] or after second generation TKI [7–11, 14, 17, 19, 20, 23, 25, 26]. Most studies analyzed the prognostic impact of a single assessment M3 or M6 [5–9, 14, 15, 17, 19–21, 23–25], and less frequently the 2 combined values [10–12, 18, 22] as recommended by the European Leukemia Net (ELN) [27]. Other studies have analyzed the transcript rate decline or the "halving time" from baseline to month 3 or month 1 as another EMR marker [13, 16, 20, 26, 28–31]. Nevertheless, for the high-level *BCR-ABL1* ratio, results are less reliable because lack of linearity particularly for laboratories using *ABL1 or GUSB*, as an internal control gene [32]. The aim of the current study was to compare clinical outcome and molecular response of CML patients on IM, depending on the percentage of decrease of *BCR-ABL1* transcript from M3 to M6 using *ABL1* as an internal control gene and to propose a reliable algorithm depending on the obtained results, taking into account M3 and M6 *BCR-ABL1* levels.

Patients and methods

Patients diagnosed with CML in chronic phase from September 2000 to October 2014 at Bordeaux or Lyon University Hospitals treated front-line with imatinib 400 mg daily, and for whom M3 and M6 molecular assessments were available, were included. All patients signed an informed consent.

RNA was extracted from peripheral white blood cells. Quantification of *BCR-ABL1* transcript levels was then performed after reverse transcription and quantitative real-time polymerase chain reaction (RT-qPCR) according to the Europe against cancer (EAC) protocol [33] using *ABL1* as an internal control gene. The ELN recommendations were followed to calculate both the percentage of *BCR-ABL1/ABL1* and the molecular response score [34]. Ratios were aligned on the international scale (IS) after application of a validated conversion factor. Major molecular response (MMR) was defined as a $BCR\text{-}ABL1/ABL1^{IS}$ ratio ≤ 0.1%. Molecular Response 4 log (MR^4) and 4.5 log ($MR^{4.5}$) were defined as either detectable disease with $BCR\text{-}ABL1/ABL1^{IS}$ ≤ 0.01% and ≤ 0.0032%, respectively, or undetectable disease with ≤ 10,000 and ≤ 32,000 total *ABL1* copies, respectively, in the same volume of cDNA used to quantify *BCR-ABL1*. MR^4 and $MR^{4.5}$ had to be confirmed on a second assessment.

The percentage of *BCR-ABL1* transcript decrease from month 3 to month 6 was calculated for each patient by applying the following formula: % of decrease = (1 − M6/M3) × 100. The analysis of the area under the time-dependent ROC curve (AUC) using the inverse probability of censoring weighting (IPCW) approach was used to define the best cut-off value for the percentage of *BCR-ABL1* transcript decline [35]. The cut-off was obtained by the closest "top left" method. Event-free (EFS), failure-free (FFS), progression-free (PFS), and overall survivals (OS) defined according to ELN definitions [36] were measured from month 6 to the date of event or death. For EFS, events included lack of milestone responses at 3, 6, 12, and 18 months; loss of hematologic; complete cytogenetic; or major molecular response, progression to accelerated phase or blast crisis, deaths, and drug discontinuation for adverse events. For FFS, all events were included except adverse events leading to discontinuation of the treatment. For PFS, progression to accelerated phase or blast crisis and deaths were taken into account, and for OS, only deaths, related to CML or not, were considered.

Only the first event was taken into account. Survival differences estimated by Kaplan-Meier analysis were assessed using a log-rank test. Patients who presented an event within 6 months before were excluded for analysis.

Associations with MR^4 or $MR^{4.5}$ at any time were also analyzed. Age, sex, Sokal and Eutos scores, M3 and M6 *BCR-ABL1* levels, and percentage of *BCR-ABL1* transcript decline were tested. Univariate and multivariate analyses were performed using Cox regression. Associations between variables were studied with usual statistical tests, such as chi-square test, non-paramatric tests (Mann-Whitney or Kruskal-Wallis), and Spearman's correlation test. All the statistical analyses were performed using R software (version 3.2.3), with "timeroc," "survival," and "ggplot2" packages.

Results

Between September 2000 and October 2014, 223 patients with available M3 and M6 molecular data were diagnosed for chronic phase CML and treated with imatinib 400 mg as front-line therapy. Seven patients were excluded because of an event during the first 6 months of therapy (Fig. 1). Among them, 6 patients were excluded for adverse events with M3 ≤ 10% ($n = 5$) and M3 > 10% ($n = 1$), one for progression at M3 with M3 > 10%.

Among patients with *BCR-ABL1/ABL1* transcript level > 10% at month 6 ($n = 11$), 4 patients (36%) had *BCR-ABL1/ABL1* ≤ 10% at month 3 and 7 (63%) patients had *BCR-ABL1/ABL1* > 10% at month 3. Overall, 35 patients (16%) had *BCR-ABL1/ABL1* > 10% at month 3.

Baseline characteristics, percentage of *BCR-ABL1/ABL1* decrease, molecular responses, and follow-up of patients are presented in Table 1. The median follow-up of the entire cohort was 59.84 months (10.40–138.3).

No impact of the percentage of *BCR-ABL1* transcript decline from month 3 to month 6 on the likelihood of later MR^4 or $MR^{4.5}$ was observed. In contrast, the percentage of *BCR-ABL1* transcript decline from month 3 to month 6 was significantly linked to the EFS and the FFS ($p < 0.001$; Table 2). A common cut-off of 67% of decline at 24, 36, and 48 months after month 6 predicted the better risk of having an event with respectively a sensitivity of 0.66, 0.65, and 0.73 and a specificity of 0.71, 0.74, and 0.72 for each time point. The same threshold was observed when we remove from all events' treatment cessation for adverse events with at 24, 36, and 48 months after month 6, a sensitivity of 0.66, 0.64, and 0.70 and a specificity of 0.69, 0.71, and 0.70 respectively. Patients with a percentage of *BCR-ABL1/ABL1* decrease below 67% have worse EFS as compared to those having a higher decrease ($p < 0.001$; Fig. 2a). The impact was maintained if we remove from all events' treatment cessation for adverse events ($p < 0.001$; Fig. 2b). The estimated 5-year FFS were significantly higher for patients with a percentage of decline ≥ 67% (90.47%; 95%CI 84.83–96.50) compared to patients with a lesser decline (70.62%; 95%CI 59.57–83.72).

In univariate analysis, *BCR-ABL1* transcript levels at month 3 (≤ 10% vs > 10%), sex, and Sokal score had an impact only on EFS (not FFS). In our cohort, male patients were less likely to present an event as well as patients with *BCR-ABL1* levels less than 10% at month 3 and patients with a low Sokal score. Nevertheless, in multivariate analysis, only sex and Sokal score had an impact on EFS (Table 3).

In contrast, percentage of transcript decrease from month 3 to month 6 and M6 *BCR-ABL1* levels (≤ 1% vs > 1%) were associated with the risk of having an event taking or not taking into account treatment discontinuation due to adverse events (Table 2).

These impacts were retained on EFS and FFS in multivariate analysis taking into account the Sokal score, sex and age, and M3 *BCR-ABL1* transcript levels (Table 3). Patients with more than 67% of *BCR-ABL1* decrease from month 3 to month 6 are about 3 times less likely to have an event than patients with lower decline ($HR^{EFS} = 0.32$; 95%CI 0.17–0.60; $p < 0.001$ and $HR^{FFS} = 0.34$; 95%CI 0.17–0.69; $p = 0.003$). Similarly, patients with more than 1% of *BCR-ABL1/ABL1* ratio at month 6 are between 2 and 3 times more likely to have an event than patients with a lower ratio ($HR^{EFS} = 2.82$; 95%CI: 1.54–5.16; $p < 0.001$ and $HR^{FFS} = 2.35$; 95%CI 1.01–5.49; $p = 0.048$).

BCR-ABL1/ABL1 decline rate was associated with M3 *BCR-ABL1* levels and M6 *BCR-ABL1* levels; likewise, M6 *BCR-ABL1* levels were associated with M3 *BCR-ABL1* levels (χ^2 $p < 0.001$) explaining, at least in part, the loss of the negative impact on EFS of the M3 *BCR-ABL1* levels (> 10%) in multivariate analysis.

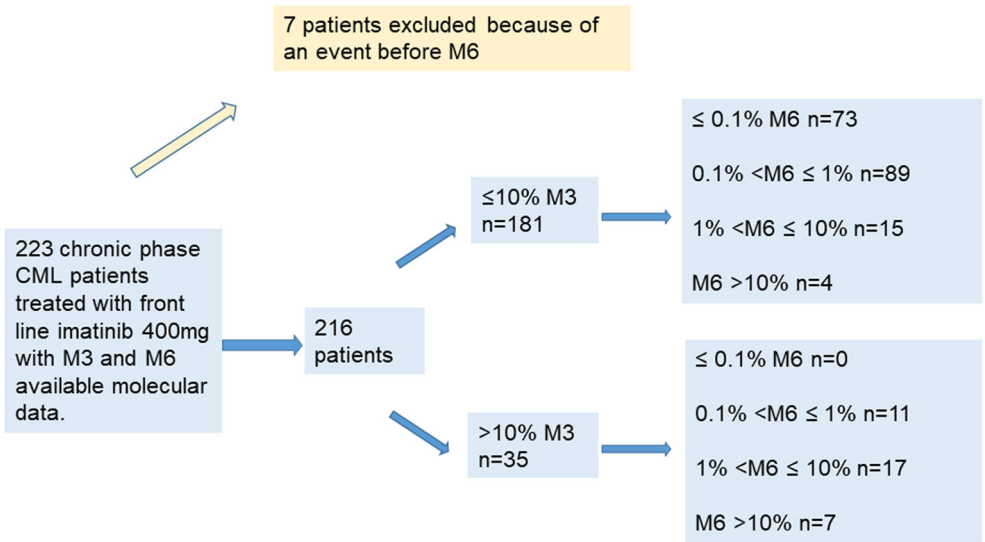


Fig. 1 Flow chart of patients according to $BCR\text{-}ABL1^{IS}$ at 3 and 6 months

Table 1 Baseline characteristics, molecular responses, and outcome of the 216 patients

Variables	Data
Age (years), mean (sd)	57 (15)
Sex, *N* (%)	
-Female	87 (40.3)
-Male	129 (59.7)
Sokal score, *N* (%)	
-Low	65 (30.1)
-Intermediate	99 (45.8)
-High	42 (19.4)
-Unknown	10 (4.6)
Eutos score, *N* (%)	
-Low	149 (69)
-Intermediate	36 (16.7)
-High	12 (5.6)
-Unknown	19 (8.8)
M3 BCR-ABL1 level, median (min; max)	1.43% (0; 119.6)
M6 BCR-ABL1 level, median (min; max)	0.20% (0; 52.65)
% decrease between M3 and M6	
-Median (min; max)	79.59 (-7.35×10^4; 100)
MR^4 at any time, *N* (%)	152 (70)
$MR^{4.5}$at any time, *N* (%)	126 (58)
Death, *N* (%)	14 (6.5)
Follow-up since 6thmonth (months)	
-Mean (sd)	61.34 (38.38)
Time from 6th month to the first event median (min; max) (months)	
-EFS	26.71 (0.0; 136.5)
-FFS	33.75 (0.05; 132.3)
-PFS	18.38 (0.05; 132.3)
-OS	53.84 (4.40; 132.3)
Primary events, *N* (%)	
-Death	8 (13.3)
-Progression to AP/BC	2 (3.3)
-No response/resistance	8 (13,3)
-CHR, CCyR loss	14 (51.1)
-MMR loss	2 (3.3)
-Other reasons for switch	5 (8.3)
-Adverse events	21 (35)

CHR complete hematologic response, *CCyR* complete cytogenetic response, *AP* accelerated phase, *BC* blast crisis, *MMR* major molecular response

If we look at the combined impact of *BCR-ABL1* decline rate and M6 *BCR-ABL1* levels on EFS (Fig. 3a), *BCR-ABL1* decline rate identifies a subgroup of patients with a worse outcome among those having a M6 *BCR-ABL1* > 1% ($p = 0.017$). Similarly, M6 *BCR-ABL1* level (> 1%) identifies a subgroup of patients with a worse outcome among those having a *BCR-ABL1* decline rate below 67% ($p = 0.006$).

Patients with a *BCR-ABL1* decline rate > 67% and M6 *BCR-ABL1* < 1% have the best outcome whereas those with a *BCR-ABL1* decline rate < 67% and M6 *BCR-ABL1* > 1% have the worse outcome ($p < 0.001$). The negative impact of a *BCR-ABL1* decline rate < 67% is canceled when M6 *BCR-ABL1* is < 1%, and the negative impact of a M6 *BCR-ABL1* > 1% is canceled when the *BCR-ABL1* decline rate is < 67%. Hence, patients with a *BCR-ABL1* decline rate > 67% and M6 *BCR-ABL1* > 1% or a *BCR-ABL1* decline rate < 67% and M6 *BCR-ABL1* < 1% have the same outcome.

Same results were obtained for FFS (Fig. 3b).

No impact of the percentage of transcript decline was observed on PFS or OS (Fig. 2c, d) as M3 and M6 *BCR-ABL1* levels in our cohort.

Discussion

Several markers of the EMR had been studied since the era of TKI. Regarding the outcome of CML patients treated with first-line imatinib, Marin et al. [23] were the first to report the negative impact of a M3 *BCR-ABL1* levels > 10%^{IS} and Brandford et al. [13] reported a better outcome of patients who had a halving time below 76 days from baseline to month 3 among patients with M3 *BCR-ABL1* levels > 10%^{IS}. However, the use of these early and very early markers may be debatable because they refer either to one single assessment or to high *BCR-ABL1* values that the kinetics of response is non-linear if *ABL1* is used as an internal gene control.

In the current study, we have analyzed the impact of second decline rate of *BCR-ABL1* transcript between month 3 to month 6 on clinical outcome, on a cohort of 216 chronic phase CML patients treated with front-line IM. Patients with a percentage of decrease below 67% have worse EFS and FFS ($p < 0.001$) independently of the *BCR-ABL1* levels at month 3 and month 6.

In other words, the percentage of *BCR-ABL1/ABL1* decline from month 3 to month 6 seems more important than individual *BCR-ABL1* transcript levels at month 3 because of an impact on EFS but also on FFS. In our study, the *BCR-ABL1* level at month 6 (> 1%^{IS}) was also associated with the risk of further event (taking or not taking into account treatment discontinuation for adverse events) irrespective of the *BCR-ABL1/ABL1* decline.

Despite the non-linearity of *BCR-ABL1/ABL1* ratios for high levels of transcripts, we still assessed the impact of the percentage of decrease between diagnosis and 3 months on EFS and FFS for almost half of the patients ($n = 100$), using *ABL1* as a control gene. An impact on EFS ($p = 0.014$) was found but not on FFS ($p = 0.177$) as for *BCR-ABL1* level at 3 months, highlighting the importance of the second decline rate in our cohort. Impact of second decline rate (between M3

Table 2 Impact of the different variables on EFS and FFS: univariate analysis

Variables		EFS			FFS		
		HR	95%CI	*p* value	HR	95%CI	*p* value
% of *BCR-ABL1* transcript decrease	< 67 (n = 75)	1			1		
	≥ 67 (n = 141)	0.35	0.21–0.59	< 0.001	0.31	0.16–0.6	< 0.001
Sex	F (n = 87)	1			1		
	M (n = 129)	0.46	0.28–0.77	0.003	0.67	0.36–1.25	0.205
Age at diagnosis		1	0.98–1.01	0.551	0.99	0.97–1.01	0.17
Sokal score	Low (n = 65)	1			1		
	Intermediate (n = 99)	1.47	0.75–2.9	0.265	1.78	0.75–4.22	0.19
	High (n = 42)	2.39	1.17–4.88	0.017	2	0.78–5.16	0.15
Eutos score	Low (n = 149)	1			1		
	Intermediate (n = 36)	0.87	0.44–1.74	0.702	0.56	0.19–1.62	0.281
	High (n = 12)	0.80	0.24–2.60	0.706	0.38	0.05–3.1	0.366
M3 BCR-ABL1 level	≤ 10% (n = 181)	1			1		
	> 10% (n = 35)	2.06	1.08–3.94	0.029	1.49	0.66–3.36	0.342
M6 BCR-ABL1 level	≤ 1% (n = 173)	1			1		
	> 1% (n = 43)	3.16	[1.74–5.74]	< 0.001	2.88	|1.42–5.85]	0.003

and M6) on EFS remains significant in multivariate analysis, taking into account the first decline rate.

Although we did not find an impact on PFS/OS, our results are in agreement with 2013 ELN recommendations [27] which advocate waiting for the month 6 molecular response before defining failure of imatinib treatment. They define an optimal response if M6 *BCR-ABL1* level is < 1%^{IS} and failure if M6 *BCR-ABL1* level is > 10%^{IS}.

In our cohort, M6 *BCR-ABL1* level (≤ 10%^{IS} vs > 10%^{IS}) was also associated with the risk of having an event and even progression or death but concerns only 5% of patients, thus making it difficult to draw firm conclusions from our cohort about this cut-off.

Other studies found a prognostic impact of the 1%^{IS} M6 *BCR-ABL1* cut-off level although they analyzed only the impact on PFS and OS for most of them [6, 7, 18]. In our cohort, only 10 patients progressed or died, and most of the patients who experienced an event had been switched to 2nd generation TKI before they progressed or died. This may in part explain why we failed to show a significant impact on PFS or OS in our cohort.

The impact of *BCR-ABL1* decline rate on EFS and FFS shows the importance of taking into account 2 points of follow-up rather than one single assessment. Some studies analyzed the combined impact of M3 and M6 *BCR-ABL1* levels [10, 12, 18, 22] but none analyzed the kinetics of decline between these 2 points. The M3–M6 *BCR-ABL1* decline rate is a new dynamic marker of the EMR which could allow the identification of high-risk patients, independently of the *BCR-ABL1* level at months 3 and 6.

Furthermore, most laboratories use *ABL1* as control gene. However, the location of *ABL1* primers has the disadvantage to amplify both the non-translocated *ABL1* and the translocated *BCR-ABL1* allele, responsible of a non-linearity of *BCR-ABL1/ABL1* percentage for high level transcripts and possibly a misestimation of the residual disease.

Thus, taking into account only *BCR-ABL1* decline from diagnosis to month 3 or M3 *BCR-ABL1* level may possibly lead to a premature switch to second generation TKI, which harbor more dangerous side effects.

To the best of our knowledge, no controlled and randomized study demonstrated the benefit of an early switch, based on M3 *BCR-ABL1* levels or halving time from baseline to month 3, on outcome of CML patients treated with first-line imatinib. It would be interesting for that to compare the outcome of patients who have been switched to second generation TKI based on a poor EMR at month 3 with the outcome of patients who have to wait until month 6 before a potential switch.

As *GUSB* can be used as a control gene in the same way as that of *ABL1*, to assess EMR [31], we verified the impact of the second decline rate using this gene control instead of *ABL1*.

Correlation between the 2 slopes M3–M6 *BCR-ABL1/ABL1* and M3–M6 *BCR-ABL1/GUSB* is highly significant (Spearman's non-parametric test (rho = 0.88) $p < 0.001$). We confirmed the impact of the second decline rate using this

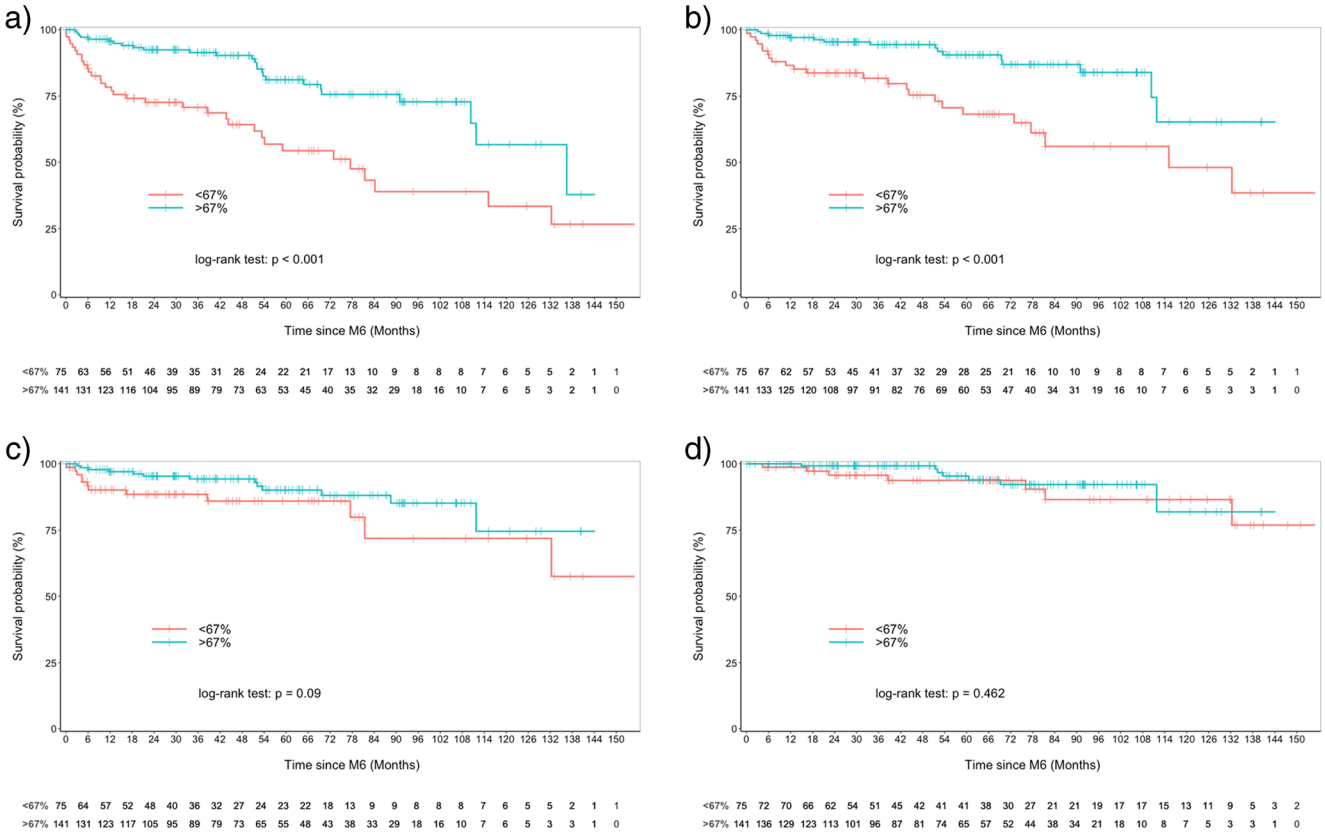


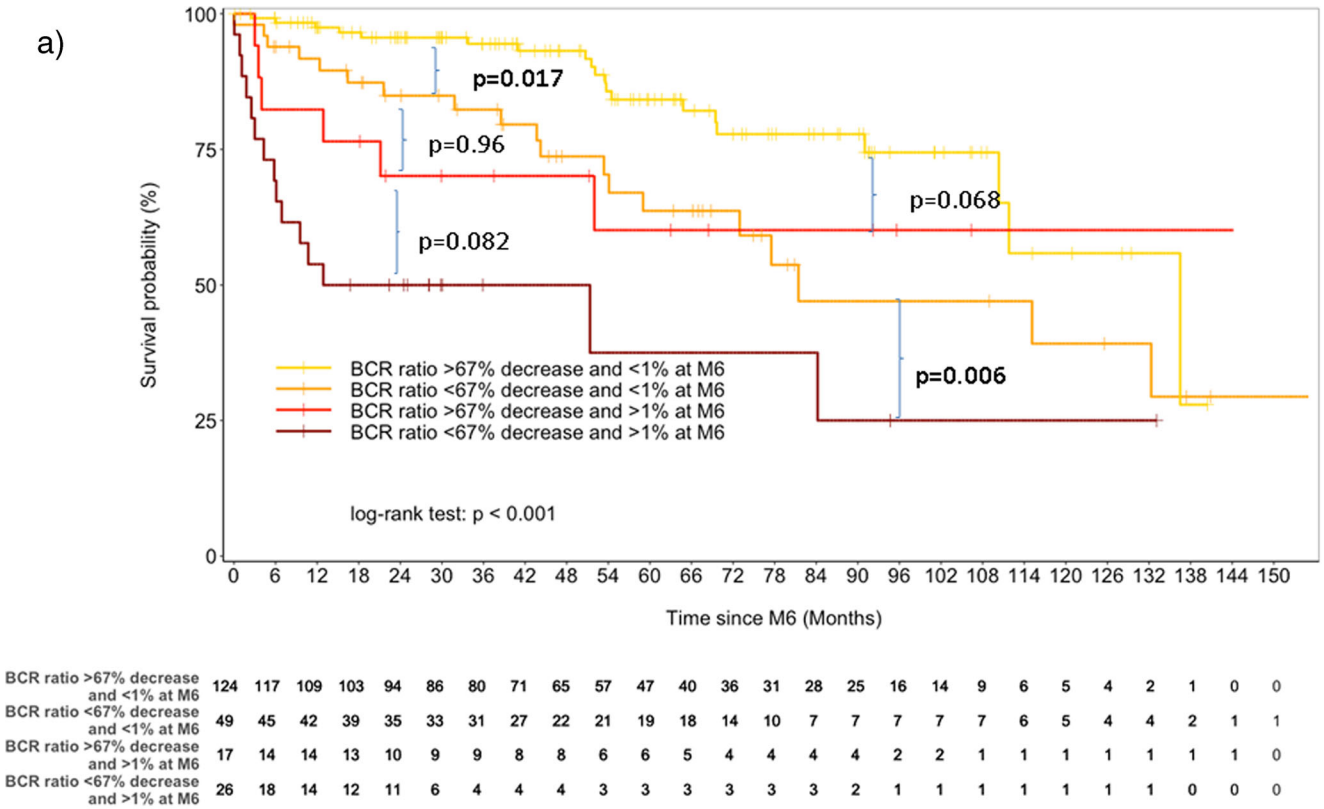
Fig. 2 EFS (**a**); FFS (**b**); PFS (**c**); and OS (**d**) according to *BCR-ABL1* decline rate. Event-free survival (EFS); failure-free survival (FFS); progression-free survival (PFS); and overall survival (OS) were measured from month 6 to the date of the first event. The BCR-ABL1 decline rate corresponds to the percentage of BCR-ABL1 transcript decrease from month 3 to month 6

control gene. Patients with more than 67% of *BCR-ABL1* decrease from month 3 to month 6 are about 10 times less likely to have an event than patients with lower decline (HR^{EFS} = 0.14; 95%CI 0.05–0.41; $p < 0.001$ and HR^{FFS} = 0.17; 95%CI 0.03–0.90; $p = 0.037$).

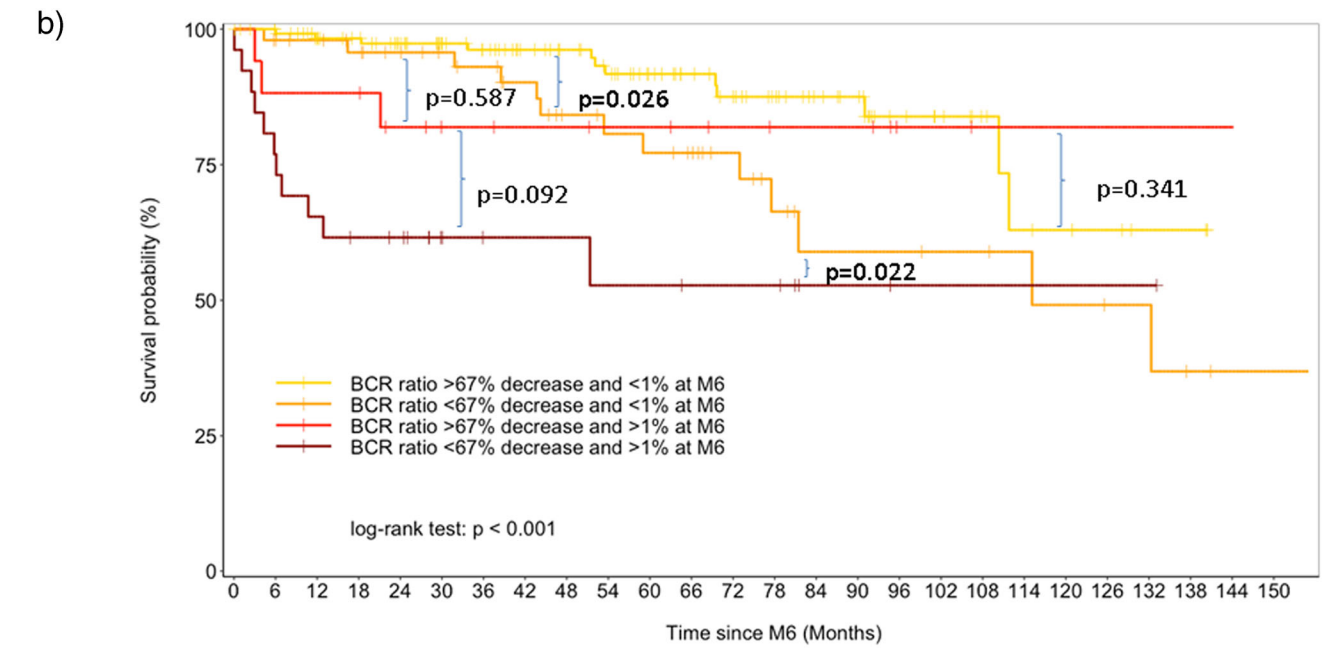
By the way, taking into account the two significant markers of EMR in our cohort, we can propose a new algorithm of patient's care (Fig. 4). In fact, M3–M6 *BCR-ABL1* decline rate helps to detect among patients with a M6 *BCR-ABL1* $\leq 1\%^{IS}$ a subgroup of patients with a worse outcome. The outcome of this subgroup

Table 3 Impact of the different variables on EFS and FFS: Multivariate analysis

Variables		EFS			FFS		
		HR	95%CI	*p* value	HR	95%CI	*p* value
% of BCR-ABL1 transcript decrease	< 67 (***n*** = **75**)	1			1		
	≥ 67 (***n*** = **141**)	0.32	0.17–0.60	**< 0.001**	0.34	0.17–0.69	**0.003**
Sex	F (***n*** = **87**)	1			1		
	M (***n*** = **129**)	0.33	0.19–0.56	**< 0.001**	0.57	0.29–1.12	0.105
Age at diagnosis		0.99	0.98–1.01	0.263	0.98	0.96–1	**0.03**
Sokal score	Low (***n*** = **65**)	1			1		
	Intermediate (***n*** = **99**)	1.37	0.65–2.89	0.409	1.86	0.77–4.51	0.169
	High (***n*** = **42**)	2.39	1.09–5.24	**0.03**	1.91	0.69–5.29	0.215
M3 BCR-ABL1 level	≤ 10% (***n*** = **181**)	1			1		
	> 10% (***n*** = **35**)	1.54	0.69–3.45	0.295	0.93	0.30–2.84	0.895
M6 BCR-ABL1 level	≤ 1% (***n*** = **173**)	1			1		
	> 1% (***n*** = **43**)	2.8	[1.54–5.16]	**< 0.001**	2.35	|1.01–5.49]	**0.048**



BCR ratio >67% decrease and <1% at M6	124	117	109	103	94	86	80	71	65	57	47	40	36	31	28	25	16	14	9	6	5	4	2	1	0	0
BCR ratio <67% decrease and <1% at M6	49	45	42	39	35	33	31	27	22	21	19	18	14	10	7	7	7	7	7	6	5	4	4	2	1	1
BCR ratio >67% decrease and >1% at M6	17	14	14	13	10	9	9	8	8	6	6	5	4	4	4	4	2	2	1	1	1	1	1	1	1	0
BCR ratio <67% decrease and >1% at M6	26	18	14	12	11	6	4	4	4	3	3	3	3	3	3	2	1	1	1	1	1	1	1	0	0	0



BCR ratio >67% decrease and <1% at M6	124	118	110	105	96	87	81	73	67	61	52	46	41	35	29	26	17	14	9	6	5	4	2	2	0	0
BCR ratio <67% decrease and <1% at M6	49	47	45	42	39	36	34	30	25	23	22	20	16	11	8	8	8	7	7	6	5	4	4	2	1	1
BCR ratio >67% decrease and >1% at M6	17	15	15	15	12	10	10	9	9	8	8	7	6	5	5	5	2	2	1	1	1	1	1	1	1	0
BCR ratio <67% decrease and >1% at M6	26	20	17	15	14	9	7	7	7	6	6	5	5	5	2	2	1	1	1	1	1	1	1	0	0	0

Fig. 3 EFS (**a**) and FFS (**b**) according to *BCR-ABL1* decline rate and M6 *BCR-ABL1* levels. Event-free survival (EFS) and failure-free survival (FFS) were measured from month 6 to the date of the first event. The BCR-ABL1 decline rate corresponds to the percentage of BCR-ABL1 transcript decrease from month 3 to month 6

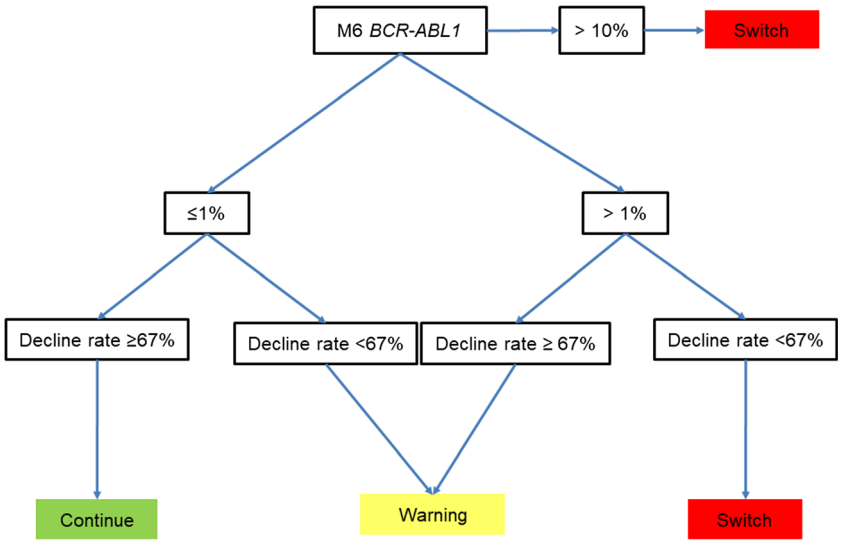


Fig. 4 Suggested treatment strategy taking into account M6 BCR-ABL1^{IS} and the M3–M6 BCR-ABL1 decline rate

of patients reaches those of patients with M6 *BCR-ABL1* > 1%^{IS} and M3–M6 *BCR-ABL1* decline rate ≥ 67%. For these patients, caution should be taken and a close monitoring should be recommended. Optimal responders were those patients with M6 BCR-ABL1 ≤ 1.0%^{IS} and M3–M6 BCR-ABL1 decline rate ≥ 67%. In contrast, > 1%^{IS} BCR-ABL1 at M6 coupled with M3–M6 BCR-ABL1 decline rate of < 67% should prompt physicians to switch to 2nd generation TKI.

Conclusions

Since the slope between diagnosis and 3 months cannot be reliable using *ABL1* as an internal gene control, the second decline rate of *BCR-ABL1* transcript between M3 and M6 could efficiently identify patients at higher risk of events and could help physicians to manage chronic phase CML patients treated with IM or its generics and to decide to switch to another TKI in "real" life conditions.

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Authors' contributions FXM conceived and designed the study; SD coordinated the study and wrote the manuscript; GE, FXM, and FN provided patients; FR monitored the local data; CC, SD, and SH performed the molecular analysis; IT and EK provided the cytogenetic data; SM performed statistical analysis; SD, FN, GE, BT, and FXM analyzed the data. All the authors reviewed the manuscript.

Data availability All data generated or analyzed during this study are included in this published article.

Compliance with ethical standards

Ethics approval and consent to participate All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Clinical and laboratory data are recorded CCTIRS N°: 14.251 and CNIL N°: 915088.

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Competing interest FXM, FN, and GE declare partnerships with Bristol-Myers Squibb, Incyte, Novartis, and Pfizer in support of educational, clinical, or scientific activities.

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Abbreviations ABL1, Abelson; AUC, area under the time-dependent ROC curve; BCR, breakpoint cluster region; cDNA, complementary deoxyribonucleic acid; CP, chronic phase; CML, chronic myeloid leukemia; DMR, deep molecular response; EAC, European Against Cancer; EFS, event-free survival; ELN, European Leukemia Net; EMR, early molecular response; FFS, failure-free survival; GUSB, β-glucuronidase; HR, hazard ratio; IM, imatinib; IPCW, inverse probability of censoring weighting; IS, international scale; M3, *BCR-ABL1* level at 3 months; M6, *BCR-ABL1* level at 6 months; MR, molecular response; MMR, major molecular response; OS, overall survival; PFS, progression-free survival; RNA, ribonucleic acid; RT-qPCR, reverse transcription–quantitative real-time polymerase chain reaction; TKI, tyrosine kinase inhibitors

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