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Patient-driven discontinuation of tyrosine kinase inhibitors – single institution experience

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Abstract

With improved outcome for patients with chronic myeloid leukemia (CML) treated with tyrosine kinase inhibitors (TKIs), treatment discontinuation has become increasingly attractive to patients. We analyzed the outcomes of patients who chose to discontinue TKI therapy regardless of their ongoing response. Thirty-five patients with chronic phase CML discontinued TKI in complete cytogenetic response. Of them 51% discontinued due to adverse effects, 23% long CMR (>5 years), 9% pregnancy, and 17% due to financial problems. After TKI discontinuation, patients were followed for a median of 16 months. Among 27 patients (77%) who discontinued TKI in CMR, 11 (41%) had molecular relapse after a median of 3.5 months. In univariate analysis we observed patients with ≥64 months of CMR before TKI discontinuation had superior cumulative proportions of sustained CMR and MMR at 12 months after discontinuation 88.9% vs. 45.5% (p=0.02) and 100% vs. 75% (p=0.05), respectively. Patients treated with high dose imatinib or second generation TKIs had higher cumulative proportion of sustained MMR at 12 months after discontinuation than patients treated with standard dose imatinib 100% vs. 72.2% (p=0.03), respectively. Of the 5 patients who stopped TKI in $MR^{4.5}$ one lost cytogenetic response. All 3 patients who discontinued TKI in MMR lost cytogenetic response; one progressed to accelerated phase. Thirteen patients (37%) re-started TKIs after loss of response; 11 improved their response, and 2 are too early to assess. Treatment discontinuation can lead to sustained CMR in some patients, but risk of relapse is higher if patients discontinue not in CMR.

Keywords

CML; Tyrosine kinase inhibitors; treatment; discontinuation

Introduction

Complete cytogenetic response (CCyR), an outcome associate with prolonged survival, is obtained by more than 85% of patients with chronic phase CML (CML-CP) treated with TKIs.[1] In addition, earlier and deeper response to TKI, as assessed by BCR-ABL

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transcript levels, correlates with improved long-term outcome.[2] Initial treatment with second generation TKIs yield earlier and deeper molecular responses compared to imatinib.[3,4] Currently, treatment with TKIs is recommended to be continued indefinitely. However, chronic therapy with TKIs may have consequences including chronic, frequently low-grade adverse events that impact patient's lives[5], and even financial consequences[6] for patients and health care systems.[6] Thus, there is much interest in the achievement of long term disease control without need for ongoing treatment. Recent prospective trials have shown that discontinuation of imatinib in complete molecular response (CMR) defined as more than 4.5 log reduction of bcr-abl transcript level is associated with sustained molecular response in 30–50% of patients after 12 months.[7–10] Most molecular relapses occurred early, within 6 months from treatment discontinuation and responded to reintroduction of imatinib. These results kindled a general interest and hope among patients willing to discontinue TKI therapy. Close monitoring enables early detection of molecular relapse minimizing the risk of disease progression. Current information on treatment cessation outcomes is available from prospective trials which recruited only patients meeting strict criteria including long periods of CMR before imatinib discontinuation. In daily practice, patients might be interested in treatment discontinuation for various reasons and occasionally when not harboring an optimal response. We thus describe the characteristics of patients with CML-CP who decided to stop TKI treatment at our institution and evaluate the factors associated with duration of sustained CMR or MMR during the follow-up of these patients.

Patients and Methods

The medical records of all patients with CML-CP who were treated with tyrosine kinase inhibitors in clinical trials at MD Anderson Cancer Center between 2000–2012 were reviewed. All patients signed Institutional Review Board (IRB)-approved informed consent document to participate in these clinical trials. Patients who discontinued therapy with TKI were identified. For the purpose of this analysis, only patients who discontinued therapy with at least a CCyR were considered. Patient records were reviewed to determine patient characteristics, the treatment for CML received prior to discontinuation, the reasons for treatment discontinuation, and the course of the disease before and after the discontinuation of TKI therapy. Response criteria were defined as previously described.[11] Briefly, cytogenetic response was assessed by conventional cytogenetics in bone marrow aspirates in at least 20 metaphases with response categories including complete cytogenetic response (CCyR), 0% Ph+ metaphases; partial cytogenetic response (PCyR), 1–35% Ph+ metaphases; minor cytogenetic response (mCyR), >35% Ph+ metaphases. Molecular response was assessed by real-time polymerase chain reaction (RT-PCR) and reported using the international scale (IS). A major molecular response (MMR) was defined as ≤0.1% BCR-ABL/ABL ratio and $MR^{4.5}$ as a ratio of ≤0.0032%. A complete molecular response (CMR) was defined as undetectable BCR-ABL transcripts with a minimum of 100,000 ABL transcripts detected. After TKI discontinuation patients were followed with cytogenetic and molecular analysis according to physician discretion and patient compliance with follow up.

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Statistical analysis

Study variables were summarized using standard descriptive statistics and measures of central tendency, including medians, ranges, frequencies, and percentages. We evaluated factors associated with sustained CMR and sustained MMR by using Kaplan-Meier analyses and determined differences using the log rank test. Due to the small sample size we reported the cumulative proportions of patients achieving CMR or MMR at 12 months of follow-up and calculated the 95% Confidence Intervals by using the methods of Newcombe R, et al[12] and Lewis, JR et al.[13] In a second step we performed a multivariate analysis and constructed a Cox proportional hazard regression model for sustained MMR including covariates factors with a p-value ≤0.10 in the univariate analysis. This model included as covariates gender, type of TKI and dose, time in months from starting TKI treatment to CMR, and duration in months of CMR before TKI discontinuation. A p-value of <0.05 (two-tailed) was considered statistically significant. We used PASW Statistics 17.0.2 for Windows (SPSS Inc., Chicago, Illinois).

Results

Patients and their treatment characteristics before TKI discontinuation are summarized in Table I. A total of 35 patients with CML-CP who discontinued TKI therapy were identified. These included 15 males and 20 females, and their median age was 47 years (range, 28–75 years). The median time from diagnosis to treatment discontinuation was 10 years (1 to 22 years). Twenty patients (57%) had received TKI as initial treatment for CML-CP within 1.4 months (0–5 months) from the diagnosis. Fifteen patients (43%) had received initial treatment with interferon-α and started TKI after a median of 63 months (range 3–178 months) from diagnosis. The median duration of TKI therapy for all patients was 96 months (range, 8 to 136 months). The initial TKI for 17 patients (49%) was standard dose (400mg/day) imatinib, and high-dose imatinib (600–800mg/day) for 16 patients (46%); only 2 patients received second generation TKIs (nilotinib and bosutinib) as initial therapy. At the time of TKI discontinuation 28 patients (80%) were receiving their initial TKI and 7 patients received their second (n=5) or third (n=2) TKI. All the patients had achieved CCyR and MMR at median of 3.3 months (range, 2.6 – 148 months) and 9 months (range 3–92 months) respectively. At the time of TKI discontinuation 27 patients (77%) had CMR, 5 patients (14%) had $MR^{4.5}$ and 3 patients (9%) MMR. The duration of CMR before TKI discontinuation for the 27 patients with undetectable transcripts at the time of discontinuation was 63 months (range, 1–106 months).

Clinical course after TKI discontinuation

Most patients discontinued TKI due to adverse events (n=18; 51%), while 8 patients (23%) discontinued treatment because of their sustained CMR (more than 5 years of CMR), 3 patients (9%) discontinued TKI before attempting to become pregnant, and 6 patients (17%) discontinued treatment due to loss of insurance or other financial reasons. After TKI discontinuation patients were followed for a median of 16 months (range 2– 106 months). Parameters of follow up after TKI discontinuation are summarized in Table II.

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Among 27 patients who discontinued TKI in CMR 11 patients (41%) had molecular relapse. (Figure 1) The median time to molecular relapse was 3.5 months with the earliest relapse occurring one month after TKI was discontinued, and the latest after 32 months on a patient previously treated with interferon-α in whom treatment was discontinued in CMR that had been sustained for 72 months while receiving a second TKI (bosutinib). One other patient relapsed after 8 months and all other patients relapsed within 4 months. Four of 11 patients (36%) who received interferon-α before TKI had molecular relapse compared with 7 of 13 (54%) patients not previously treated with interferon-α. The median BCR-ABL transcripts at the time of relapse was 0.029 IS (range, 0.0035 to 0.098), and relapse was documented on more than one PCR in 7 patients (64%). Ten of the 11 patients with molecular relapse resumed TKI therapy. Their treatments and responses are summarized in Table IV. They achieved the best response within 6 months (range 2–18) after which 6 regained CMR, 3 improved to $MR^{4–5}$and one remained in MMR after 13 months of treatment. One patient did not resume therapy; he is in MMR (BCR-ABL/ABL ratio 0.04%) 32 months after TKI discontinuation. Three patients with CMR at discontinuation had transient molecular relapse (BCR-ABL/ABL ratio of 0.07, 0.07, and 0.0035 IS, respectively) with spontaneous return to undetectable transcript levels 5, 4 and 4 weeks after the molecular relapse. After a median follow up of 16 months, 5 of 27 patients (19%) who discontinued TKI in CMR were not in CMR (3 had $MR^{4.5}$, 2 MMR). Fourteen patients discontinued TKI after being in CMR for more than 5 years before TKI discontinuation and none of them relapsed after a median follow up of 10 months (range, 3 – 40 months). In contrast, 6 patients discontinued with CMR sustained for <2 years (median 9 months; range 1 to 13 months), 5 of them relapsed within 2 months (range 1 to 8 months).

Eight patients (23%) discontinued TKI not in CMR: 5 in $MR^{4.5}$ and 3 in MMR. Of the 5 patients who stopped TKI in $MR^{4.5}$, the reasons for discontinuation were drug toxicity in 3 patients and insurance problems in 2 patients. They had sustained $MR^{4.5}$ for a median of 10 months (range, 3 to 29 months) before discontinuation. Among these patients 1 lost cytogenetic response, resumed therapy and he is in MMR after 6 months. The other 4 patients remained untreated, one is in $MR^{4.5}$ after 22 months, 2 are in MMR after 7 and 14 months, and one is in CCyR after more than 4 years without TKI.

Three patients discontinued TKI in MMR. All of these patients lost their cytogentic response. One patient had just achieved MMR when she interrupted therapy to become pregnant. She resumed treatment after pregnancy with 45% Ph+ metaphases, and she is in MMR after 4 months of treatment. One patient declined further treatment after maintaining MMR for 9 months, was lost to follow up and died 87 months later of unknown cause. The third patient stopped therapy because of insurance problems with an MMR sustained for 15 months and relapsed in accelerated phase (AP) after 3 years without treatment. He received treatment with bosutinib and after 2 years he is in MMR.

Outcome of patients re-starting treatment after TKI discontinuation

Thirteen patients (37%) who lost response after TKI discontinuation re-started therapy after a median of 12 months (range 2–37 months). Their clinical course is summarized in Table IV. At the time of retreatment one patient was in AP, 3 in PCyR, 7 in CCyR and 2 patients

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in MMR. All improved their response by at least one log reduction of BCR-ABL transcript level as compared to BCR-ABL transcript at time of retreatment. At the last follow up 22 patients (63%) are in CMR, 4 patients (11%) in $MR^{4.5}$, 6 patients (17%) in MMR, 1 in CCyR, 1 in PCyR and 1 died after being lost to follow up while in minor CCyR. (Table II) Twenty one patients (60%) remain untreated, 17 of them with a sustained CMR (median follow-up from treatment discontinuation 14 months, range 5 to 106 months), one with $MR^{4.5}$, 2 with MMR and one with CCyR.

Factors associated with sustained CMR or MMR

We identified factors associated with persistence of CMR or MMR among patients who discontinued TKI while in CMR. Variables included in this analysis are shown in Table III. The Kaplan-Meier analysis indicated the duration of CMR before TKI discontinuation was significantly associated with sustained CMR after discontinuation (p=0.02) but only marginally associated with sustained MMR (p=0.05). (Figure 2) Compared to patients treated with standard-dose imatinib (400 mg per day), treatment with high dose imatinib (600 – 800 mg per day) or second generation TKIs was significantly associated with sustained MMR (p=0.03) but not with sustained CMR (p=0.3). (Figure 3)

Discussion

After more than 10 years of experience with imatinib therapy, recent clinical trials suggested that discontinuation of imatinib might be applicable in some carefully selected patients who are under continuous monitoring.[7,9,10,14–16] The prospective multicenter Stop Imatinib Trial (STIM) indicated that 41% of patients with sustained CMR for at least 2 years, maintained CMR 12 months after the imatinib discontinuation.[7] Most patients who relapsed, did so in the first 6 months after imatinib discontinuation. Patients with molecular relapse remained sensitive to retreatment with imatinib and most of the patients (62%) regained CMR. Similar results have been obtained in other studies. Trials of imatinib discontinuation, included patients in long term CMR. In daily practice, patients may want or need to discontinue therapy for various reasons when the optimal conditions may not be present.

In the present study we retrospectively evaluated the clinical outcome after patient-directed TKI discontinuation. Among the 27 patients who discontinued TKIs in CMR, 59% maintained CMR for a median of 16 months. These results are compatible with the molecular relapse free survival at 6 to 12 months after TKI discontinuation of 30–40% reported in other studies.[7,9,10,14,15] An interesting observation is the lack of relapse among the 14 patients who discontinued therapy with a CMR that had been sustained for more than 5 years. Mahon et al had identified duration of imatinib therapy for more than 5 years as an important predictive factor of sustained remission after discontinuation although there was a trend for better survival without relapse for patients with CMR of greater than 47 month duration.[7] Molecular relapse with fast kinetics was reported in patients who stopped imatinib shortly after CMR is achieved.[17] Other factors have been identified that might be associated with the probability of relapse such as Sokal risk score, [7,16,18] prior interferon-α treatment, [7] its duration,[10] and previous allogeneic stem cell

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transplantation.[16] In our series Sokal was not available for many patients who initiated therapy prior to coming to MDACC thus we were unable to confirm the predictive value of this score. Most of these factors cannot be affected by intervention. Thus, it appears that patients with the longest CMR duration before treatment discontinuation might be at the lowest risk of relapse, an important consideration when such an approach is being considered.

Interestingly, we observed higher probability of sustained MMR at 12 months in patients who discontinued high dose imatinib or newer TKIs than in patients that had been treated with standard dose imatinib. The TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) trial and the European Leukemia Net (ELN) trial showed more rapid CCyR and MMR with imatinib 800mg daily.[19,20] The use of second generation TKIs dasatinib, nilotinib or bosutinib yields faster and deeper molecular responses as compared with imatinib.[3,4,21] These observations however remain preliminary as are mostly derived from retrospective studies. Prospective studies are required to identify whether the use of these agents may yield more sustainable remissions even after treatment discontinuation.

The current estimate of the proportion of CML patients who would be eligible for TKI discontinuation based on the 2-year sustained CMR requirement is 10–15%.[22] In our experience, only 16% of patients treated with TKI (standard-dose imatinib, high-dose imatinib, nilotinib or dasatinib) as initial therapy have met the criteria of 2-year sustained CMR.[23] With a rate of sustained CMR after discontinuation of 59%, only approximately 9% of patients are currently expected to potentially benefit from this approach. This emphasizes the need to develop ways to improve the rate and quality of CMR. Whether higher proportion of patients with sustained CMR or MMR, induced by novel TKIs, can increase the number of possible candidates for TKI discontinuation remains to be determined in ongoing and future trials [7,22] Preliminary results on 33 patients who stopped second generation dasatinib or nilotinib had 73% treatment free MMR after median follow up of 9 months.[24] Due to different level of response at TKI retreatment these results cannot be compared to studies with imatinib. It is also likely that other therapeutic interventions might be needed for some patients considering that in vitro data suggest that the leukemic stem cell is not eradicated by tyrosine kinase inhibitors.[25–28]

In our series, approximately 20% of patients requested to discontinue TKI while not in CMR, whether in $MR^{4.5}$ or MMR. The request for discontinuation was for various reasons. Importantly, the risk of the relapse and the quality of relapse in these patients were significantly different. Out of 5 patients who discontinued TKI in $MR^{4.5}$, one lost CCyR and regained MMR within 6 month of retreatment. In contrast all 3 patients who discontinued TKI in MMR lost CCyR and one progressed to accelerated phase. This observation, although limited in numbers, supports the general notion that 3-log reduction of BCR-ABL transcript level is not safe enough to stop treatment. Although the sample size in this cohort is small it is prominent that patients who discontinued TKIs in less than CMR lost the relatively safe status of being in CCyR and even progressed. In these instances, re-start of therapy does not always lead to an optimal response. Thus, it is important that no attempt at treatment discontinuation should be made when CMR (with adequate sensitivity, i.e., at least 100,000 ABL copies) has not been achieved and maintained for at least 2 years.

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There are ongoing trials with imatinib and second generation TKIs that propose treatment re-challenge at MMR rather than at loss of CMR.[18,24] A pilot study of the French CML Group (FILMC) on 34 patients who discontinued imatinib after 2 years of CMR demonstrated that when using the loss of MMR criteria for resuming imatinib, 63% of patients remained treatment free at 2 years after imatinib discontinuation.[18] We observed that early retreatment was associated with good responses irrespective to the level of response at retreatment. In addition 53% of the patients in the FILMC study had at least one positive MRD value after achievement of CMR. We have observed 3 patients in CMR who had transient loss of molecular response and spontaneously regained CMR. This observation suggests that low level of detectable residual disease after TKI withdrawal may not automatically herald relapse and retreatment. However, the monitoring of these patients requires frequent assessments and adequate sensitivity of the PCR to minimize the risks for the patients. It is also important to emphasize that the follow-up for our series and all others reported in the literature is still relatively short. Patients treated with stem cell transplant, a treatment option of unquestionable curable potential, relapses can occur late. In a series of patients who received a SCT for CML and had been alive and in complete remission for 5 years, the cumulative risk of relapse at 15 years was 2–8%, with relapses observed as late as 18 years after SCT.[29] This emphasizes the need for extreme caution when considering treatment discontinuation among patients treated with TKI.

The survival of CML patients treated with TKI's nowadays is increasing each year. In patients with CCyR for more than 2 years, survival is not significantly different from the general population.[30] On the contrary, health related quality of life is worse comparing to the general population, particularly in young patients.[31] Long term chronic toxicity is not uncommon and at least one non-serious adverse effects were reported in more than half of the patients. Indeed, our study shows that the primary reason that patients discontinue TKI therapy is treatment toxicity (51% of patients). Other causes of TKI discontinuation were patients' decision after long time in CMR (more than 5 years of CMR) 8 patients (23%), attempting to get pregnant 3 patients (9%), loss of insurance or other financial reasons 6 patients (17%). This underlines two important aspects of TKI therapy. In spite of having 5 TKIs with different profiles of adverse events still treatment toxicity remain a major problem that leads to treatment discontinuation. The financial considerations are also relevant[6] and were the reason for treatment discontinuation in a significant number of patients in our series.

Despite the limitation of relatively small and heterogeneous sample of patients in our study we observed that deep and long duration of response as well as close follow up and early retreatment at molecular relapse, are important factors to consider when patients decide to stop TKIs. Patients with less than CMR at time of TKI discontinuation are at risk of losing CCyR and disease progression. Most patients who discontinue therapy in CMR and relapse respond to retreatment and regain their level of response before TKI discontinuation if retreatment is initiated early at molecular relapse. Thus, close follow up after treatment cessation is imperative when TKI discontinuation is inevitable.

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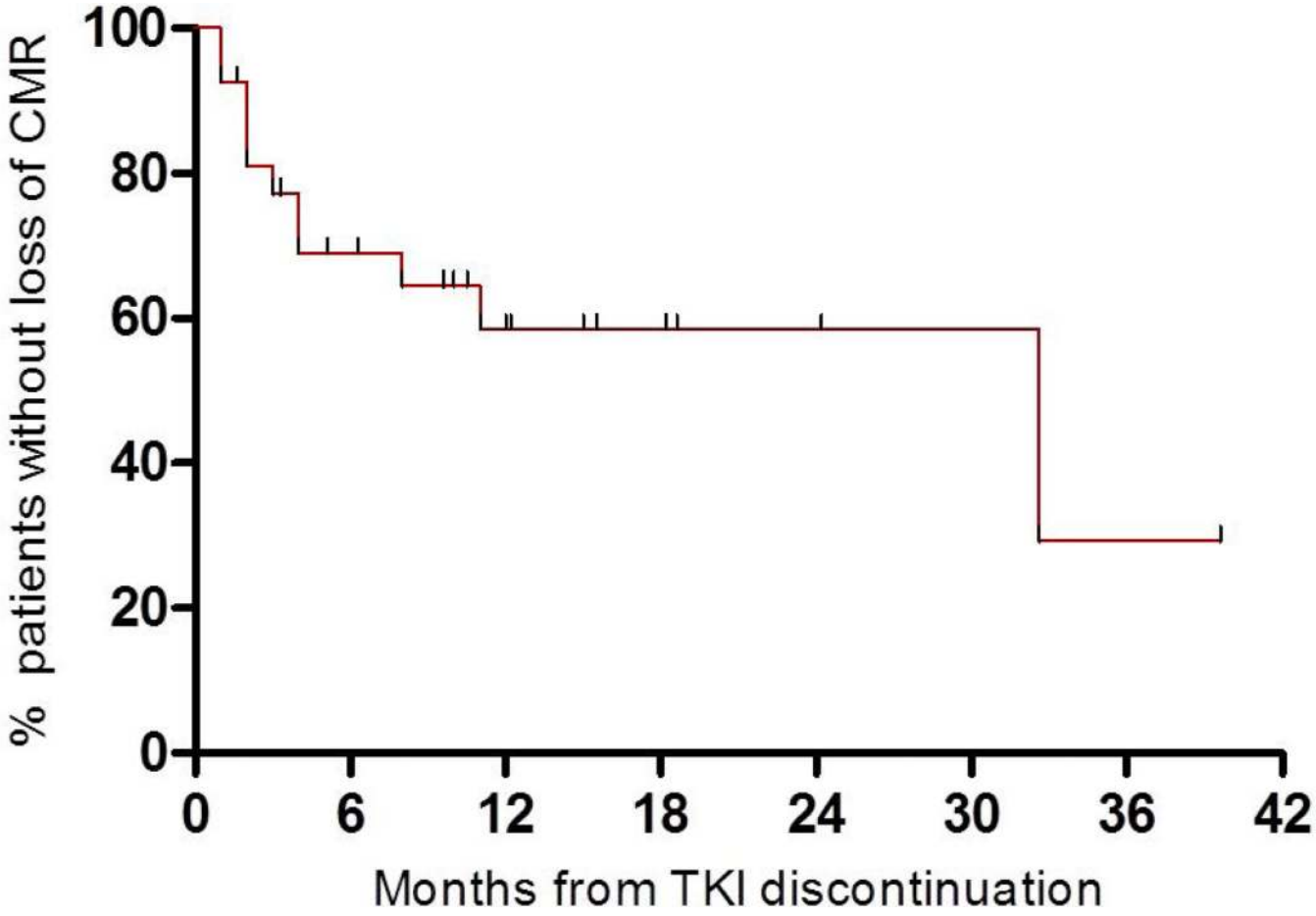

Figure 1. Kaplan-Meier curve of months in sustained complete molecular response (n=27)
TKI: tyrosine kinase inhibitor.

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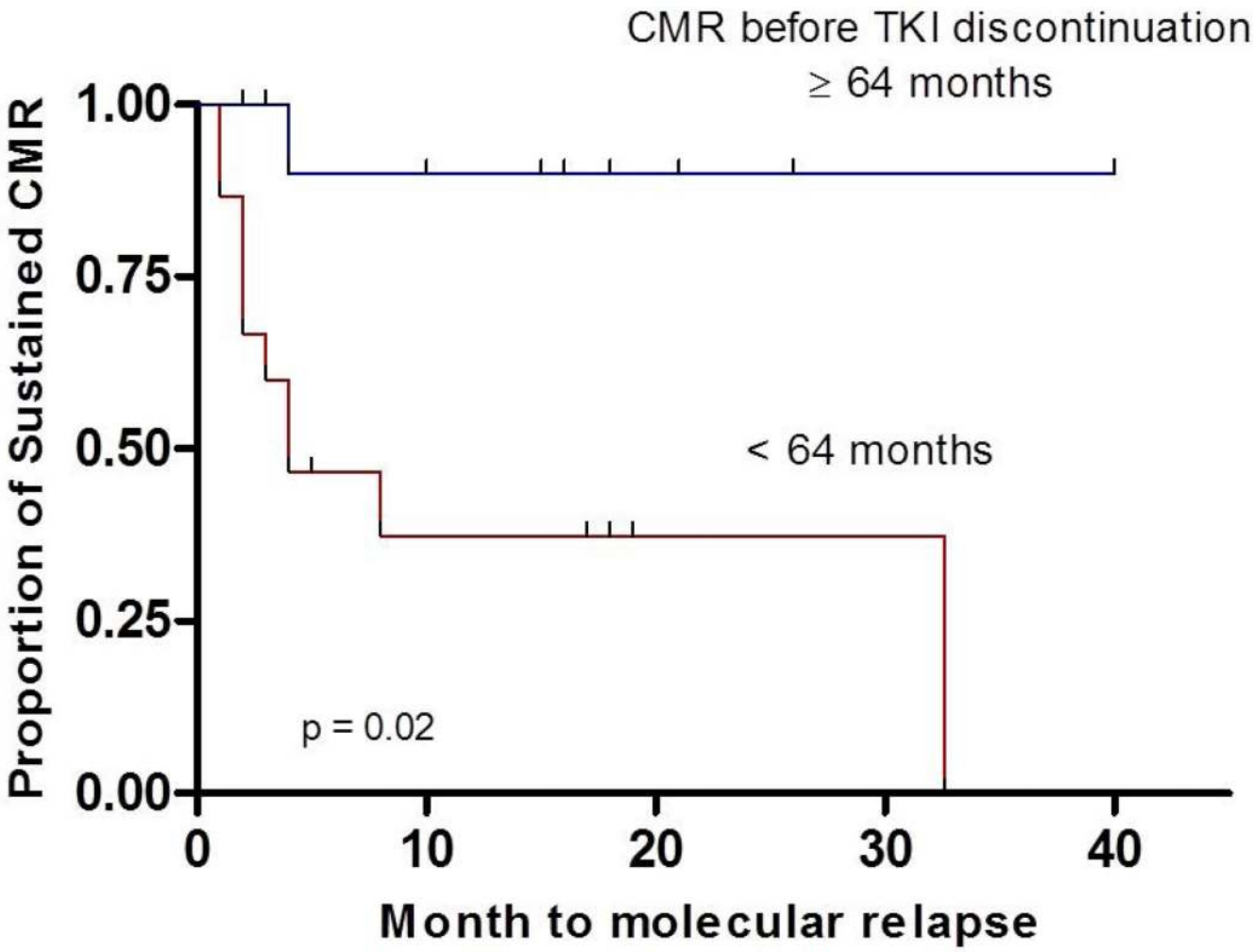

Figure 2. Kaplan-Meier curves of months in sustained complete molecular response after treatment discontinuation according to the duration of CMR before TKI discontinuation

Cumulative proportions of sustained CMR at 12 months after discontinuation were 88.9% and 45.5% in patients with ≥64 or <6 months of CMR before TKI discontinuation (p=0.02). CMR: complete molecular response, TKI: tyrosine kinase inhibitor.

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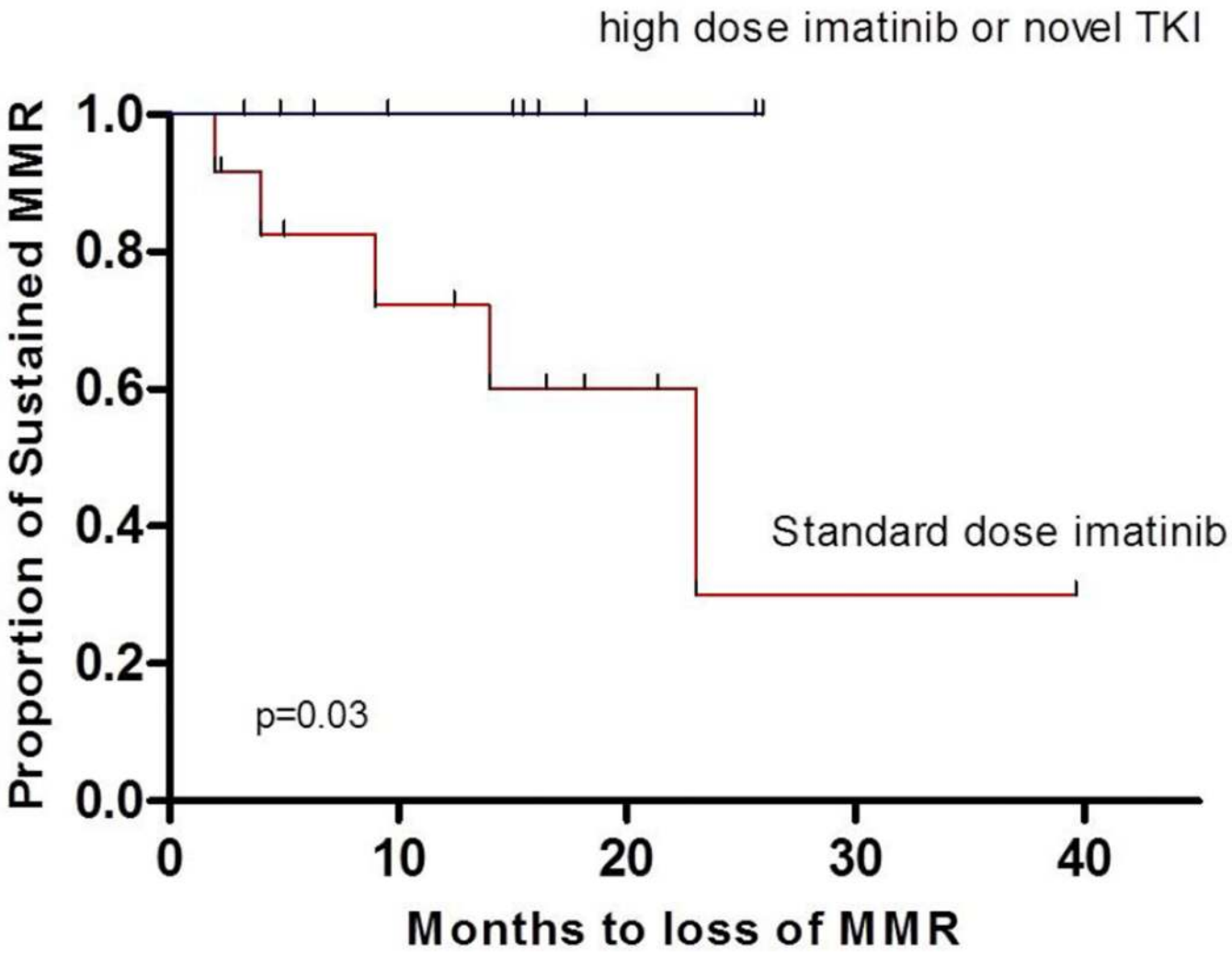

Figure 3. Kaplan-Meier curves of months in sustained major molecular response according to the type and dose of treatment received

Cumulative proportion of sustained MMR at 12 months after discontinuation were 100% and 72% in patients treated with high dose imatinib or second generation TKIs vs. standard dose imatinib (p=0.03). MMR: major molecular response. TKI: tyrosine kinase inhibitor.

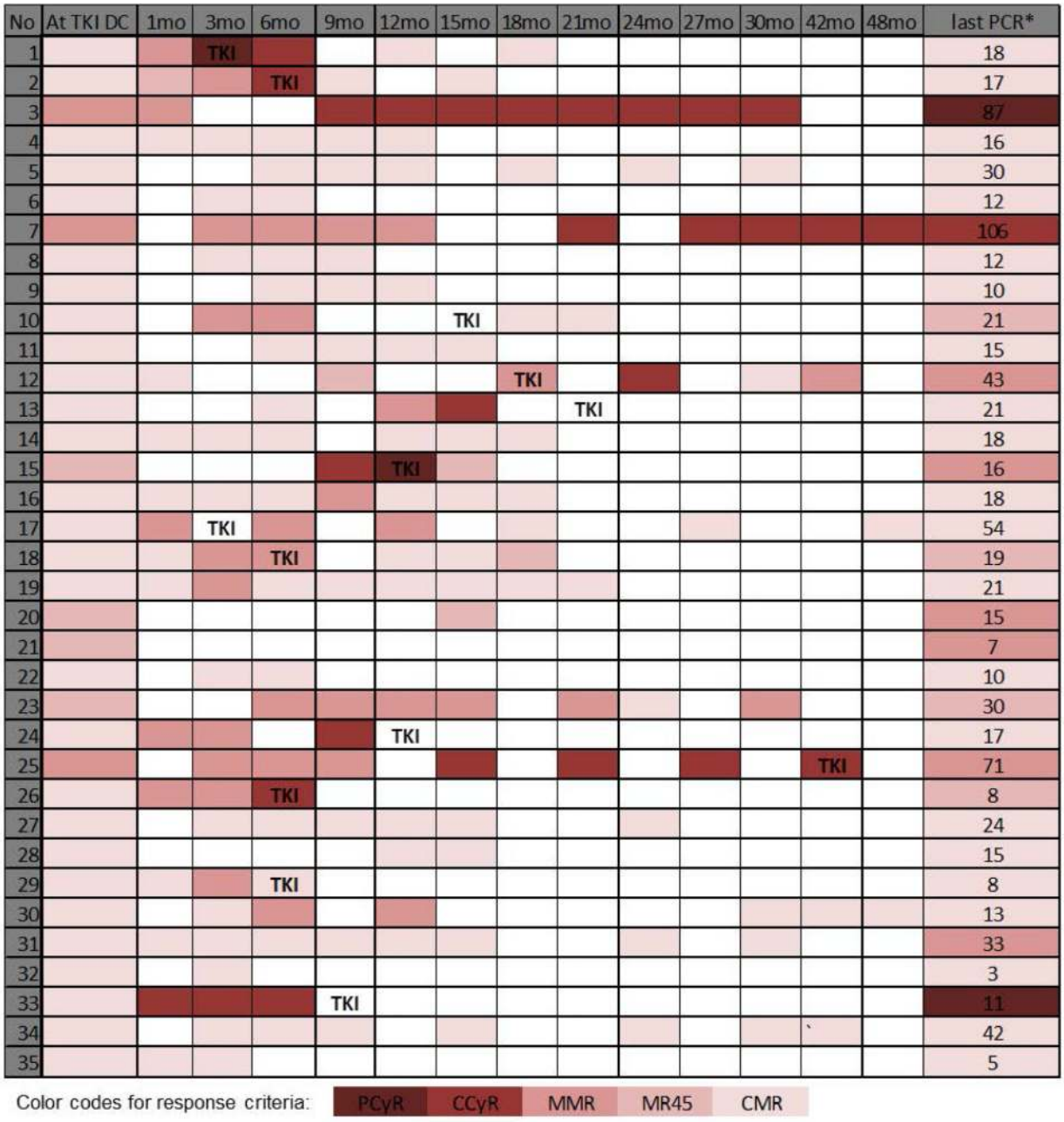

Figure 4. Molecular tests for bcr-abl after TKI discontinuation

The results of the molecular test at follow up are color coded and indicate the depth of response. TKI: tyrosine kinase inhibitor, CMR: complete molecular response, $MR^{4.5}$: molecular response of 4.5-log reduction from baseline MMR: major molecular response. DC: discontinuation. *last RT-PCR from TKI discontinuation (months)

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Table I

Patient characteristics before TKI discontinuation

Parameters	Median [range]	n (%)
Age years (range)	47 [28–75]	
Male/Female		15 (43) / 20 (57)
Median months from initial treatment	98 [42–138]	
Median months to frontline TKI (n=20)	1.4 [0–5]	
Initial treatment with interferon-α		15 (43)
Median months to TKI in patients initially treated with interferon-α	63 [3–178]	
Initial TKI		
Imatinib 400mg/day		17 (49)
Imatinib 600–800mg/day		16 (46)
2nd generation† TKIs		2 (5)
Median months to CCyR	3.3 [2.6 –148]	
Median months to MMR	9 [3–92]	
Median months to CMR	18 [3–97]	
TKI before discontinuation		
Imatinib		29 (77)
Dasatinib		4 (11)
Nilotinib		2 (6)
Bosutinib		2 (6)
Response at TKI discontinuation		
CMR		27 (77)
MR4.5		5 (14)
MMR		3 (9)
Median months of TKI therapy	96 [8–136]	
Median months in CMR before TKI discontinuation	63 [1 –127]	
Median follow up months after TKI discontinuation	16 [2–106]	

abbreviations: TKI: tyrosine kinase inhibitor; n:number; CMR: complete molecular response; $MR^{4.5}$ molecular response of 4.5-log reduction from baseline; MMR: major molecular response.

† nilotinibe, bosutinib

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Table II

Characteristics at TKI discontinuation and clinical course

Parameters	median (range)	n (%)
Reason for TKI discontinuation		
Adverse events		18 (51)
Patients request after prolonged CMR (> 5 years)		8 (23)
Financial or insurance problems		6 (17)
Pregnancy		3 (9)
Follow up after TKI discontinuation	16 [2–106]	
Median months to molecular relapse	4 [1–32]	
Response at last follow up		
CMR		22 (62)
MR[4–5]		4 (11)
MMR		6 (17)
CCyR		1 (3)
Partial-CyR		1 (3)
Minor-CyR		1 (3)

abbreviations: TKI: tyrosine kinase inhibitor; n:number; CMR: complete molecular response; $MR^{4.5}$ molecular response of 4.5-log reduction from baseline; MMR: major molecular response; CCyR: complete cytogenetic response; Partial-CyR: partial cytogenetic response; minor-CyR: minor cytogenetic response

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Table III

Univariate analysis of demographic and clinical factors associated with sustained CMR or MMR after treatment discontinuation among patients who had CMR at the time of TKI discontinuation

variables	N	Cumulative proportion of sustained CMR at 12 months % (95% CI)	*P*	N	Cumulative proportion of sustained MMR at 12 months % (95% CI)	*P*
	27	60.7 (42.3 –79.1)	NA	22	84.4 (69.2 –84.4)	NA
Age			0.92			0.59
< 65	22	58.3 (37.7 – 78.9)		19	83.1 (66.1 –99.9)	
≥65	5	75.0 (NR)		3	100 (80)**	
Gender			0.12			0.10
Male	12	35.3 (8.3 –62.3)		8	83.3 (57.4 –100)	
Female	15	73.3 (50.9 –98.4)		14	85.1 (66.4 –100)	
Transcript type			0.64			0.99
b3a2	14	53.9 (27.8 – 80)		11	90 (72.3 –100)	
b2a2	10	70 (41.6 – 98.4)		9	74.1 (45.5 –100)	
Interferon-α			0.25			0.72
No	11	53 (23.5 –82.5)		12	78.6 (55.4 –100)	
Yes	16	71.6 (49.5 –93.7)		10	90 (71.4 –100)	
TKI and dose			0.30			0.03
Low dose IM	13	51.9 (24.7 –79.1)		12	72.2 (46.8 –97.5)	
High dose IM or novel TKI	14	70.1 (46.1 –94.1)		10	100 (92)**	
Time from TKI Tx to CMR			0.91			0.07
<18	13	66.6 (41 –92.2)		10	100 (92)**	
≥18	13	60.6 (34 –87.2)		11	81.8 (59 –100)	
Duration of CMR before TKI discontinuation†			0.02			0.05
<64	11	45.5 (16.1 –74.9)		8	75.0 (45 –100)	
≥64	11	88.9 (70.3 –100)		10	100 (92)**	

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variables	N	Cumulative proportion of sustained CMR at 12 months % (95% CI)	*P*	N	Cumulative proportion of sustained MMR at 12 months % (95% CI)	*P*
Duration of TKI Tx‡			0.11			0.62
<98	12	41.7 (13.8 –69.6)		9	76.2 (48.4 –100)	
≥98	15	77.8 (56.8 –98.8)		13	90.9 (75.3 – 100)	

abbreviations: TKI: tyrosine kinase inhibitor; n:number; CMR: complete molecular response; MMR: major molecular response; N: number; CI: confidence interval; IM: imatinib; Tx: treatment; NR: not reached, ≤5 cases;

† cutoff based in is median duration of CMR;

‡ cutoff is median duration of TKI therapy before discontinuation.

** One sided calculation

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Table IV

Outcome of patients that re-started therapy after relapse

Patient	Status at treatment interruption	TKI stopped	Months without TKI	Status at retreatment	TKI retreatment	Time to best response	Response at last follow up
1	CMR	Imatinib	3	PCyR	Nilotinib	9	CMR
2	CMR	Imatinib	5	CCyR	Nilotinib	4	CMR
3	CMR	Imatinib	2	CCyR	Imatinib	18	CMR
4	CMR	Nilotinib	6	MMR	Dasatinib	2	CMR
5	CMR	Imatinib	7	CCyR	Dasatinib	5	MR^{4-5}
6	CMR	Nilotinib	5	CCyR	Nilotinib	3	MR^{4-5}
7	CMR	Dasatinib	4	MMR	Imatinib	NA	MR^{4-5}
8	CMR	Dasatinib	18	CCyR	Dasatinib	13	MMR
9	CMR	Dasatinib	10	CCyR	Dasatinib	7	CMR
10	CMR	Imatinib	21	CCyR	Dasatinib	2	CMR
11	MR^{4-5}	Dasatinib	10	PCyR	Dasatinib	6	MMR
12	MMR	Imatinib	37	AP	Bosutinib	23	MMR
13	MMR	Imatinib	9	PCyR	Dasatinib	NA	PCyR

abbreviations: TKI: tyrosine kinase inhibitor; CMR: complete molecular response; $MR^{4.5}$ molecular response of 4.5-log reduction from baseline; MMR: major molecular response; CCyR: complete cytogenetic response; PCyR: partial cytogenetic response; NA; not available; AP: accelerated phase

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